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ORIGINAL INVESTIGATION

Reward processing in male adults with childhood ADHD—a comparison between drug-naïve and methylphenidate-treated subjects

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Abstract
Rationale Dysfunctional reward processing has been proposed as a main deficit in attention-deficit/hyperactivity disorder (ADHD), which could be modulated by treatment with methylphenidate (MPH).
Objectives We examined differences in reward processing in adulthood (independent of actual ADHD) depending on MPH treatment during childhood.
Methods Eleven males with childhood ADHD treated with MPH, 12 drug-naïve males with childhood ADHD, and 12 controls matched by age, handedness, and smoking behavior were studied drug-free using functional magnetic resonance imaging. BOLD-responses were compared during a monetary incentive delay task using an ANOVA design focusing on the ventral striatum during anticipation and the orbitofrontal cortex during outcome.
Results Controls, drug-naïve, and treated subjects did not differ significantly in their activations in the ventral striatum and orbitofrontal cortex. Explorative analyses revealed decreased insula activation during outcome of loss avoidance in drug-naïve subjects in comparison to both groups, while treated subjects did not differ from controls. Insula activation correlated significantly positive with harm avoidance in the treated group. Furthermore, comparing subjects with actual ADHD symptoms, remitters and controls we observed decreased putamen activition in ADHD persisters.
Conclusions Basal ganglia reward processing seemed to be unrelated to MPH pretreatment, but was related to remission. On the other hand, the revealed differences between treated and drug-naïve subjects with childhood ADHD, i.e., in the insula, give evidence for more pronounced abnormal activation in reward-associated brain regions in untreated subjects with childhood ADHD and underpin the need of prospective studies on long-term effects of psychostimulant treatment.

Keywords Attention-deficit hyperactivity disorder · Methylphenidate · Reward · Punishment · fMRI · Ventral striatum · Insula

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Introduction

A growing body of literature supports reward dysfunctions as a promising endophenotype of attention-deficit/hyperactivity disorder (ADHD). Besides executive dysfunctions, the dual-pathway model (Sonuga-Barke 2003) postulates (1) alterations in the thalamo-cortico-striatal reward system, leading to (2) a shorter and steeper delay-of-reinforcement gradient (Sagvolden et al. 2005) and consecutively to (3) delay aversion and dysfunctional compensatory behavior (e.g., self-stimulating hyperactivity, impulsive choices).

Consistently, recent neuroimaging studies revealed alterations in the mesolimbic dopaminergic system. Ventrostriatal volume reductions have been reported in children with ADHD (Carmona et al. 2009) as well as decreased activity in the ventral striatum during an intertemporal choice paradigm in adults (Plichta et al. 2009). Monetary incentive delay tasks (MID) allow us to measure functional activation in reward circuits separately for the anticipation and outcome of reward (Knutson et al. 2001a, b). Recent studies revealed a decreased response of the ventral striatum to the anticipation of monetary rewards in adolescents (Scheres et al. 2007) and adults with ADHD (Ströhle et al. 2008; Plichta et al. 2009). During outcome of reward, disorder-specific underactivation of the posterior cingulate cortex has been found in children with ADHD (Rubia et al. 2009a), while hyperresponsiveness has been reported in the orbitofrontal cortex in children (Rubia et al. 2009b) and in adults with ADHD (Ströhle et al. 2008).

Methylphenidate (MPH) is a drug of first choice in the treatment of ADHD with acute effects on the dopaminergic and the noradrenergic system. There is evidence from positron emission tomography studies for a disruption in the mesodopaminergic pathway in ADHD, in the nucleus accumbens and midbrain regions (Volkow et al. 2009). Clinical doses of methylphendidate block about 60% of DAT (Volkow et al. 1998), which increases extracellular dopamine (Volkow et al. 2002; Rosa Neto et al. 2002). There is also evidence, that MPH modulates dysfunctions in reward processing by increasing dopamine release in response to reward cues (Robbins 1978; Wade et al. 2000; Cardinal et al. 2001). Functional neuroimaging studies on acute and chronic MPH effects on task-related brain activity reported inconsistent findings. Whereas acute MPH doses seem to improve suppression of the default-mode activity in the anterior cingulate cortex in youths with ADHD (Peterson et al. 2009), Kobel et al. (2009) could not find normalization of neural activity in children with ADHD during a working memory task, but improvement on behavioral level. Neural activity in the striatum has been shown to be up-regulated by MPH in healthy subjects during response switching in reversal learning (Dodds et al. 2008), in children with ADHD during response inhibition (Vaidya et al. 1998), and time estimation (Rubia et al. 2009c), as well as in adolescents with ADHD during switching (Shafritz et al. 2004). Neural activity in the orbitofrontal cortex has been shown to be modulated task-specifically, e.g., down-regulated in response to reward during a rewarded continuous performance test (Rubia et al. 2009b), but up-regulated during time estimation in children with ADHD (Rubia et al. 2009c).

Bush et al. (2008) reported no differences in brain activity between adults with ADHD with placebo compared with MPH at baseline, but an increase of activity in the dorsal anterior cingulate after 6 weeks. Other studies on long-term effects suggest an improvement of performance in executive tasks, but only marginal normalizations on the neural level after 3 weeks of treatment (Schweitzer et al. 2004).

Treatment with MPH has been discussed considerably on account of its long-term effect on drug addiction, with inconsistent findings (Faraone and Wilens 2003; Goksoyr and Nøttestad 2008; Biederman et al. 2008; Manuzza et al. 2008). Several structural studies comparing chronically treated with drug-naïve ADHD subjects give evidence for neuroprotective effects of MPH over longer time intervals. A 5-year longitudinal study found smaller total white matter volume in unmedicated compared with medicated ADHD children (Castellanos et al. 2002). More normative volumes in several brain areas, i.e., the inferior frontal cortex (Shaw et al. 2009), cerebellum (Bledsoe et al. 2009), basal ganglia (Sobel et al. 2010), and anterior cingulate cortex (Semrud-Clikeman et al. 2006) have been found in chronically treated compared with unmedicated children. Pliszka et al. (2006) reported more pronounced differences in the anterior cingulate cortex and ventrolateral prefrontal cortex during an inhibition task in drug-naïve ADHD compared with healthy children, but direct comparisons between drug-naïve subjects and subjects with a history of psychostimulant treatment revealed no differences. One year of treatment had no effect on the key area of hypofunction, the anterior cingulate cortex, in an attentional reorientation task, but decreased activity in the insula and striatum (Konrad et al. 2007). Evidence for an influence of early treatment with MPH on the dopamine metabolism has been shown by Ludolph et al. (2008). They found a lower FDOPA influx rate in the insula and putamen in MPH-treated subjects. The authors attribute these results to a down-regulation of dopamine turnover as a potential long-term effect of MPH on dopamine metabolism. As reward functions are strongly connected to the dopaminergic system, a potential long-term treatment effect of MPH could be due to a persisting effect on the dopamine metabolism or to an indirect effect when MPH is given in an age critical for development. Accordingly, a very recent study revealed a decreased activity in the ventral striatum and subgenual cingulate in drug-naïve subjects with childhood ADHD in response to emotional stimuli, but not in

subjects with childhood ADHD which were treated with MPH at least for 1 year during childhood (Schlochtermeier et al. 2010). However, in this study an emotional picture paradigm was used, not a classical reward paradigm.

The purpose of this study was to characterize reward processing in adults with childhood ADHD with and without MPH treatment using a MID task (Knutson et al. 2001a, b). We therefore investigated two groups of adult males with childhood ADHD, one group that had never been pharmacologically treated and one group treated with MPH in childhood at least for 1 year. A third group of matched healthy controls was included.

As the first region of interest we chose the ventral striatum, which is primarily associated with reward dysfunctions in ADHD during anticipation (Plichta et al. 2009; Scheres et al. 2007; Ströhle et al. 2008), and the orbitofrontal cortex second region of interest as it is associated with dysfunctions during outcome of reward (Ströhle et al. 2008). Additionally, a whole-brain analysis was performed to exploratively investigate alterations in other parts of the brain and remitters were compared with participants with actual ADHD diagnosis.

Based on previous evidence for reduced ventral striatal activation (Scheres et al. 2007; Ströhle et al. 2008; Plichta et al. 2009), we hypothesized (1) a decreased activation in the ventral striatum during the anticipation of incentive cues. Based on evidence for orbitofrontal cortex overactivation in children (Rubia et al. 2009b) and adults (Ströhle et al. 2008) during reward outcome, we hypothesized (2) an increased activation in the orbitofrontal cortex during the outcome of reward in subjects with childhood ADHD as well as (3) differences between MPH-treated and drug-naïve subjects as potential direct or indirect persisting effect after MPH treatment.

Materials and methods

Subjects

The study was approved by the local ethics committee. Twenty-eight right-handed (assessed with the Edinburgh Handedness Inventory (Oldfield 1971)) male adults with confirmed childhood ADHD diagnosis (independent of actual ADHD symptoms or diagnosis during adulthood) and 12 right-handed healthy male control subjects participated after providing written informed consent (for group characteristics see Table 1). Five subjects with childhood ADHD had to be excluded due to incompliance with the scanning protocol, functional magnetic resonance imaging (fMRI) artifacts or movements during the data acquisition. Eleven of the included subjects with childhood ADHD had been treated with MPH in childhood (childhood-ADHD-MPH), while 12 had never been pharmacologically treated (childhood-ADHD-drug-naïve). Childhood ADHD was diagnosed according to ICD-9/DSM-III-R or ICD-10/DSM-IV diagnostic criteria by experienced psychiatrists in the Charité child psychiatric department as part of a longitudinal study by Huss et al. (2008). The described symptom severity included several indicators assessed in childhood from standardized psychological tests, clinical judgments, and qualitative behavior ratings from clinical as well as family and school settings. Accordingly, the groups did not differ in childhood symptom severity (Table 1). There were also no differences in the additional retrospective assessment of childhood symptom severity using the Wender Utah Rating Scale (Ward et al. 1993; $p=0.565$) as well as in current ADHD symptom severity (all $p=.341$ to .890), assessed using the Conners Adult ADHD Rating Scale (Connors et al. 1999). Clinical experts diagnosed current ADHD according to DSM-IV criteria subsequent to medical workup and neuropsychological testing. In the drug-naïve childhood ADHD group, seven subjects were remitted, five fulfilled the diagnosis of adult ADHD. In the childhood ADHD group with MPH treatment six subjects were remitted, and five fulfilled the diagnosis of adult ADHD (for current subtypes and neuropsychological data see Tables 1 and 2). Exclusion criteria for the whole sample were other psychiatric disorders including personality disorders [Structural Clinical Interview for DSM-IV (SCID I/II), (First et al. 2001)], medical problems such as severe neuropsychological deficits or head injury. Subjects with childhood ADHD underwent a particular examination of recent and current drug abuse using a computer based semi-structured interview (diagnostic expert system for ICD-10 and DSM-IV (DIA-X); Wittchen and Pfister 1997) and urine screenings just before the scanning session, which were all negative. None of the subjects with childhood ADHD fulfilled lifetime or current criteria for drug addiction (exclusive nicotine), but some fulfilled the criteria of drug abuse (during the past 12 months, alcohol ($n=1$); >12 months ago, alcohol ($n=5$) and amphetamine ($n=1$). Control participants were recruited from the local community by advertisement and had no family history of any psychiatric disorder or pharmacological treatment. Groups were matched for age and cigarette smoking.

Monetary incentive delay task

We used a "monetary incentive delay" (MID) task as described by Knutson et al. (2001a, b) to study neural responses to anticipation and outcomes related to monetary gain and loss. During each trial, volunteers saw one of seven shapes ("cue"; 250 ms), which indicated that they would, subsequently, be able to respond and either win or avoid losing money or that they should respond for no

Table 1 Group characteristics and clinical data

	ADHD subjects drug-naïve (M (SD; *N*=12))	ADHD subjects with MPH (M (SD; *N*=11))	Healthy controls (M (SD; *N*=12))	*p*
Age (years)	26.17 (3.7)	28.45 (3.9)	28.08 (6.2)	.469
Cigarette smoking (*n*)	6	7	5	.570
BDI	7.17 (5.5)	6.00 (6.7)	3.08 (3.1)	.167
STAI I (State)	41.73 (7.9)	38.82 (9.6)	33.50 (6.9)	.113
STAI II (Trait)	40.92 (8.6)	35.46 (9.1)	32.92 (5.7)	.088
Adulthood ADHD symptom characteristics				
CONNERS (T-scores)				
DSM-IV inattentive	61.58 (12.6)	56.64 (11.7)	–	.341
DSM-IV impulsive	53.00 (11.2)	56.45 (12.2)	–	.485
DSM-IV ADHD symptoms total	59.83 (15.2)	59.00 (13.3)	–	.890
Current subtypes				
None/Inattentive/	(7/3/0/2)	(6/2/2/1)		
Impulsive/Combined (*n*)				
Childhood ADHD symptom characteristics				
Hyperactivity	76.84 (16.7)	81.35 (11.8)		.468
Impulsivity	52.47 (13.5)	53.23 (28.8)		.935
Attention deficit	72.39 (17.6)	75.72 (16.2)		.643
Age at first diagnosis (range)	8.08 (2.1; 4–12)	8.36 (2.2; 5–12)	–	.828
Current WURS (sum of ADHD items)	98.17 (27.5)	90.73 (33.4)		.565
Medication				
Age at beginning (years; range)	–	8.66 (1.7; 6–12)	–	
Duration of treatment (years; range)	–	4.34 (2.8; 2–9)	–	
MPH dose (mg; range) per day	–	19.72 (9.6; 10–40 mg)		
Drugs of abuse	2× alcohol, >12 months ago; 1× alcohol, <12 months ago	3× alcohol, >12 months ago; 1× amphet, >12 months ago	0	

M, SD, and frequencies (*n*) of group characteristics; ANOVAs ($p<0.05$)

M means, *SD* standard deviations, *BDI* Beck depression inventory, *STAI* State Trait Anxiety Inventory, *CONNERS* Conner's Adult ADHD Rating Scale, *WURS* Wender Utah Rating Scale

monetary outcome (neutral cues). Cues signaling potential gain were denoted by circles ("anticipation of gain"), potential loss was denoted by squares ("anticipation of loss"), and no monetary outcome was denoted by triangles ("anticipation of neutral"); the possible amount of money that subjects were able to win was indicated by one horizontal line for 0.10€, two horizontal lines for 0.60€ and three horizontal lines for 3.00€. Similarly, loss cues signaled the possibility of losing the same amounts of money. After the cue, volunteers waited a variable interval (delay; mean, 3,990 ms) and then responded to a white target square that appeared for various lengths of time (mean target including delay, 500 ms). The initial response time for the target duration was individually adapted according to reaction times during the training session (400–1,000 ms). Target duration was automatically adapted depending on previous reaction times to permit approximately 66% successful trials. After target presentation, the outcome appeared (1,650 ms) on the screen, notifying volunteers whether they had won or lost money and indicating their cumulative total at that point. The MID task has five possible outcome conditions: after the anticipation of gain (1) outcome of gain, if the participant was fast enough ("outcome of gain") or (2) outcome of no gain, if the participant was to slow ("outcome of no gain" (0€)). After the anticipation of loss (3) outcome of loss, if the participant was to slow ("outcome of loss") or (4) outcome of no loss, if the participant was fast enough ("outcome of no loss" (0€)). After the anticipation of "nongain" the outcome "0€" was presented independent of task performance (condition 5). Trial types were randomly ordered within each session.

To minimize learning effects during scanning, each subject completed a practice version of the task beforehand, for which they did not receive monetary payment, while we collected anatomical scans. A functional MID task session

Table 2 Behavioural, neuropsychological data, and personality

	ADHD subjects drug-naïve (M (SD; *N*=12)	ADHD subjects with MPH (M (SD; *N*=11)	Healthy controls (M (SD; *N*=12)	*p*
Neuropsychololological data			–	
Verbal IQ (WST)	95.67 (8.5)	95.45 (13.6)	110.83 (6.8)	.001
T-scores				
TMT selective attention	52.08 (10.3)	47.40 (7.6)	–	.258
Stroop interference	45.00 (13.3)	48.50 (13.1)	–	.991
Word fluency	49.42 (9.4)	50.20 (9.7)	–	.783
Digit span forward	49.83 (11.1)	43.30 (9.3)	–	.265
Digit span backward	47.75 (7.7)	46.00 (8.2)	–	.506
VLMT learning	49.75 (9.9)	42.09 (7.9)	–	.660
VLMT delay	45.70 (9.4)	40.09 (13.6)	–	.503
VLMT recognition	49.00 (6.2)	47.45 (9.7)	–	.300
Rey copy	57.42 (9.2)	53.78 (10.3)	–	.660
Rey delay	49.17 (9.5)	47.56 (8.8)		.725
Personality data-TCI				
T-scores				
Novelty seeking	55.08 (6.2)	63.36 (10.2)	–	.027
Harm avoidance	56.75 (14.2)	43.00 (10.1)	–	.015
Reward dependency	52.00 (12.2)	48.55 (11.7)	–	.498
Persistence	47.50 (13.9)	47.91 (5.3)	–	.928
Self-directedness	43.50 (12.8)	46.82 (9.0)	–	.485
Cooperativeness	52.17 (8.9)	46.91 (9.2)	–	.168
Self-transcendence	48.92 (11.6)	46.45 (7.7)	–	.559
Behavioral data				
Reaction time (ms)				
Total	240.71 (72.8)	270.98 (129.9)	231.42 (45.0)	.542
Gain	233.20 (69.0)	259.38 (114.7)	225.00 (44.1)	.571
Loss	241.57 (73.2)	271.34 (146.4)	229.11 (44.7)	.566
Neutral	258.08 (77.1)	304.76 (129.8)	260.23 (59.2)	.419
VAS effort				
Total	7.50 (1.8)	7.39 (1.7)	6.98 (1.5)	.728
Gain	7.97 (1.8)	8.51 (1.5)	7.76 (1.6)	.532
Loss	7.58 (2.5)	6.91 (3.4)	7.82 (1.3)	.678
Neutral	5.83 (3.2)	5.45 (3.6)	2.08 (3.0)	.015

M, SD, and frequencies (*n*) of group characteristics; ANOVAs ($p<0.05$)

M means, *SD* standard deviations, *VAS* Visual Analog Scale, *WST* Word Sorting Test, *TMT* Trail-Making Test, *VLMT* Verbal Learning and Memory Test, *TCI* Temperament and Character Inventory

consisted of two runs including 72 trials each. Each trial lasted 6.4 s and the mean inter-trial interval was 5 s. After scanning, subjects retrospectively rated their own exertion in response to each of the seven cues on a visual analog scale (VAS effort).

Functional magnetic resonance imaging

Event-related fMRI was performed on a 1.5 Tesla scanner (Magnetom VISION Siemens®) using gradient-echo echo-planar imaging (GE-EPI, TR=1.9 s, TE=40 ms, flip angle=90°, matrix=64×64). To optimize signal-to-noise and minimize signal drop-out in our main target region, the ventral striatum, we used a voxel size of 4×4×3.3 mm (Schmack et al. 2008; Ströhle et al. 2008; Wrase et al. 2007a) (similar sequence (3.75×3.75×4 mm³), TE=40 ms (Knutson et al. 2001a, b, 2005)). Eighteen slices approximately parallel to the bicommissural plane (ac-pc-plane) were collected. The slices covered the mesolimbic and prefrontal regions of interest, as delineated by prior research (Knutson et al. 2001a, b). For anatomical reference, a 3D magnetization prepared

rapid gradient echo (TR=9.7 ms; TE=4 ms; flip angle 12°; matrix=256×256, voxel size 1×1×1 mm) image data set was acquired.

Data analysis

Functional MRI data were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). After discharging the first three volumes, slice time correction, realignment, spatial normalization into the MNI standard space and smoothing with an 8 mm FWHM kernel were performed. Subjects with childhood ADHD and controls did not differ in their maximum, mean and cumulative head motion (repeated measures analysis of variance (ANOVA) with time as intra-subject factor and group as between-subject factor: all main effects and interactions $p>0.1$).

At the first level analysis, changes in the BOLD response for each subject were assessed by linear combinations of the estimated GLM parameters (beta values), which are displayed by the individual contrast images (effect size equivalent to percent signal change). This analysis was performed by modeling the seven cue conditions, the target and the five outcome conditions separately as explanatory variables convolved with the canonical hemodynamic response function as provided in SPM5. Realignment parameters were included as additional regressors in the statistical model. We analyzed the anticipation phase by contrasting the anticipation of gains vs. the anticipation of neutral ("anticipation of gain") and the anticipation of losses vs. the anticipation of neutral ("anticipation of loss"). To analyze the outcome phase we distributed trials based on the outcome phase by controlling for the anticipation phase and contrasted outcome of gain vs. outcome of no gain ("outcome of gain") and outcome of no loss vs. outcome of loss ("outcome of loss avoidance"), because these outcome conditions had the same condition in the anticipation phase.

A 3×1 ANOVA using group as a between-subject factor (controls vs. childhood-ADHD-drug-naïve vs. childhood-ADHD-MPH) was calculated for the contrast images for gain and loss anticipation as well as outcome described above. We report the results of comparisons between the groups. The entire results of the ANOVA and within-group activations are presented in Tables S1 and S2 in the Electronic supplementary materials.

To test the confirmatory hypotheses, SPM's small volume correction (S.V.C.) was performed for the contrasts "anticipation of gain" and "anticipation of loss" on the ventral striatal volume of interest (VOI; search vol.: right and left, 1,485 mm^3, 55 voxels), for the contrasts "outcome of gain" and "outcome of loss avoidance" on the orbitofrontal cortex (VOI; search vol.: right and left 3,564 mm^3, 132 voxels) according to a publication-based probabilistic MNI atlas (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html). The significance level for these group contrasts was $p<0.05$ FWE-corrected for VOI. All other activations were reported at $p<0.001$ (uncorrected $p<0.001$) and cluster extend of $k\geq10$. Transformation of MNI to Talairach coordinates was performed with the script "mni2tal" provided by Matthew Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

Behavioral and clinical data

Clinical and behavioral data were analyzed with SPSS 12.0 for Windows (www.spss.com). Group differences (controls vs. childhood-ADHD-drug-naïve vs. childhood-ADHD-MPH) in reaction times and self-reported motivation were analyzed within a 3×3 ANOVA with cue (anticipation of gain/loss vs. neutral) as intra-subject factor and reported at $p<0.05$. All other analyses were performed in separate one-way analyses of variance with group as inter-subject factor.

Results

Behavioral and clinical data

Neuropsychological data

As depicted in Table 2 both ADHD groups had a lower verbal IQ compared with healthy controls (ANOVA: $p=0.001$; Word Sorting Test (WST); Schmidt and Metzler 1992). Drug-naïve and MPH-treated subjects with childhood ADHD did not differ significantly in any performed neuropsychological test ($p>.265$). Data controlled for verbal IQ is shown in the Electronic supplementary materials.

Personality data

The temperament and character inventory by Cloninger (1999) revealed higher scores of harm avoidance in drug-naïve subjects with childhood ADHD (drug-naïve, $T=56.75$; MPH, $T=43.00$; $p=.015$), but lower novelty seeking scores (drug-naïve, $T=55.08$; MPH, $T=63.36$; $p=.027$) compared with the treated group with childhood ADHD (see Table 2).

Task performance

All groups displayed significantly faster responses on incentive trials compared with neutral trials (main effect of cue, $F=13.470$; $p<.001$), but there was no significant group difference ($F=.593$; $p=.559$) nor interaction ($F=$

1.268; p=.241). Analysis of self-reported effort to gain or loss revealed a significant effect of cue (F=19.585; p<.001), indicating greater self-reported effort during incentive trials compared with neutral trials and a group-by-cue interaction (F=2.364; p=.007), indicating a greater effort in the childhood-ADHD-drug-naïve group compared with controls in the neutral trials (F=4.775; p=.015; mean difference=−3.75; p<.05). No other significant main effects or interactions were observed (see Figs. S1 and S2 in the Electronic supplementary materials and Table 2).

Brain activation

Differences between controls, drug-naïve, and MPH-treated subjects with childhood ADHD

Anticipation of gain and loss In our ROI analyses of the anticipation phase, the ANOVA did not reveal a main effect of group in the ventral striatum for the gain or the loss contrast. However, a significant main effect of condition was found during gain and loss anticipation in the ventral striatum (see Table S1 in the Electronic supplementary materials).

During gain anticipation an explorative whole-brain analysis revealed a significant effect of group in the inferior frontal cortex (see Table S1 and Fig. S3 in the Electronic supplementary materials). While drug-naïve subjects displayed less activity than controls in the left BA 45 (T=4.14; p=.000; Tal: −50, 35, 4), MPH subjects showed significantly reduced activity compared with controls in the right BA 46 (T=4.80; p=.000; Tal: 42, 38, 4).

During loss anticipation a significant effect of group was found in the middle frontal gyrus (BA 10; see Table S1 in the Electronic supplementary materials). MPH-treated subjects with childhood ADHD showed less activity compared with controls (T=4.31; p<.001; Tal: 33, 38, 6), but did not differ from drug-naïve ADHD subjects (see Table 3).

Outcome of gain and loss Even in our ROI analysis of the outcome phase, the ANOVA did not reveal a main effect of group in the orbitofrontal cortex for the gain and loss contrast.

Whole-brain analyses did not reveal a main effect of group during the outcome of gain (see Table S1 in the Electronic supplementary materials and Table 3).

During the outcome of loss avoidance, our explorative whole-brain analysis revealed an interesting effect of group in the left and right insula (left: F(1, 32)=13; uncorrected p=.000, Tal: −36, 11, −6; right: F(1, 32)=9.82; uncorrected p=.000, Tal: 39, 11, −8). Drug-naïve subjects with childhood ADHD showed less activity compared with healthy controls in the left (T=5.08; p=.000, Tal: −36, 11, −6) and in the right insula (T=4.11; p=.000, Tal: 39, 11, −8) even if the result in the right insula did not reach our criterion of >/10 voxels (k=7). In contrast, subjects with childhood ADHD with MPH treatment did not show any significant differences compared with healthy controls. The activation in the right insula was significantly higher in subjects with MPH treatment than in drug-naïve subjects (T=3.46; p=.001, Tal: 39, 11, −8; k=1). This effect resulted mainly from an increased activation during the condition outcome of loss (see Fig. 1).

Additionally, we revealed a main effect of group in the precentral gyrus (T=4.94; p<.001, Tal: 33, 7, 22) indicating a reduced activity in drug-naïve subjects with childhood ADHD compared with controls during the outcome of loss-avoidance.

To explore the potential effect of IQ differences between the ADHD groups and healthy controls we conducted ANCOVAs controlling for verbal IQ (WST). Our main findings remained significant, but some findings were no longer observed. During gain anticipation, there were no differences in the BA 45 between controls and drug-naïve subjects. During loss anticipation, the effect of group in the middle frontal gyrus (BA 10) was not observed. After controlling for IQ, we found no effect in the precentral gyrus.

Differences between controls, remitted and actual diagnosed subjects with childhood ADHD

To test the influence of current diagnosis, we calculated a similar 3×1 ANOVA comparing ADHD subjects with ongoing ADHD during adulthood (n=10), remitted subjects with childhood ADHD (n=13), and healthy controls (n=12). Patients and controls differed in their verbal IQ (p=.000), in harm avoidance (p=.020), and in the subjective effort to gain or avoid losing money (p=.003); state and trait anxiety (p<.028) as well as adulthood ADHD symptom characteristics (p<.001; for demographics see Tables S3 and S4 in the Electronic supplementary materials).

Although not correctable for small volume the analysis of variance revealed a significant effect of group in the putamen (left: F(1, 23)=14.98; uncorrected p=.000, Tal: −21, −2, 11; right: F(1, 23)=10.25; uncorrected p=.000, Tal: 27, 5, 11; see Table S5 in the Electronic supplementary materials), indicating a higher neural response during gain anticipation in controls compared with subjects with adult ADHD (T=5.26, Tal: −21, −2, 11; uncorrected p=.000), while remitted subjects with childhood ADHD did not differ from controls. Post hoc t tests revealed a higher neural response in the left putamen in remitted subjects compared with subjects with ongoing ADHD (T=3.99,; uncorrected p=.000, Tal: −27, 3, 11). There was no main effect of group in the orbitofrontal cortex during the outcome phase (Fig. 2 and Table 4). Controlling for IQ differences did not change this result.

Table 3 Differences in neural responses between controls, drug-naïve and MPH-treated subjects with childhood ADHD

Region	Voxels	BA	*T*	*Z*	*p*	Talairach		
						x	*y*	*z*
Anticipation of gain								
ADHD-drug-naïve<controls								
Inferior frontal gyrus[a]	24	45	4.14	3.68	.000	−50	35	4
ADHD-drug-naïve>controls	No significant activations							
ADHD with MPH<controls								
Inferior frontal gyrus[a]	46	46	4.80	4.13	.000	42	38	4
Inferior frontal gyrus	48	45	4.32	3.81	.000	−48	27	7
Inferior parietal lobule	13	40	3.85	3.46	.000	56	−28	26
ADHD with MPH>controls	No significant activations							
Anticipation of loss								
ADHD-drug-naïve<controls								
Cuneus[a]	208	18	6.27	5.03	.000	−15	−81	15
Middle temporal gyrus[a]	69	21	5.11	4.34	.000	−59	−55	6
ADHD-drug-naïve>controls	No significant activations							
ADHD with MPH<controls								
Cuneus	27	18	4.65	4.04	.000	−15	−84	15
Middle frontal gyrus[a]	14	10	4.31	3.80	.000	33	38	6
ADHD with MPH>controls	No significant activations							
Outcome of gain								
ADHD-drug-naïve<controls	No significant activations							
ADHD-drug-naïve>controls								
Inferior frontal gyrus	10	45	4.08	3.63	.000	−48	29	4
ADHD with MPH vs. controls	No significant activations							
Outcome of loss avoidance								
ADHD-drug-naïve<controls								
Insula[a]	13	13	5.08	4.32	.000	−36	11	−6
Precentral gyrus[a]	45	6	4.94	4.23	.000	33	7	22
ADHD-drug-naïve>controls	No significant activations							
ADHD with MPH vs. controls	No significant activations							

Significant differences in brain activations in the center of maximum of the clusters between healthy controls, drug-naïve, and MPH-treated subjects with childhood ADHD. No significant difference was found between drug-naïve childhood ADHD subjects and MPH-treated subjects. All results $p<0.001$ uncorrected and $k\geq10$ voxels

[a] Significant effect of group in the ANOVA

Correlations between brain activation, ADHD symptoms, and personality

The insula is thought to be associated with aversive stimuli, risk taking, and harm avoidance (Wächter et al. 2009; Preuschoff et al. 2008; Paulus et al. 2003; Stein et al. 2007). Therefore, we exploratively correlated the individuals maxima (i.e., beta values) of subjects with childhood ADHD in the right insula (Tal: 39, 11, −8)) with the TCI values of the harm avoidance scale using Pearson's linear correlation coefficients. For both groups together partial correlation was not significant (r=.383; p=.067), but harm avoidance correlated significantly positive with brain activation during outcome of loss in subjects with MPH treatment (r=.596; p=.026), but not in drug-naïve subjects (p=.362). We found no correlations between brain activation in the insula and current subjective symptom measures of ADHD (Conners; all p>.196).

Additionally, we correlated current subjective symptom measures with the individuals maxima of the contrast 'anticipation of gain' of subjects with and without ADHD persistence in the putamen (Tal: 21, −2, 11). Reactivity of the putamen was not correlated with any of these measures (all p>.321).

Discussion

Our results do not confirm the hypothesis of hyporeactivity in the ventral striatum during the processing of incentive monetary cues in male adults with childhood ADHD in contrast to previous findings in adolescents and adults with current ADHD (Plichta et al. 2009; Scheres et al. 2007; Ströhle et al. 2008). Even if slightly more pronounced in healthy subjects, all three groups displayed a significant activation in the ventral striatum during the anticipation of

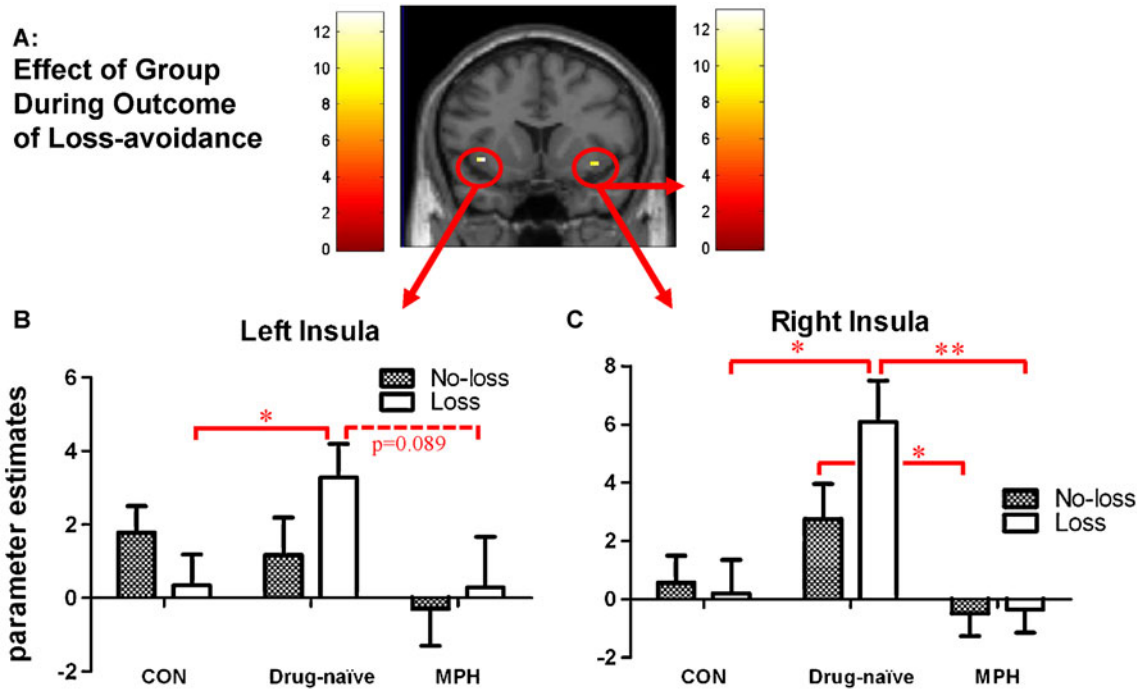

Fig. 1 Outcome of loss. **a** Effect of group in the left and right insula for the contrast "outcome of loss>no loss" (displayed at Tal: 39, 11, −8; F=9.82). **b**, **c** Parameter estimates for the contrast "outcome of loss-avoidance" in the insula peak voxel (Tal: *left*, −36, 11, −6; *right*, 39, 11, −8). Significant differences between beta values of the condition "outcome of loss:" *p<.05; **p<.001

gains and also no significant group effect was found for anticipation of losses. Additionally, we could not reveal a hyperresponsiveness towards monetary outcome in the prefrontal cortex (Rubia et al. 2009a; Ströhle et al. 2008).

Within our design we cannot infer "normalization effects" in the striatum. Striking similarities in fMRI studies between adults and children with ADHD have been reported (for review see Cubillo and Rubia 2010). However, in a longitudinal study of Castellanos et al. (2002) striatal volumes normalized with increasing age in adolescents with ADHD. A possible explanation for our finding is that more than half of our subjects with childhood ADHD did not fulfill the criteria for persisting ADHD in adulthood and were therefore remitters. Indeed, explorative analyses comparing healthy controls, remitted males with childhood ADHD and males with ongoing ADHD in our sample support this suggestion. While still affected ADHD patients displayed less reactivity in the putamen during gain anticipation compared with healthy controls remitted subjects did not differ from the healthy. Subjects with persisting ADHD displayed higher activity to neutral and gain cues and reported higher subjective effort (see Electronic supplementary materials), but differentiated less between neutral and rewarding cues compared with both groups. Our

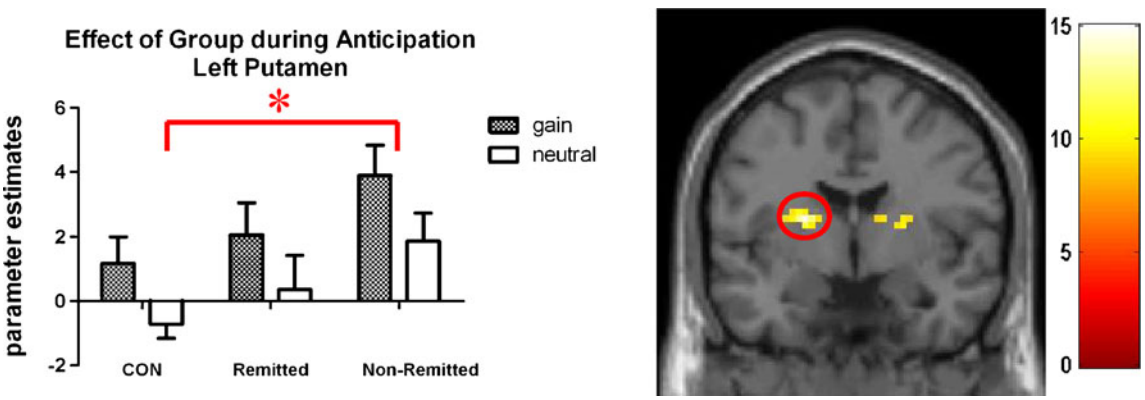

Fig. 2 Anticipation of Gain (controls/ADHD-remitted/-non-remitted): Effect of group in the left putamen for the contrast "anticipation of gain> anticipation of neutral" with the parameter estimates (Tal: −21, −2, 11; F=14.98)

Table 4 Differences in neural responses between controls, remitters and persisters

Region	Voxels	BA	*T*	*Z*	*p*	Talairach		
						x	*y*	*z*
Anticipation of gain								
Remitted<controls								
Inferior frontal gyrus	18	45	4.06	3.62	.000	−50	35	4
Remitted>controls	No significant activations							
ADHD<controls								
Lentiform nucleus[a]	100		5.26	4.43	.000	−21	−2	11
Inferior parietal lobule	34	40	4.44	3.89	.000	56	−28	26
Lentiform nucleus	79		4.39	3.86	.000	24	−2	8
Inferior frontal gyrus	15	46	4.22	3.73	.000	45	38	4
Postcentral gyrus	16	2	4.20	3.72	.000	−39	−22	29
Insula	26	13	4.13	3.67	.000	−36	−14	17
Inferior frontal gyrus	40	45	3.97	3.55	.000	−50	26	4
Precentral gyrus	32	4	3.90	3.50	.000	−59	−7	25
ADHD>controls	No significant activations							
ADHD<remitted								
Insula	158	13	4.56	3.97	.000	−45	−17	15
Anterior cingulate	18	24	3.86	3.47	.000	6	33	12
Caudate	20		3.71	3.36	.000	−21	10	19
ADHD>remitted	No significant activations							
Anticipation of loss								
Remitted<controls								
Cuneus	46	18	4.96	4.24	.000	12	−15	−84
Remitted>controls	No significant activations							
ADHD<controls								
Cuneus[a]	156	18	5.53	4.60	.000	−15	−84	15
Inferior frontal gyrus[a]	79	45	5.07	4.31	.000	−45	18	5
Middle occipetal gyrus	32	19	4.69	4.06	.000	30	−78	9
Middle temporal gyrus	25	37	4.00	3.57	.000	48	−58	0
Lentiform nucleus	12	3.87	3.48	.000	30	−8	9	
ADHD>controls	No significant activations							
ADHD<remitted								
Posterior cingulate	42	23	4.73	4.09	.000	−6	−57	19
Middle frontal gyrus	22	10	4.06	3.62	.000	30	38	12
Thalamus	15		3.61	3.28	.001	−6	−25	18
ADHD>Remitted	No significant activations							
Outcome of gain								
Remitted<controls	No significant activations							
Superior temporal gyrus[a]	34	22	4.92	4.21	.000	48	−3	3
Middle temporal gyrus	12	39	4.09	3.64	.000	50	−64	11
Inferior frontal gyrus	10	46	3.85	3.46	.000	−48	41	9
ADHD vs. controls	No significant activations							
ADHD<remitted								
Cuneus[a]	13	18	4.03	3.60	.000	0	−72	15
ADHD>remitted	No significant activations							
Outcome of loss								
Remitted vs. controls	No significant activations							

Table 4 (continued)

Region	Voxels	BA	*T*	*Z*	*p*	Talairach		
						x	*y*	*z*
ADHD<controls								
Insula[a]	13	13	4.46	3.90	.000	−36	11	−6
Precentral gyrus[a]	39	6	4.42	3.88	.000	36	1	22
ADHD>controls	No significant activations							
ADHD vs. remitted	No significant activations							

Significant differences in brain activations in the center of maximum of the clusters between healthy controls, subjects with ADHD and remitted ADHD subjects. All other results $p<0.001$ uncorrected and $k\geq10$ voxels

[a] Significant effect of group in the ANOVA

results could potentially suggest a normalization of dysfunctions in the putamen independent of previous medication, but dependent on symptomatology, which would stand in contrast to the postulate of reward dysfunctions as a stable endophenotype of ADHD (Henriquez-Henriquez et al. 2010).

Although not the primary focus of this study, our whole-brain analyses revealed significant differences between the ADHD groups and healthy participants as well as between drug-naïve and MPH-treated subjects during the anticipatory and outcome phase. During the anticipation of gain drug-naïve subjects displayed a decreased activity in the left (BA 45), while MPH-treated subjects displayed decreased activity in the right (BA 46) inferior frontal cortex compared with controls. Even if our ADHD groups did not differ from each other, this lateralization is in line with a longitudinal study reporting more abnormal enhanced cortical thinning in unmedicated ADHD adolescents in the left inferior frontal cortex compared with participants taking psychostimulants (Shaw et al. 2009). The functional significance of this lateralization effect is unclear, however. IQ has been shown to correlate negatively with ADHD symptoms (Goodman et al. 1995). As we did not want to remove disorder-relevant variance from the ADHD groups, we did not covary for IQ, but the result in the BA 45 did not remain after controlling for IQ (see Electronic supplementary materials). Also, even if controlled for IQ, remitted subjects displayed less activity in the left inferior frontal cortex and persisters showed decreased activity in both, left BA 45 and right BA 46. Inferior frontal hypoactivation has recently been reported in adults with childhood ADHD during motor inhibition and cognitive switching (Cubillo et al. 2010). Our effect in the inferior frontal cortex was mainly driven by an increased activation during the presentation of neutral cues, which could reflect higher bottom up control towards irrelevant cues. This result is in line with our behavioral data, indicating greater effort in the neutral condition in subjects with childhood ADHD than in controls. Increased response both on the neural as well as on the behavioral level (pleasantness ratings) to neutral stimuli were also reported in an emotional picture paradigm in ADHD patients (Schlochtermeier et al. 2010). Another explanation could be an altered activity of the default network during neutral cues, possibly reflecting increased "mind wandering" during rest (Mason et al. 2007), which could lead to decreased vigilance for salient external cues on behavioral level.

A main question of this study was whether neural activity during reward processing differs depending on previous medication. Even if Schlochtermeier et al. (2010) reported a hyporesponsiveness of the ventral striatum during emotion processing in drug-naïve subjects with childhood ADHD, which was not present in MPH-treated subjects, we could not reveal such differences in the ventral striatum using a reward paradigm. Our finding does not fit well with recent longitudinal findings suggesting a normalization of anatomical dysregulation in the putamen in psychostimulant treated, but not in untreated ADHD subjects (Sobel et al. 2010). To the best of our knowledge, this is the first functional fMRI study comparing remitted males with childhood ADHD and males with ongoing ADHD. The demonstrated dysfunction in the putamen in persisters, but not in remitters gives potential evidence for a stronger effect of the "growing out" of dysfunctions in the putamen in remitted males with childhood ADHD (Castellanos et al. 2002; Krain and Castellanos 2006), than effects of previous medication.

Noteworthy and an interesting finding was the significant difference between subjects with childhood ADHD treated with MPH and drug-naïve subjects with childhood ADHD during the outcome of loss in the insula. While MPH-treated subjects did not differ from controls, drug-naïve subjects with childhood ADHD displayed a hyporesponsiveness of the insula during the outcome of successful loss-avoidance (i.e., negative reinforcement) compared to loss (i.e., punishment), which was mainly due to an

increased neural response to punishment in drug-naïve males. Decreased insula activity has also been found in adults with persisting ADHD during motor inhibition and cognitive switching (Cubillo et al. 2010), while increased during decision making in adults with ADHD (Ernst et al. 2003). In line with our results, MPH treatment effects in the insula have been reported previously: Konrad et al. (2007) used an Attention Network Test in children with ADHD and reported higher insula BOLD response during reorientation compared with controls before treatment which normalized after 1 year of MPH medication. Here, we found higher BOLD response to loss outcome in the untreated subjects with childhood ADHD compared with treated subjects and controls (see Fig. 1). Ludolph et al. (2008) reported a decreased FDOPA influx rate. In both studies, the wash out phase was only 1 week prior to the scanning session, while in our study ADHD subjects were free of medication at least 1 year.

Insula activation is involved in responding to punishment/aversive stimuli in healthy subjects (Elliott et al. 2000; Sanfey et al. 2003; Daw et al. 2006; Wächter et al. 2009) and is thought to integrate emotionally salient stimuli with the representation of bodily signals (Craig 2009). Furthermore, activation within this area is associated with processing, representing and learning about risk and uncertainty (Huettel et al. 2006; Paulus et al. 2003; Preuschoff et al. 2008) and has been proposed to reflect a prediction error for uncertain/unpredicted aversive stimuli (Sarinopoulos et al. 2009; De Martino et al. 2009; Kuhnen and Knutson 2005). In line with previous studies, we could find a positive correlation between insular activity during punishment and harm avoidance at least in MPH-treated subjects (Paulus et al. 2003; Stein et al. 2007). Subjects with childhood ADHD did not differ in their task performance and subjective effort to avoid loss. As we did not use a learning paradigm we cannot account for better learning from penalties or deficits during negative reinforcement learning. It remains speculative, if this dysfunction leads behaviorally to an unaffected sensitivity to the frequencies of penalties, but reduced sensitivity to the magnitude of penalties (Luman et al. 2009). However, the higher harm avoidance scores make dysfunctions in integrative processes (Craig 2009) and/or processing of risk (Huettel et al. 2006; Paulus et al. 2003; Preuschoff et al. 2008) more plausible.

If these differences are due to a direct effect of MPH treatment on the dopaminergic system or an indirect effect due to an improvement of social functioning together with a decrease of problems in school, thus facilitating normal reinforcement learning and developmental processes remains speculative.

There are several limitations to our study. The groups were defined according to childhood treatment, and no randomized allocation to treatment and non-treatment groups had been realized. Huss et al. (2008) however, could show that treatment with MPH was related to the therapists' attitude towards ADHD pharmacotherapy. While some doctors consistently promoted treatment with stimulants, others preferred not to give medication. As the therapists were assigned according to a waiting list in a consecutive manner, the allocation to groups may be considered to be pseudo-randomized. Another drawback of the study is the small sample size due to the exclusive recruitment from a group of patients included in the former study done by the child psychiatric department (Huss et al. 2008). This restriction was chosen because of the big advantage of ensuring reliability of documentation of medication as well as of childhood diagnosis, as the retrospective assessment of childhood ADHD is not validated. ADHD groups differed in verbal IQ from healthy controls. Control analyses did not change our main results in the putamen and the insula (see Electronic supplementary materials). However, IQ had an influence on our results in the prefrontal cortex and therefore these results should be interpreted with caution. In addition, because of the high comorbidity of ADHD with substance use disorders, we were unable to exclude cases with history of drug abuse. While most of the results only changed marginally when excluding subjects with history of drug abuse (see Electronic supplementary materials), the effect in the insula was lost. If this difference is due to less power in the now small sample or due to an influence of drug abuse should be clarified in larger samples. However, in our study all participants had no current drug abuse at the time of fMRI measurement and no subject fulfilled the criteria for lifetime diagnosis of addiction. All subjects (except one) stopped abuse more than 1 year before scanning and the one with abuse in the last 12 months did not consume alcohol 1 month before scanning. Studies on substance use disorders report hypoactivity in main areas of the reward system, e.g., the ventral striatum during anticipation of monetary reward in detoxified alcoholics (Wrase et al. 2007b). Therefore our subjects with history of drug abuse (mainly alcohol, only one with amphetamine) should have amplified differences in the ventral striatum, which we could not find. The described pattern we found is not typical of substance use disorders. Therefore we think that our results reflect dysfunctions in ADHD.

Despite these limitations this study provides first insights in dysfunctions in reward processing in adults with childhood ADHD independent of current diagnosis as well as evidence for differences in reward processing depending on early medication with MPH. Age of treatment, duration and dosage may modulate this effect and the question arises whether these differences are limited to MPH or may also be achieved by treatment with other drugs. Additionally, to the best of our knowledge acute effects of MPH on neural

responses during a monetary incentive delay task in ADHD patients have as yet not been investigated.

In summary our findings could potentially suggest that there is normalization independent of MPH pretreatment, which was further supported by findings of striatal abnormalities in persisters but not remitters with ADHD. On the other hand, the revealed differences between treated and drug-naïve subjects with childhood ADHD, i.e., in the insula, give evidence for more pronounced abnormal activation in reward-associated brain regions in untreated subjects with childhood ADHD and underpin the need of prospective studies on long-term effects of psychostimulant treatment.

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Author contributions A. Ströhle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest None

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Ethical standards This study complies with the current laws of Germany.

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