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Differentiating Brain Function of Punishment versus Reward Processing in Conduct Disorder with and without Attention Deficit Hyperactivity Disorder

Sarah Baumann[1], Arne Hartz[2], Wolfgang Scharke[3], Stephane A. De Brito[4], Graeme Fairchild[5], Beate Herpertz-Dahlmann[1], Kerstin Konrad[2], Gregor Kohls[2,6]

[1]*Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital RWTH Aachen, Aachen, Germany.*

[2]*Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital RWTH Aachen, Aachen, Germany.*

[3]*Cognitive and Experimental Psychology, Institute of Psychology, RWTH Aachen University, Aachen, Germany.*

[4]*Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, UK.*

[5]*Department of Psychology, University of Bath, Bath, United Kingdom.*

[6]*Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Dresden, Germany.*

Corresponding author: Sarah Baumann, MSc, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital RWTH Aachen, Neuenhofer Weg 21-22, D-52074 Aachen, Germany. **Email:** sbaumann@ukaachen.de

Running head: Neural Punishment Processing in CD versus ADHD

Abstract

Objective: Conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD) are reported to co-occur in about 30-50% of affected individuals. Research suggests that poor reinforcement-based decision-making may contribute to impaired social functioning in both youths with CD and ADHD. Considering its frequent co-occurrence this raises the question whether decision-making deficits in both disorders have a disorder-specific and/or shared neurobiological basis.

Method: 138 participants with CD, ADHD, or CD+ADHD, and typically developing controls (TDCs) aged 9-18 years (48% girls) were included in the study. Participants completed a reinforcement-based decision-making task in the fMRI scanner, investigating decision-making capabilities under different reinforcement contingencies (i.e. punishment vs. reward). Whole-brain and ROI analyses were used to test for potential group differences.

Results: For punishment versus reward contingencies, relative to TDCs, youths with CD+ADHD displayed lower brain activity in dorsal striatum (incl. caudate), middle temporal gyrus (MTG), inferior frontal gyrus (IFG) and lateral occipital cortex, and they showed lower activity in dorsal striatum (incl. putamen), orbitofrontal cortex (OFC) and IFG relative to participants with ADHD. All other group comparisons were found to be non-significant.

Conclusion: Participants with comorbid CD+ADHD are neurobiologically the most severely impaired group regarding reinforcement-based decision-making, particularly in response to punishment.

Keywords: conduct disorder, attention-deficit/hyperactivity disorder, reinforcement learning, punishment, fMRI

Introduction

Conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD) are two of the most prevalent externalizing disorders in childhood and adolescence (Polanczyk et al. 2015). These disorders are reported to co-occur in about 30-50% of affected individuals (Banaschewski et al. 2005; Rubia et al. 2010). By acknowledging their frequent co-occurrence, the International Classification of Diseases (ICD-10) by the World Health Organization (World Health Organization 1992) even gave the condition it's own diagnostic category known as hyperkinetic conduct disorder (ICD-10: F90.1). Compared to pure CD and pure ADHD, youths with hyperkinetic conduct disorder (CD+ADHD), are considered the more severe cases as they typically have an earlier age-of-onset of a more serious and persisting set of symptoms that require broader, i.e., cross-disorder, multimodal treatment approaches (Banaschewski et al. 2005; Connor & Doerfler 2008). However, it remains debatable whether CD+ADHD truly constitutes a distinct syndrome or whether it is simply a hybrid of CD and ADHD (Schachar & Tannock 1995). Research suggests that both CD and ADHD share certain behavioural (e.g., emotion dysregulation), cognitive (e.g., executive dysfunction), and neurobiological (e.g., ventral striatal dysfunctions) characteristics, but they also present with disorder-specific (brain) abnormalities (Rubia 2011). Disentangling disorder-specific from overlapping neural dysfunctions will help to better understand the etiology of the two conditions as well as their comorbid presentation, and may thus inform theories of developmental psychopathology and treatment practices.

According to Sonuga-Barke and colleagues (2016) poor reinforcement-based decision-making contributes to impaired social functioning and reduced quality of life in youths with both CD and ADHD. However, it has been proposed that the mechanisms underlying decision-making deficits may differ between the two disorders: While CD is linked to reckless risk-taking and failure to learn from negative consequences (i.e., punishment), ADHD is

associated with deficient (i.e. insufficiently reflective, and inconsistent) and impulsive actions (i.e., favoring immediate over delayed outcomes such as rewards) (Sonuga-Barke et al. 2016). Still, little is known about the neurobiological underpinnings of poor reinforcement-based decision-making in CD versus ADHD, and crucially, it is unclear to what extent decision-making deficits in both conditions have a disorder-specific and/or shared neurobiological basis (Banaschewski et al. 2005).

In an attempt to pinpoint particularly the distinct brain substrates of CD relative to ADHD, Rubia (2011) reviewed the relevant structural and functional magnetic resonance imaging (fMRI) studies and concluded that CD is associated with disorder-specific deficits in circuits known to regulate affective and motivational control processes (i.e., "hot" executive functions), including regions such as orbitofrontal (OFC) and ventromedial prefrontal cortices (vmPFC), anterior cingulate cortex (ACC), striatum, and amygdala. The disorder-specific dysfunctions in ADHD, by contrast, appear in fronto-striato-parieto-cerebellar circuits that regulate motor, attentional, and cognitive control processes (i.e., "cool" executive functions), most prominently the lateral inferior frontal cortex (for a more recent review, see also Puiu et al. 2018). Although both "hot" and "cool" control circuits are involved in the decision-making process (Ernst & Paulus 2005), the vast majority of fMRI studies reviewed by Rubia (2011) did not utilize experimental tasks that truly tap into reinforcement-based decision-making (Scholl & Klein-flügge 2018). Thus, it still remains unclear to what extent the disorder-specific neural dysfunctions of CD versus ADHD, as highlighted by Rubia (2011), are linked to the differential decision-making deficits seen in both disorders.

More recently, fMRI studies have examined the neural substrates of reward and punishment processing as two pivotal computational mechanisms that may underlie the reinforcement-based decision-making deficits in CD and ADHD (Plichta & Scheres 2014; Blair et al. 2018). Dysfunctions in these two processes are thought to increase the risk of

impulsiveness, frustration-induced reactive aggression and antisocial behaviour more generally (Alegria et al. 2016; Blair et al. 2018; Puiu et al. 2018). In comparison to typically developing controls (TDCs), youths with CD show reduced striatal and vmPFC responses to rewarding stimuli (e.g., monetary gains), whereas these two brain regions are overactive in CD in response to punishing stimuli (e.g., monetary loss) (Blair et al. 2018). A similar, but less consistent, pattern of neural dysfunction has been reported for ADHD (Plichta & Scheres 2014; Rubia 2018). Although these findings point to functional abnormalities concerning both reward and punishment processing that are partially shared by CD and ADHD, most studies have – either for practical or scientific reasons – grouped youths with different externalizing disorders together, particularly CD and ODD, but also CD/ODD and ADHD, or have investigated externalizing symptoms as a dimensional variable in high-risk samples (Fairchild et al. 2019). Thus, one has to be cautious in interpreting the available fMRI data in terms of any disorder-specific and/or shared pathophysiology of CD versus ADHD.

Notably, a recent fMRI meta-analysis on a variety of reinforcement-based decision-making paradigms, revealed that youths with disruptive behaviour and conduct problems versus TDCs have decreased activation in ventral and dorsal medial prefrontal cortex (including ACC), accompanied by increased dorsal striatal activation in caudate nucleus, even after ADHD comorbidity was statistically controlled (Alegria et al. 2016). Although these are the most thorough findings to date regarding a potential CD-specific neural dysfunction of reinforcement-based decision-making, this meta-analysis' conclusions are somewhat limited because (1) it did not separate youths with CD from youths with ODD, and (2) it meta-analyzed reward and punishment processing in a combined fashion, rather than separately.

Thus, to address the above-mentioned research gaps, we directly compared reward and punishment processing in a group of youths with comorbid CD+ADHD and those with the individual disorder (i.e., CD only, and ADHD only) relative to TDCs, while they performed a

reinforcement-based decision-making task in the MRI scanner (Kim et al. 2006). This design allowed us testing whether similar or different patterns of neural dysfunction characterize the two pure disorders and potentially identifying a profile that is unique to the comorbid group (i.e., distinctive vs. additive pathophysiology).

In line with the fMRI meta-analyses by Alegria et al. (2016) and Plichta & Scheres (2014), we predicted that, compared to TDCs, (1) youths with CD would show atypical reinforcement signaling in ACC, and dorsal striatum (primarily caudate nucleus), (2) youths with ADHD would show atypical activation in the ventral striatum, and (3) the comorbid CD+ADHD group would show the most severe dysfunctions in prefrontal and striatal circuits. We additionally explored brain-behaviour associations between: (1) CD symptom severity and prefrontal as well as dorsal striatal brain activity, and (2) ADHD symptom severity and ventral striatal brain activity.

Method

Participants

180 participants, aged 9-18 years, were recruited through community outreach, mental health clinics and welfare institutions to participate in this cross-sectional fMRI study. Subsequently, 42 individuals were excluded because of excessive head movements, i.e. more than 3mm of translational motion during the fMRI scan: CD = 2 (13.3%), ADHD = 10 (24.7%), CD+ADHD = 10 (18.2%), and TDC = 20 (34.5%) ($\chi^2(df=3) = 3.75$, $p = .30$). Thus, the final study sample comprised of 138 participants (CD: n = 13, ADHD: n = 19, CD+ADHD: n = 45, and TDC: n = 61) (Table 1). Overall exclusion criteria were autism spectrum disorder, psychosis or schizophrenia, mania or bipolar disorder, genetic syndromes, neurological disorders, an IQ < 70, and any MRI contraindications. The study protocol was approved by

the local ethics committee, and participants and their caregivers gave written informed consent. Participants were compensated for their participation (50€ in addition to the money they gained during the task).

The four different groups were specified as follows: (1) CD: current diagnosis of CD but no current or past diagnosis of ADHD, (2) ADHD: current diagnosis of ADHD but no current or past diagnosis of CD or ODD (3) CD+ADHD: current diagnosis of CD and ADHD, and (4) TDC: no current psychiatric diagnoses and no lifetime diagnoses of CD, ODD and ADHD. All diagnoses were based on DSM-IV-TR criteria (American Psychiatric Association 2000). Participants who were taking psychotropic medication (Table 1) were tested while on medication.

All participants were clinically evaluated with the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). The K-SADS-PL interview was administered by trained staff separately to participants and their caregivers, and clinical summary ratings were achieved to determine group allocation and to identify possible comorbid psychiatric diagnoses. Disorder severity of CD and ADHD was defined as the number of total symptoms endorsed in the K-SADS-PL interviews. Using the K-SADS-PL, we also determined CD-onset type (i.e., CO-CD: presence of at least one characteristic CD behaviour prior to age 10; AO-CD: absence of any CD behaviours prior to age 10) and ADHD subtypes. Full-scale IQs were estimated using the vocabulary and matrix reasoning subtests of the Wechsler Intelligence Scale for Children-Fourth Edition (Wechsler 2011), or the Wechsler Intelligence Scale for Adults-Fourth Edition (Wechsler 2012). The level of callous-unemotional traits was assessed by using the total score of the subscales “remorselessness”, “callousness” and “unemotionality” of the self-report version of the Youth Psychopathic traits Inventory (YPI) (Essau et al. 2006).

FMRI Task

We used a monetary reinforcement-based decision-making task, originally described by Kim et al. (2006), to measure decision-making capabilities based on reward and punishment vs. neutral, non-reinforcing contingencies (Figure 1). In the scanner, the task was presented on a rear projection LCD screen and viewed by the participants through a mirror attached to the head coil. Behavioural data collection and stimulus presentation were controlled by the MATLAB R2014a software (The MathWorks Inc. 2014).

Trials started with the presentation of a pair of cue stimuli (i.e., fractals) side-by-side. Each pair marked the onset of one of three different trial types (i.e., conditions): reward (REW; i.e., monetary gain), punishment (PUN; i.e., monetary loss), and neutral outcome (NEUT; i.e., neither monetary gain nor loss). Throughout the task, occurrence of trial types was fully randomized, and the assignment of the three fractal pairs to the different conditions was fully counterbalanced across all participants. Participants were instructed to select one of the two simultaneously presented fractals by pressing the left or right key on a button box, placed in their right hand and keys corresponded to the location of the two cues presented on the screen (i.e., left or right of a fixation cross). The chosen cue increased in brightness and was followed by visual feedback 4s later, indicating whether participants received a reward (a picture of a 20 Eurocent coin, and the description: "You won 20 cent"), a punishment (a picture of a 20 Eurocent coin overlaid with a red cross, and the description: "You lost 20 cent"), a neutral outcome (a picture of a scrambled 20 Eurocent coin, and the description: "No change"), or nothing (a blank screen with a crosshair in the center).

On each trial, participants could either select a high probability or a low probability cue. In REW trials, choosing the high probability cue either resulted in reward (+0.20 €) with a probability of 70%, or in no feedback (i.e., no reward = crosshair) with a probability of

30%. Conversely, choosing the low probability cue either resulted in reward (+0.20 €) with a probability of 30%, or in no feedback (i.e., no reward = crosshair) with a probability of 70%. In PUN trials, choosing the high probability cue either resulted in no feedback (i.e., no punishment = crosshair) with a probability of 70%, or in punishment (-0.20 €) with a probability of 30%. Conversely, choosing the low probability cue either resulted in no feedback (i.e., no punishment = crosshair) with a probability of 30%, or in punishment (-0.20 €) with a probability of 70%. The NEUT trials served as baseline for the two other conditions, controlling for motor responses and simple visual effects. In this case, participants either had a 70% or 30% chance of obtaining a neutral outcome (a scrambled 20 Eurocent), thereby receiving no feedback on the remaining trials. Participants completed a total of 3 consecutive runs, each lasting approximately 6 minutes and containing a total of 135 trials with 45 trials per condition: 15x REW, 15x PUN, and 15x NEUT. The whole task procedure lasted approximately 25 minutes.

Prior to the scan, participants were told that they would see three different pairs of unfamiliar stimuli (i.e., fractals) as cues during the experiment, and on each trial they had to choose one out of the two simultaneously presented cues. Depending on their choices, they would win money, lose money, obtain a neutral outcome, or receive no feedback. It was, explicitly stressed that they should try to win as much money as possible. Each participant started the experiment with a fixed amount of 10€, and was told that any wins or losses would be added or subtracted, respectively, from this total. As per instructions, participants were paid according to their performance at the end of the experiment, receiving on average an amount of 11.35 ± 1.52€.

[*Figure 1*]

Behavioural Data Analyses

We compared the four groups on demographic and clinical variables using ANOVA and Chi-Square tests (SPSS v25.0; IBM Corp., Armonk, NY). At the task level, accuracy (in %, i.e. choosing the cue with a probability of 70%) and reaction times for correct choices (RTs in ms) on the decision-making task were analyzed using a repeated-measures MANOVA model with group (CD vs. ADHD vs. CD+ADHD vs. TDC) as between-subjects factor, and condition (REW vs. PUN vs. NEUT) as within-subjects factor, followed by post-hoc pairwise comparisons in case of significant main or interaction effects using the Games–Howell procedure to control for multiple comparisons, as this procedure is recommended in case that sample sizes are very different and if one is uncertain whether the population variances are equivalent (Field 2009). As age and IQ did not correlate with the dependent measures, these variables were not included as covariates in the analyses. We decided to use ANOVA models rather than a 2 × 2 full-factorial design in all analyses, because the latter implicitly assumes that the combined behavioural as well as brain activation pattern are the sum of the single-disorder factors. Such an analysis would bias the results, while the present study aimed to test whether comorbidity of CD+ADHD is a unique disorder or simply the addition of the two individual clinical conditions. Thus, the ANOVA is the appropriate analysis approach here because it is blind to any direction of possible group differences. The alpha level was set at 0.05. Effect sizes were calculated using partial eta squared (η^2_p), where 0.01, 0.06, and 0.14 represent small, medium and large effects, respectively (Cohen 1988).

Image Acquisition

T2* weighted BOLD images were obtained with echoplanar imaging using a Siemens Prisma fit 3.0 T scanner (Erlangen, Germany) and a 20-channel head coil. Whole-brain volumes of 41, 3-mm thick transversal slices (TR/TE = 2500/30 ms; flip angle = 83°; FOV = 192 x 192

mm^2; matrix size = 64 x 64, and voxel size = 3.0 x 3.0 x 3.0 mm^3) were collected throughout three functional runs. A total of 465 functional volumes (plus 5 "dummy" scans per run allowing for T1 magnetic saturation) were acquired for each participant. Prior to the functional runs, 192 high-resolution T1-weighted structural images of the entire brain were acquired using a MPRAGE sequence (TR/TE = 1900/3.4 ms; flip angle = 9°; FOV = 192 x 192 mm^2; matrix size = 256 x 256, and voxel size = 1 x 1 x 1 mm^3).

Image Analysis

Data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm), implemented in MATLAB. Prior to image analysis, the first 5 volumes of each functional run were discarded because of the non-equilibrium state of magnetization. Images were realigned to the first volume in the time series, anatomical scans were co-registered to the mean image and spatially normalized into a standard anatomical reference space, spatial smoothing was applied using a Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm. Regression analysis was carried out on the pre-processed functional time series of each participant using a general linear model (GLM) for an event-related design as implemented in SPM12. Motion parameters were entered as regressors, and simple contrasts were created for the following three conditions: (1) PUN, (2) REW, and (3) NEUT by modelling the whole trial duration, i.e. including cue onset, choice selection, and outcome presentation (Galvan et al. 2006). Given our particular interest in the most basic form of reward and punishment mechanisms, we did not distinguish between different components of the reinforcement process in the current study (e.g., anticipation vs. outcome; see (Knutson & Wimmer 2007). This approach would provide more of a common ground in terms of comparability with prior studies that each examined different aspects of reinforcement processing in youths with CD and/or ADHD (Plichta & Scheres 2014; Alegria et al. 2016).

At the second level, contrasts were entered into a full-flexible ANOVA with group (CD vs. ADHD vs. CD+ADHD vs. TDC) as between-subjects factor and condition (PUN vs. REW) as within-subjects factor. High-level contrast images were created for the comparisons (1) PUN > REW, and (2) REW > PUN to investigate whether the two contingencies differentially affected striatal and prefrontal brain regions (Delgado et al. 2000). Our main motivation to follow such approach (i.e., not modeling punishment vs. neutral, or reward vs. neutral) was that neutral outcomes that are intermixed with reward and punishment trials in the context of risk-taking tasks (incl. probabilistic reinforcement tasks) are actually not processed as neutral (i.e., neutral events can become affectively charged depending on the context in which they are presented) (see Grossberg & Gutowski 1987). For the whole-brain analyses across groups, Z-statistic maps were thresholded using clusters with $Z \geq 3.1$ (i.e., $p \leq .001$) at the voxel level and an FWE-corrected cluster-significance threshold at $p \leq .05$ to strictly control for type I errors (Eklund et al. 2016). Our a priori regions of interest (ROIs) comprised the caudate nucleus and the ACC (Alegria et al. 2016), the ventral striatum (Plichta & Scheres 2014), and the vmPFC/OFC (Blair 2016). Anatomical masks were created in standard MNI space using the FSL Harvard-Oxford cortical and subcortical structural atlas (Oxford Centre for Functional MRI of the Brain, Oxford, UK.). All ROI analyses were thresholded at $p < .05$ (voxel level), FWE-corrected for the specific ROI. Parameter estimates were extracted for all regions, and beta plots were generated for each group and both high-level contrasts. For the group comparisons, we will only refer to the results of the PUN > REW contrast, as the REW > PUN contrast only indicates the inverse of the group comparison results. ANOVAs with group as between-subjects factor were conducted on the beta values of the ROIs. Parameter estimates of the ROIs were correlated with ADHD and CD symptom severity (i.e., symptom counts from the K-SADS-PL interviews). We used the total counts of ADHD and CD symptoms, as well as symptoms of hyperactivity/impulsivity (ADHD) and aggression (CD), as specified in the DSM-5 (American Psychiatric Association 2013).

Results

Demographic Characteristics

Mean age and sex distribution did not differ significantly between groups. However, the two groups of youths with CD had lower IQs than TDCs. The CD+ADHD group had the highest level of CD symptoms (K-SADS-PL) and CU traits (YPI), followed by the CD group, relative to both youths with ADHD and TDCs. Onset of CD symptomatology (childhood vs. adolescence) did not differ significantly between both CD groups. Level of ADHD symptoms (K-SADS-PL) was highest for both youths with CD+ADHD and ADHD, followed by the CD group, with the lowest symptom level for TDCs. Distribution of ADHD subtypes did not differ significantly between the two ADHD groups. Lastly, psychotropic medication use was highest for the ADHD group, followed by youths with CD and CD+ADHD, relative to TDCs.

[Table 1]

Task Performance

The repeated-measures MANOVA revealed a significant main effect of condition [$F(4, 536) = 44.9$, $p < .001$, $\eta^2_p = .25$], which was related to both accuracy ($p < .001$, $\eta^2_p = .10$) and RT ($p < .001$, $\eta^2_p = .43$) (Table 2). The post-hoc comparisons for accuracy revealed that the correct response rate (in %) was significantly lower for the NEUT condition compared to both the REW and PUN conditions (all ps < .001, all η^2_ps > .10; REW vs. PUN: $p = .07$, $\eta^2_p = .02$), which is in line with the findings by Kim et al. (2006). Regarding RTs, the post-hoc comparisons showed the fastest RTs for REW, followed by the NEUT condition, and the slowest RTs for PUN (all ps < .001, all η^2_ps > .15); this, again, fits the data reported by Kim et al. (2006). The group by condition effect [$F(12, 536) = 0.34$, *ns*, $\eta^2_p = .01$] and the group

effect [$F(6, 268) = 1.2$, *ns*, $\eta^2_p = .02$] were non-significant, suggesting that the different reinforcement conditions similarly affected task performance in all groups.

[Table 2]

Whole-Brain between-group Comparisons

Using whole-brain cluster thresholding that strictly controls against type I errors, the high-level PUN > REW contrast revealed significant differences in brain responses in the CD+ADHD group compared to both the TDC group and ADHD group (Table 3): For punishment versus reward contingencies, the youths with CD+ADHD displayed lower brain activity in the dorsal striatum (incl. caudate), medial temporal gyrus (MTG), inferior frontal gyrus (IFG) and lateral occipital cortex relative to TDCs (Figure 2+3), and they showed lower activity in the dorsal striatum (incl. putamen), orbitofrontal cortex (OFC; extending into insula) and IFG relative to the ADHD group (Figure 4+5). All other group comparisons (incl. CD vs. TDC, and CD vs. CD+ADHD) were found to be non-significant at the whole-brain cluster-corrected level.

[Table 3]

[Figure 2, 3, 4, 5]

Between-Group Comparisons using a priori ROIs

For the high-level PUN > REW contrast, the extracted *ß*-values of our a priori anatomical ROIs (i.e. caudate nucleus, ventral striatum, ACC, and vmPFC/OFC) were entered into four separate ANOVA models with group as between-subjects factor. However, none of these analyses revealed significant group effects.

Correlations between ROI Activity and Clinical Symptomatology

Our correlational analyses did not reveal any significant associations between brain activity and CD or ADHD symptom severity (as assessed with the K-SADS-PL interview) after correcting for multiple comparisons.

Discussion

To our knowledge, this is the first fMRI study investigating reinforcement-based decision-making in youths with CD and/or ADHD versus TDCs to reveal whether similar or different patterns of neural dysfunction characterize the two pure disorders and to potentially identify a profile that is unique to the comorbid group. Clinically, we found that patients with a comorbid condition of CD+ADHD were more severely impaired, including greater CD and ADHD symptoms and CU traits, than patients with either of the pure disorders. At the behavioural level, there were significant differences in task performance across groups depending on reinforcement type (accuracy: REW = PUN > NEU; reaction times: REW < NEU < PUN), which is likely attributable to differences in the cognitive processes required to execute the different trial conditions. For example, concerning punishment trials, individuals first have to inhibit the incorrect response, followed by selecting the correct one in order to avoid potential punishment. One can assume that this adds an intermediate processing step to proper choice selection, resulting in longer reaction times for such trials. At the whole-brain level, we were able to show that youths with CD+ADHD, in comparison to TDCs and youths with ADHD, demonstrated diminished reinforcement signaling in dorsal striatal (i.e., caudate nucleus and putamen) and prefrontal brain regions (i.e., OFC, IFG), specifically in response to punishment in the form of monetary loss. There were, however, no significant activation differences between reinforcement conditions between TDCs and youths with ADHD,

indicating that those with ADHD reacted equally well as TDCs during decision-making under different reinforcement contingencies (Rubia 2011).

Our group-specific predictions were only partially confirmed. In contrast to our hypothesis, we did not find atypical ventral striatal activity in patients with ADHD alone. This might be due to the fact that we did not analyze the different phases of reinforcement processing separately (e.g., anticipation, choice selection, and outcome). Notably, the previously reported diminished ventral striatal activity in patients with ADHD vs. TDCs in response to appetitive stimuli, were largely based on imaging data obtained with regard to the anticipation phase (see Plichta & Scheres 2014).

As predicted, patients with the comorbid condition of CD+ADHD were clinically and neurobiologically the most severely impaired group. Youths with a CD+ADHD diagnosis, in comparison to TDCs and youths with ADHD only, displayed lower brain responses in dorsal striatum (incl. caudate), OFC (extending into the anterior insula), IFG and MTG in response to punishment. Interestingly, we did not find any significant differences in brain responses during reinforcement processing between the groups of patients with pure CD and CD+ADHD. This might indicate that these two clinical groups share disorder-specific deficits in brain circuits related to the management of affective decision-making that is primarily associated with the CD phenotype. This is in line with the notion that particularly motivational and affective decision-making processes are impaired in youths with CD, primarily reflected in atypical brain responses in striatal and prefrontal brain regions as highlighted by Rubia 2011.

However, contrary to the meta-analysis of Alegria et al. (2016), we did not observe differential brain responses in the ACC between groups. Note, though, that Alegria and colleagues analyzed reward and punishment processing in a combined fashion, rather than separately as done here. This makes it difficult to compare across study designs and might explain the different results regarding the ACC.

Our study had several strengths: We were able to test our hypotheses by using well-defined groups with participants who were extensively clinically assessed and reliably diagnosed. Our overall sample size of 138 participants is relatively large for an fMRI study conducted with children and adolescents. Additionally, we were able to include a large number of girls with a CD (+ ADHD) diagnosis which is rare in fMRI studies of disruptive behaviour disordered samples (Fairchild et al. 2013; Fairchild et al. 2014; Alegria et al. 2016). Although the sample sizes of our four groups varied substantially, the sex ratio was similar across groups. Moreover, our CD and CD+ADHD groups consisted of participants who fulfilled diagnostic criteria for CD. Usually, most of the previous fMRI studies included mixed samples of CD or ODD cases or those with (subclinical) conduct problems (see Alegria et al. 2016).

However, our study had also several limitations: The four groups varied substantially in sample size which likely meant that some of our statistical analyses were underpowered (incl. ROI analyses), particularly with regard to the CD and ADHD groups versus the two other groups. Similarly, the lack of significant brain-behaviour correlations (i.e., CD and ADHD symptoms and brain activity in the pre-specified ROIs) in the present study fits well with recent experimental evidence that relatively small sample sizes might be insufficient for obtaining reproducible brain-behaviour correlations, regardless of analytic approach (Grady et al. 2021). It should be noted that recruiting a group of cases with CD without comorbid ADHD is a rather difficult task given the high co-occurrence rate of both disorders (see also: Rubia et al., 2009: noncomorbid CD: n = 14, noncomorbid ADHD: n = 18 which is comparable to our study). This is also reflected in the fact that many prior studies on reinforcement processing in youths with externalizing problems often included mixed samples of youths with CD or ODD who had comorbid ADHD (e.g. Finger et al. 2008; White et al. 2013, 2014). Also, our two CD groups had significantly lower IQs than TDCs, which however is a typical finding in the CD literature (Murray & Farrington 2010), making our CD

sample representative for this disorder. Noteworthy, the four groups did not differ in any task performance measures, and IQ did not correlate with these measures. This indicates that the reinforcement manipulations were similarly effective across groups and were not influenced by IQ, and, thus, it is unlikely that group differences in brain activation were confounded by IQ differences. Finally, for praticial reasons we neither excluded participants who took psychotropic medications nor asked them to withdraw them (e.g., stimulants) prior to being scanned. This, however, could have affected our findings. Thus future studies with medication-naïve youths are warranted.

In conclusion, the results of the current study provide new evidence for a disorder-related neural profile underlying impaired punishment processing in CD, but not ADHD, which supports the notion that deficient reinforcement-based decision-making is more closely related to CD than ADHD (Banaschewski et al. 2005). Moreover, patients with a comorbid condition showed the most severe dysfunctions in dorsal striatal and prefrontal circuits indicating "additive" psychopathology that aggravates decision-making deficits that have been observed in both individual disorders (Finger et al. 2011). In clinical practice, CD without co-occurring ADHD has been shown to be extremely rare (Turgay 2004; Rubia, Smith, et al. 2009), raising the question whether comorbid patients might need different treatment approaches than youths with CD only. Research has shown that psychostimulants (e.g. methylphenidate and amphetamines) reduce impulsive aggression (Pringsheim et al. 2015), a symptom which is commonly observed in CD and in ADHD. Deficient reinforcement-based decision-making, including impaired punishment processing at the neural level, as being observed in our sample of youths with CD+ADHD may contribute to frustration-based impulsive aggression (Blair 2016). It would be interesting to investigate whether the administration of psychostimulants to patients with CD with and without ADHD could reduce or even eliminate neural decision-making deficits, as previously shown with ADHD patients (Rubia, Halari, et al. 2009). Psychostimulants such as methylphenidate

increase the activity of the central nervous system through inhibiting the reuptake of dopamine and norepinephrine which is thought to exert a positive effect on the decision-making process (Solanto 1998). Note, in our study only 38% of youths with CD+ADHD were treated with psychostimulants compared to almost 80% of youths with ADHD. Therefore, future studies need to investigate whether psychostimulants can have a positive effect on reinforcement-based decision-making in CD (vs. ADHD). Moreover, it should be investigated to what extent impaired decision-making in CD is associated with general impairments in the decision-making process or related to deficiencies in specific decision-making phases (i.e. punishment anticipation vs. choice selection vs. outcome processing). This knowledge could inform effective treatments tailored to the specific needs of the affected individuals.

Disclosure of interest: We have no potential conflicts of interests to declare.

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Tables

Table 1. Sample demographics and clinical characteristics.

	CD	ADHD	CD+ADHD	TDC	Group	Post-hoc comparisons
	N = 13	N = 19	N = 45	N = 61	(CD- vs. CD+ vs. ADHD vs. TDC) $F/X^{2\#}$	t-tests#
Sex (f/m)	5/8	10/9	23/22	29/32	0.85	
Age (years)	14.8 (2.7)	12.8 (2.7)	13.8 (2.2)	14.2 (2.7)	2.0	
Estimated IQ	94.5 (12.1)	100.5 (10.6)	97.1 (12.0)	103.3 (11.6)	3.54*	TDC > CD+ADHD = CD; ADHD = TDC & CD & CD+ADHD
CD total symptoms (max. 15)	3.9 (2.0)	0.1 (0.3)	5.4 (2.3)	0.1 (0.2)	136.3***	CD+ADHD > CD > ADHD = TDC
CD subtype *n* (%)					3.64	
Childhood-onset	6 (46.2)	N/A	25 (55.6)	N/A		
Adolescent-onset	6 (46.2)	N/A	20 (44.4)	N/A		
Unspecified	1 (7.7)	N/A	0	N/A		
ADHD total symptoms (max. 18)	6.0 (4.2)	14.3 (3.5)	15.2 (3.2)	0.1 (0.4)	342.5***	CD+ADHD & ADHD > CD > TDC
ADHD subtype *n* (%)					4.31	
Inattentive	N/A	7 (36.8)	8 (17.8)	N/A		
Hyperactive	N/A	0	2 (4.4)	N/A		
Combined	N/A	12 (63.2)	32 (71.1)	N/A		
Unspecified	N/A	0	3 (6.7)	N/A		
Psychotropic medication *n* (%)	3.0 (23.1)	15 (78.9)	18.0 (40.0)	N/A	54.25***	
Stimulants	1 (7.7)	15 (78.9)	17 (37.8)	N/A		
Antidepressants	2 (15.4)	0	1 (2.2)	N/A		
Neuroleptics	0	0	2 (4.4)	N/A		
Comorbid Diagnoses *n* (%)						
CD	13 (100)	0	45 (100)	N/A	119.64***	
ODD	11 (84.6)	0	45 (100)	N/A	131.97***	CD + ADHD > CD; CD & CD+ADHD > TDC = ADHD

ADHD	0	19 (100)	45 (100)	N/A	139.00***	CD+ADHD = ADHD > CD = TDC
MDD	5 (38.5)	2 (10.5)	15 (33.3)	N/A	27.41***	CD = CD+ = ADHD, CD & CD+ADHD > TDC, ADHD = TDC
PTSD	1 (7.7)	0	9 (20.0)	N/A	17.34***	CD+ADHD > TDC, CD = ADHD, ADHD = TDC; CD+ADHD > ADHD
Anxiety disorders	3 (23.1)	0	12 (26.7)	N/A	23.62***	CD = CD+ADHD > TDC =ADHD
SUD	1 (7.7)	0	9 (20.0)	N/A	17.34***	CD > TDC, CD = ADHD, CD+ > ADHD = TDC, CD+ = CD
YPI (CU total score)	29.3 (8.9)	24.8 (6.4)	32.4 (8.4)	28.4 (7.0)	4.97**	CD+ADHD > ADHD = TDC ; ADHD & CD+ ADHD = CD

Note: ADHD=attention deficit hyperactivity disorder; CD= conduct disorder; TDC = typically developing controls; f/m = female/male; IQ= intelligence quotient; MDD=major depressive disorder; N/A = not applicable; ODD=oppositional defiant disorder; PTSD=post-traumatic stress disorder; SUD=substance use disorder (including substance abuse and dependence); YPI=youth psychopathic traits inventory.
Diagnoses and CD/ADHD symptoms and subtypes are based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL). [#]*p-values are based on F-tests (or* χ^2*-tests,) and follow-up pairwise comparisons with Bonferroni correction.*p≤.05; **p≤.01; ***p≤.001*

Table 2. Task performance between groups on the three different conditions of the monetary instrumental task.

	CD	ADHD	CD+ADHD	TDC
Accuracy (in %)				
Reward	72.6 (32.8)	70.6 (28.7)	69.3 (32.9)	69.2 (30.8)
Punishment	64.5 (17.3)	62.6 (11.9)	65.4 (12.3)	65.8 (13.3)
Neutral	58.1 (31.2)	53.6 (30.2)	48.2 (28.8)	48.9 (27.1)
Reaction time (in msec.)				
Reward	833.4 (135.8)	906.0 (197.0)	863.2 (150.2)	817.5 (119.8)
Punishment	1067.4 (178.5)	1084.0 (150.8)	1072.0 (142.9)	1011.3 (174.2)
Neutral	987.4 (143.1)	1015.5 (115.6)	1010.5 (150.6)	966.5 (166.4)

Note: ADHD=attention deficit hyperactivity disorder; CD= conduct disorder; TDC = typically developing controls.

Table 3. Whole brain activation table for the group comparisons on the PUN > REW contrast.

Brain region	L/R	Cluster size (mm^3)	Z	MNI coordinates x	y	z
Punishment > Reward						
TDCs > CD+ADHD						
Caudate	R	195	4.64	10	12	8
			4.46	14	2	12
			4.00	10	4	4
Middle temporal gyrus	L	168	4.23	-42	14	36
Inferior frontal gyrus	L	108	4.31	-52	18	22
Lateral occipital cortex	L	152	4.18	-44	-60	54
ADHD > CD+ADHD						
Putamen	R	115	4.91	30	-10	-6
			3.92	24	0	0
			3.35	28	6	-6
Orbitofrontal cortex	R	198	4.56	40	22	-8

Note: ADHD=attention deficit hyperactivity disorder; CD= conduct disorder; L/R = left/right, MNI = Montreal Neurological Institute. TDC = typically developing controls. Results were significant at p<.05 (FWE-corrected at cluster level, p <.001 voxel level, k = 10 voxels)

Figure titles and captions

Figure 1. Illustration of the monetary instrumental task.

Figure 2. The caudate was more strongly activated in response to punishment versus reward in TDCs than CD+ADHD. Whole-brain results were significant at $p \leq .001$ at the voxel level, and for the cluster-level, a FWE-corrected cluster-significance threshold at $p \leq .05$ was set. For illustrative purposes, the uncorrected level is presented here, but results are reported for the cluster-level correction in the main text.

Figure 3. Beta plots (i.e., parameter estimates) generated for the differences in brain activity in the caudate in response to punishment versus reward separately for each group. Betas for the caudate were extracted based on the results of the whole-brain between-group comparisons for the significant difference between TDCs > CD+ADHD (see Table 3).

Figure 4. The OFC (extending into the insula) was more strongly activated in response to punishment versus reward in ADHD than CD+ADHD. Whole-brain results were significant at $p \leq .001$ at the voxel level, and for the cluster-level, a FWE-corrected cluster-significance threshold at $p \leq .05$ was set. For illustrative purposes, the uncorrected level is presented here, but results are reported for the cluster-level correction in the main text.

Figure 5. Beta plots (i.e., parameter estimates) generated for the differences in brain activity in the OFC in response to punishment versus reward seperately for each group. Betas for the OFC were extracted based on the results of the whole-brain between-group comparisons for the significant difference between ADHD > CD+ADHD (see Table 3).