Neural mechanisms of social-emotional dysfunction in autism spectrum disorder and conduct disorder

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2 Brain responses during empathy in autism and conduct disorder

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Abstract

Deficits in empathy are reported in autism spectrum disorders (ASD) and also underlie antisocial behavior of individuals with conduct disorder and callous-unemotional traits (CD/CU+). Many studies suggest that individuals with ASD are typically impaired in cognitive aspects of empathy, and individuals with CD/CU+ typically in affective aspects. In the current study we compared the neural correlates of cognitive and affective aspects of empathy between youth with ASD and youth with CD/CU+. Functional magnetic resonance imaging (fMRI) was used to assess boys with ASD (N = 23), boys with CD/CU+ (N = 23), and typically developing (TD) boys (N = 33), aged 15-19 years. Angry and fearful faces were presented and participants were asked to either infer the emotional state from the face (other-task; emotion recognition) or to judge their own emotional response to the face (self-task; emotional resonance). During emotion recognition, boys with ASD showed reduced responses compared to the other groups in the ventromedial prefrontal cortex (vmPFC). During emotional resonance, the CD/CU+ and ASD groups showed reduced amygdala responses compared to the TD controls, boys with ASD showed reduced responses in bilateral hippocampus, and the CD/CU+ boys showed reduced responses in the inferior frontal gyrus (IFG) and anterior insula (AI). Results suggest differential abnormal brain responses associated with specific aspects of empathic functioning in ASD and CD/CU+. Decreased amygdala responses in ASD and CD/CU+ might point to impaired emotion processing in both disorders, whereas reduced vmPFC responses suggest problems in processing cognitive aspects of empathy in ASD. Reduced IFG/AI responses, finally, suggest decreased emotional resonance in CD/CU+.

Introduction

Empathy, the ability to share and understand the feelings of other people, is a crucial aspect of human social interactions and everyday communication (Bernhardt & Singer, 2012). Diminished empathy is assumed to be a core feature both in

autism spectrum disorders (ASD) and conduct disorder (CD), particularly in individuals with CD and high levels of callous-unemotional traits (CU+; e.g., lack of guilt and empathy, callous use of others for one's own gain) (Decety & Moriguchi, 2007). However, accumulating evidence suggests that the empathy impairment in ASD differs qualitatively from the impairment seen in CD/CU+. Although many definitions of empathy exist, most definitions distinguish several cognitive (e.g., emotion recognition, perspective-taking, self-other distinction) and affective (e.g., shared affect, emotional resonance) aspects of empathy (Baron-Cohen & Wheelwright, 2004; Blair, 2005; Decety & Jackson, 2004; Schulte-Ruther et al., 2014). Closely related to but not the same as the cognitive aspects of empathy is mentalizing (or theory of mind), which is the ability to represent other people's mental states (Frith & Frith, 2006). Individuals with ASD are more likely than individuals with CD/CU+ to show deficits in mentalizing and in cognitive aspects of empathy (Blair, 2008; Frith, 2001; Schwenck et al., 2012), whereas deficits in affective aspects of empathy are more prevalent in CD/CU+ than in ASD (Blair, 2008; Jones et al., 2010; Lockwood et al., 2013b; Marsh et al., 2013). Such differences are not only of theoretical interest but have implications for the development of diagnostic instruments and interventions that are specifically aimed at different aspects of empathic functioning. Nevertheless, there is a current lack of understanding of the different brain mechanisms underlying empathic processing in ASD and CD/CU+.

One important cognitive aspect of empathy is the ability to recognize emotions from other's facial expressions. Notwithstanding that the evidence for emotion recognition deficits in ASD is mixed, a recent meta-analysis suggests at least some marginal differences between ASD and control groups in recognizing basic emotions (Uljarevic & Hamilton, 2013). However, a review focusing on ASD youth concluded that no emotion recognition difficulties seem to exist in ASD youth when straightforward basic emotional expression pictures are used instead of more difficult to recognize stimuli (e.g., blended emotions or low intensity of emotion) (Bons et al., 2013). Concerning the neural processes involved in emotion recognition, diminished response of the fusiform gyrus during face perception is a common finding in neuroimaging studies in ASD (Greimel et al., 2010;

Schultz, 2005). In addition, decreased amygdala responses in ASD have been reported frequently in implicit emotional face tasks (Ashwin et al., 2007; Pelphrey et al., 2007; Wang et al., 2004), whereas in tasks that require participants to attend to the emotions, no differences in amygdala responses are usually found between ASD and control groups (Harms et al., 2010; Piggot et al., 2004). Meta-analytic evidence of behavioral studies suggests that youth with CD/CU+ have difficulties in recognizing basic emotions, and especially in recognizing fearful faces (Dawel et al., 2012; Marsh & Blair, 2008). Importantly, fear recognition can be improved in children with CU when they are instructed to orient their attention towards the eyes of others (Dadds et al., 2006). In addition, neuroimaging studies have found that youths with CD/CU+ display a decreased amygdala response to fearful expressions (Jones et al., 2009; Marsh et al., 2008).

Studies that focused on affective aspects of empathy in ASD and CD/CU+ seem to suggest that there are difficulties especially in CD/CU+ and less so in ASD. One study found reduced responses in the inferior frontal gyrus (IFG) in adolescents with ASD when they judged their own emotional response to other's emotions, which suggests decreased resonance (or mirroring) with other's emotions in ASD (Greimel et al., 2010). However, individuals with ASD do show normal autonomic reactions to distress cues and normal neural responses when viewing facial expressions of pain (Blair, 1999; Hadjikhani et al., 2014). In contrast, individuals with CD/CU+ show reduced autonomic responses to the distress of others (Anastassiou-Hadjicharalambous & Warden, 2008; de Wied et al., 2012) and altered neural responses in affective regions such as the amygdala, anterior insula (AI) and IFG to witnessing other persons in pain (Cheng et al., 2012; Jones et al., 2009; Lockwood et al., 2013b; Marsh et al., 2013), suggesting deficits in resonating with the feelings of others. These findings are in line with the idea that without experiencing the negative reactions of others (i.e., emotional resonance) it is harder to inhibit aggressive and violent behavior (Blair, 1995; Miller & Eisenberg, 1988). Hence, the diminished feelings towards others might be one of the factors that lead to the aggressive and violent behavior often seen in CD/CU+.

Notwithstanding the aforementioned evidence for distinct empathy deficits in ASD and CD/CU+ and its theoretical and clinical relevance, only a handful of

behavioral studies directly compared these groups (Jones et al., 2010; Schwenck et al., 2012). Recently, one study compared brain activity patterns using fMRI between adolescents with ASD and adolescents with conduct problems (CP) with high levels of CU traits (CP/CU+) during a mentalizing task (O'Nions et al., 2014). Adolescents with ASD displayed reduced responses in the medial prefrontal cortex (mPFC) during mentalizing compared to CP/CU+ adolescents and controls, whereas no differences were found between the CP/CU+ group and controls. This study suggests that ASD and CP/CU+ differ in the neural processing of mentalizing, which is related to cognitive aspects of empathy. However, a direct comparison between these groups aimed at the neural processing of different cognitive and affective aspects of empathy is still lacking.

In the current functional MRI study, we therefore aimed to examine the neural correlates of two different processes involved in empathy in youth with ASD, youth with CD/CU+ and typically developing (TD) controls using a modified version of a previously used explicit empathy task (Greimel et al., 2010; Schulte-Ruther et al., 2011). In one condition participants were required to recognize the emotional state from another person's face (other-task; emotion recognition) and in another condition participants had to evaluate one's own emotional response to these faces (self-task; emotional resonance). Although it is hard to disentangle cognitive and affective aspects of empathy within one experimental design, this task taps into both emotion recognition (i.e., recognizing others' affect) as a cognitive aspect of empathy and emotional resonance (i.e., echoing others' affect) as an affective aspect (cf., Walter, 2012). The other-task assesses the understanding and perception of someone else's emotional state, whereas the self-task assesses explicit emotional self-reference in response to that state (Schulte-Ruther et al., 2014). Our study provides a first step in elucidating the differences and commonalities in the neural mechanisms of empathic processing in youth with ASD and youth with CD/CU+. We expected the ASD group to show reduced responses in brain regions associated with cognitive social processing (e.g., mPFC) during the other-task compared to controls as well as the CD/CU+ group. Conversely, in line with previous studies we expected reduced responses in affective brain regions (e.g., amygdala, AI, IFG) during the self-task in the CD/CU+ group compared to controls and the ASD group.

Methods

Participants

For the current study, male adolescents with ASD were recruited from specialized child psychiatric centers providing both inpatient and outpatient care for persons with ASD, male adolescents with CD/CU+ were recruited from a juvenile detention centre and a forensic psychiatric unit, and TD controls were recruited through local advertisement (see Table 1). Groups were matched on age (no significant difference; p = .28) and only right-handed males could participate. Participants and their parents (for minors under 18 years) gave their written informed consent to participate in the study. The study protocol was approved by the ethics committee of the Leiden University Medical Center.

Table 1. *Group characteristics*

	Autism spectrum disorders (ASD) (N = 23)		Conduct disorder and CU traits (CD/CU+) (N = 23)		Typically developing (TD) (N = 33)		Difference
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	17.0	1.2	16.6	1.0	17.1	1.2	
IQ **	107.1	10.4	94.7	5.2	97.2	9.2	ASD > CD/CU+,TD
Minority [N / %]	0	0.0	20	87.0	11	33.3	
Empathy scores [a]							
Cognitive empathy	34.4	4.1	34.3	6.8	36.7	5.1	
Affective empathy **	36.2	8.0	25.0	6.3	36.5	6.0	ASD,TD > CD/CU+
Autistic traits [b] **	66.7	21.6	37.2	10.1	34.5	13.9	ASD > CD/CU+,TD
Callous-unemotional traits **	27.8	7.0	37.6	7.0	19.5	5.9	CD/CU+ > ASD > TD

*** Significantly different at p < 0.001.*
[a] Self-report of affective and cognitive empathy was measured using the Basic Empathy Scale (BES; Jolliffe & Farrington, 2006).
[b] ASD symptomology was assessed in participants from all three groups using the Social Responsiveness Scale (SRS) self-report version (Constantino & Gruber, 2002).

Participant selection

All participants were aged 15-19 years. Exclusion criteria for all participants were neurological abnormalities, a history of epilepsy or seizures, head trauma,

left-handedness, and IQ less than 75. To obtain an estimate of intelligence, participants completed the Wechsler Adult Intelligence Scale – third edition (WAIS-III) or Wechsler Intelligence Scale for Children – third edition (WISC-III) subscales Vocabulary and Block Design.

The ASD group comprised 23 adolescent boys with a clinical ASD diagnosis. Three were diagnosed with autistic disorder, 11 with Asperger's syndrome, and nine with pervasive developmental disorder not otherwise specified (PDD-NOS) according to the DSM-IV-TR criteria. In addition, according to diagnostic information from their clinicians, four participants also met DSM-IV-TR criteria for ADHD, two for dysthymia, and one for major depression. The Autism Diagnostic Observational Schedule-Generic (ADOS-G; Lord et al., 2000) and autism diagnostic interview-revised (ADI-R; Lord et al., 1994) were administered besides clinical judgment as they are considered the "gold standard" for diagnostic assessment. Twenty-one participants met the criteria for autism or ASD on the Social Interaction and Communication domains of the ADOS-G, and two scored above the cut-off point only in one of these domains. However, these two participants fulfilled the ADI-R criteria for autism. We were able to administer the ADI-R for 20 participants and all 20 fulfilled the autism criteria on the ADI-R Social Interaction and Communications domains. Review of the medical charts of the other three indicated that autistic features were already present from an early age. Twelve participants with ASD took medication at the time of testing (N = 3 atypical antipsychotics, N = 3 psychostimulants, N = 3 selective serotonin re-uptake inhibitors, N = 3 multiple medications).

The CD/CU+ group consisted of 23 adolescent boys that were recruited from forensic settings, since relatively high amounts of boys with CD are present there (Colins et al., 2010). Diagnoses were confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) Behavioral Disorders screening (Kaufman et al., 1997), a widely used semi-structured diagnostic interview. Boys that fulfilled DSM-IV-TR criteria for CD with at least one aggressive symptom (e.g., used a weapon, has been physically cruel to people, has stolen while confronting a victim) were included (N = 54). Finally, subjects with CD/CU+ were selected from this larger pool of boys with CD based on scores on the

self-report Inventory of Callous-Unemotional traits (ICU; Kimonis et al., 2008). Participants (N = 26) scoring above the median ICU score of the full CD sample (median score = 27.0) were included in the CD/CU+ group. Eight participants with CD/CU+ also met DSM-IV-TR criteria for ADHD. None of the participants with CD/CU+ took medication at the time of testing. Data from three CD/CU+ participants was excluded due to excessive motion, leaving a final sample of 23 participants with CD/CU+.

Thirty-three TD control boys were recruited and screened using the K-SADS-PL behavioral disorders module in order to exclude participants with behavioral disorders. Moreover, general psychopathology and autistic traits were screened to confirm that they were typically developing. The Youth Self Report (YSR; Achenbach, 1991) was used to assess general psychopathology; none of the TD boys scored in the clinical range on the YSR externalizing and internalizing scales.

Experimental task

The three groups were scanned while completing a modified version of an explicit empathy task that has been used in previous studies with ASD adolescents (Greimel et al., 2010; Schulte-Ruther et al., 2011). In this task angry and fearful faces from the Radboud Faces Database (Langner et al., 2010) were presented and participants were either asked to infer the emotional state from the face (other-task) or to judge their own emotional response to the face (self-task). Response options were "angry", "fearful" or "neutral". To reduce potential social desirability bias, subjects were explicitly told that there are no correct or wrong answers in the self-task. A perceptual decision on the width of neutral faces was included as a control-task using "thin," "normal," or "wide" as response options. Subjects responded with their right hand using a three-button response device.

Each block (20.9 s) was preceded by an instruction cue (3 s), and comprised six face trials (each 2.47 s), separated by a fixation cross (jittered .95–1.45 s). Twelve blocks of each task were presented in quasi-random order, resulting in 36 blocks. All participants first practiced the task outside the scanner on a laptop to familiarize them with task requirements. After the fMRI experiment, participants were asked how they resolved the different tasks; all were able to recall and describe how they resolved the tasks.

fMRI data acquisition

Imaging was carried out at the Leiden University Medical Center on a 3T Philips Achieva MRI scanner. Prior to scanning, participants were familiarized with the scanner environment using a mock scanner. More detail on scan parameters is provided in the appendix.

fMRI data analysis

FMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) version 6.00, part of FSL 5.0.8 (www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied; motion correction using MCFLIRT; non-brain removal using BET; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Functional scans were registered to the T1-weighted images, which were registered to the 2mm MNI-152 standard space template. Regressors for each task (i.e., other, self, control) in the general linear model were convolved with a gamma hemodynamic response function. To account for residual movement artifacts, the six realignment parameters were included in the model as covariates of no interest. Individual participant data were then entered into a higher-level group analysis using a mixed effects design (FLAME) whole-brain analysis. The general linear model included the three groups (ASD, CD/CU+, and TD) and to account for possible age effects, age (mean-centered) was included as covariate of no interest. In order to avoid type II errors, we tested for between group differences by mutually comparing all three groups on the other > control (indicating emotion recognition) contrast and the self > control (indicating emotional resonance) contrast. For transparency, we also report between group differences revealed by F tests on these contrasts. Correction for multiple comparisons across all brain voxels was done using cluster-based thresholding, using an initial cluster-forming threshold of $z > 2.3$ and a family wise error corrected cluster significance threshold of $p < 0.05$. We used Featquery to conduct region of interest (ROI) analyses to correlate questionnaire outcomes with patterns of

activity from regions that were identified in the whole-brain analyses. Functional ROIs from these regions were generated by masking the activation maps of the self > control and other > control contrasts with binarized anatomical ROIs using the Harvard-Oxford structural atlases distributed with FSL. Significant group differences were found in IQ (see Table 1), we therefore repeated our analyses using IQ as a covariate. Finally, we explored whether additional clinical factors, such as medication exposure or comorbidity, might have influenced the results. These analyses were conducted with the ROI *z* statistics in SPSS to compare participants with ASD and CD/CU+ (excluding either those with a comorbid disorder, those using medication, or both) to TD controls. Additionally, we compared ASD and CD/CU+ participants with a comorbid disorder to those without, while also comparing ASD participants who were on medication to those who were not.

Results

Behavioral results

Reaction times (RT) were analyzed with a 3 x 3 mixed ANOVA (group x task). We found a main effect of group, $F(1, 77) = 3.63, p < .05$, a main effect of task, $F(1, 77) = 5.02, p < .05$, and there was a significant interaction between group and task, $F(1, 77) = 4.41, p < .005$. Post-hoc comparisons revealed that the CD/CU+ group reacted faster than the TD group across the three tasks, $p < .01$, and that RTs in the control-task were slower compared to the self-, $p < .01$, and other-, $p < .001$, tasks. The interaction effect was due to the CD/CU+ group reacting faster than the ASD, $p < .05$, and TD, $p < .005$, groups on the self-task but not on the control- and other-tasks.

Task performance on the other-task was analyzed with a 3 x 2 mixed ANOVA (group x emotion). We found a main effect of emotion, $F(1, 77) = 28.65, p < .001$, caused by a higher percentage of correct identification of fearful (M = 84.6 %; SD = 14.3) compared to angry emotions (M = 72.8 %; SD = 23.1). The interaction effect and the main effect of group were nonsignificant, indicating that there were no group differences in the identification of others' emotional expressions in the

other-task. Behavior for the self-task was also analyzed with a 3 x 2 mixed ANOVA (group x emotion), comparing the percentage congruent emotions reported. There were no main effects of group or emotion, both $F < 1$, but we did find a significant interaction between group and emotion, $F(1, 77) = 3.83, p < .05$. Post hoc comparisons revealed that the interaction effect was due to differences in the percentage congruency between angry and fearful emotions in the CD/CU+ group, $p = .042$, but not in the ASD or TD group, ps $> .1$. The CD/CU+ reported more congruency during angry (22.6 %) compared to fearful (14.0 %) emotions.

fMRI results

Emotion recognition: Other-task vs. control-task

TD > ASD: Whole-brain analysis showed that the TD group showed a greater response in the right hippocampus, the right premotor cortex, and the midcingulate cortex than the ASD control group (see Table 2 for all other-task vs. control-task results). No significant differences were found in the reverse contrast (ASD > TD).

TD > CD/CU+: The TD group showed a greater response in the right thalamus and the left and right occipital cortex compared to the CD/CU+ group in the other- versus control-task. No significant differences were found in the reverse contrast (CD/CU+ > TD).

ASD > CD/CU+: The ASD group showed a greater response than the CD/CU+ group in the right occipital cortex in the other- versus control-task, but they showed reduced responses in the ventromedial prefrontal cortex (vmPFC; see Figure 1) and the right superior temporal sulcus compared to the CD/CU+ group.

Emotional resonance: Self-task vs. control-task

TD > ASD: Whole-brain analysis showed that the TD group showed a greater response in the left and right hippocampus (see Figure 2), the left amygdala (see Figure 3), and the right premotor cortex than the ASD group (see Table 3 for all self-task vs. control-task results). No significant differences were found in the reverse contrast (ASD > TD).

TD > CD/CU+: The TD group showed a greater response in the left AI (see appendix Figure S1) and IFG (see Figure 4), the left inferior parietal lobule, the left midbrain and left amygdala (see Figure 3), the paracingulate gyrus, and the occipital cortex than the CD/CU+ control group. No significant differences were found in the reverse contrast (CD/CU+ > TD).

ASD > CD/CU+: The ASD group showed a greater response than the CD/CU+ group in the occipital cortex and the left caudate in the self- versus control-task. The CD/CU+ group showed a greater response than the ASD group in the right hippocampus (see Figure 2), the superior temporal sulcus, the occipital cortex extending into the angular gyrus, the vmPFC and the posterior cingulate cortex.

Table 2. *MNI coordinates, z values and cluster size for brain regions revealed by the whole brain pairwise comparisons of the other > control contrasts (emotion recognition), p < .05 cluster-corrected.*

Anatomical region	**Max *z***	**MNI peak coords**			**Size in voxels**
		x	y	z	
TD >ASD					
R hippocampus	4.86	22	-10	-26	777
R premotor cortex	3.90	34	-22	62	1003
Midcingulate cortex	3.90	-6	-14	44	617
TD > CD/CU+					
L/R occipital cortex	4.07	4	-74	-8	3321
R thalamus	3.44	14	-24	10	444
ASD > CD/CU+					
L occipital pole	3.88	-14	-72	12	1412
CD/CU+ > ASD					
R superior temporal sulcus	4.05	48	-10	-10	472
Ventromedial prefrontal cortex	3.70	10	44	-2	590

Table 3. *MNI coordinates, z values and cluster size for brain regions revealed by the whole brain pairwise comparisons of the self > control contrasts (emotional resonance), p < .05 cluster-corrected.Asterisk indicates regions that are also revealed by an F test in which all three groups were compared.*

Anatomical region	Max *z*	MNI peak coords			Size in voxels
		x	y	z	
TD >ASD					
R hippocampus *	5.04	28	-24	-18	1157
L hippocampus *	4.85	-24	-18	-22	1299
L amygdala *	4.09	-20	-4	-18	(part of above)
R premotor cortex	3.73	28	-30	58	894
TD > CD/CU+					
R occipital cortex *	4.61	28	-92	12	2241
L occipital cortex *	4.40	-30	-92	4	1642
L anterior insula / inferior frontal gyrus	4.06	-36	22	4	1187
L midbrain	3.61	-4	-24	-14	495
L amygdala	3.35	-20	-8	-14	(part of above)
Paracingulate gyrus	3.56	-2	16	44	478
L inferior parietal lobule	3.54	-48	-52	54	522
ASD > CD/CU+					
R occipital cortex	4.20	30	-92	12	832
L occipital cortex	3.78	-18	-88	0	579
L caudate	3.63	-16	2	22	473
CD/CU+ > ASD					
R superior temporal sulcus	5.05	58	-8	-18	824
R hippocampus	4.21	32	-16	-22	484
R occipital / angular gyrus	4.04	48	-68	20	742
Ventromedial prefrontal cortex	3.82	-4	64	10	537
Posterior cingulate cortex	3.55	2	-46	24	524

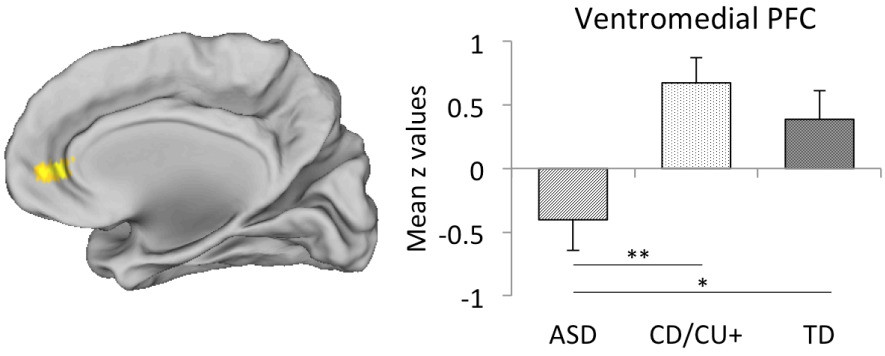

Figure 1. *Significant group differences in the ventromedial prefrontal cortex for the other > control contrast (emotion recognition) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD group showed reduced responses in this area compared to the CD/CU+ and TD groups (* = p < .05; ** = p < .005).*

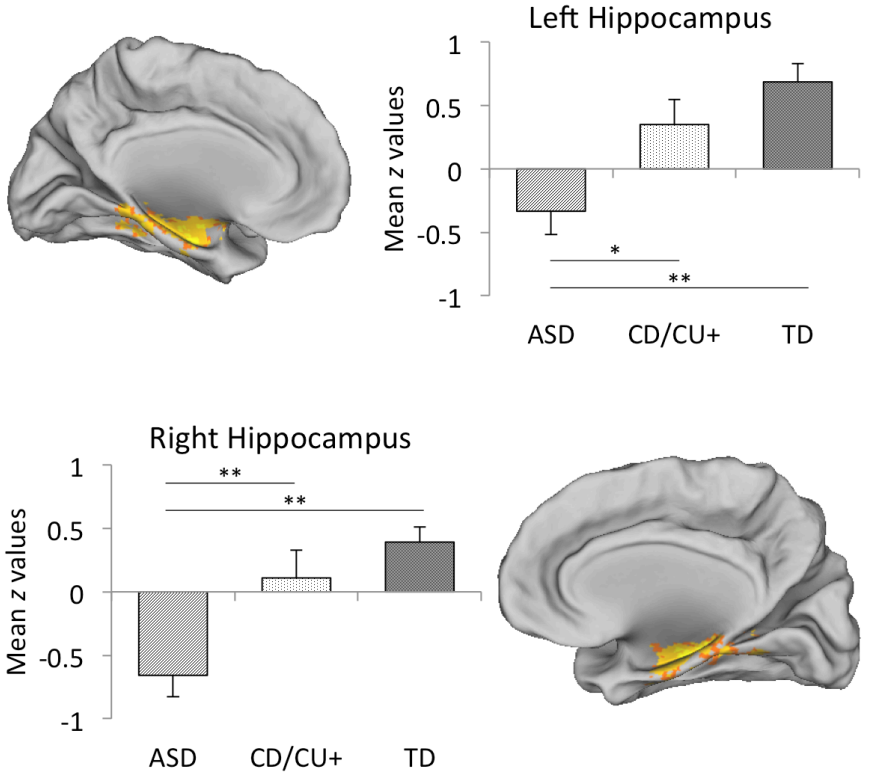

Figure 2. *Significant group differences in the left and right hippocampus for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD group showed reduced responses in these areas compared to the CD/CU+ and TD groups (* = p < .05; ** = p < .005).*

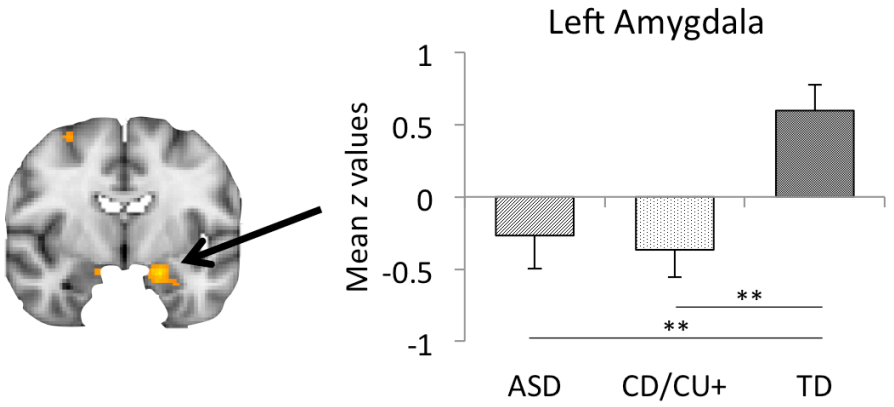

Figure 3. *Significant group differences in the left amygdala for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD and CD/CU+ groups showed reduced responses in this area compared to the TD controls (* = p < .05; ** = p < .005).*

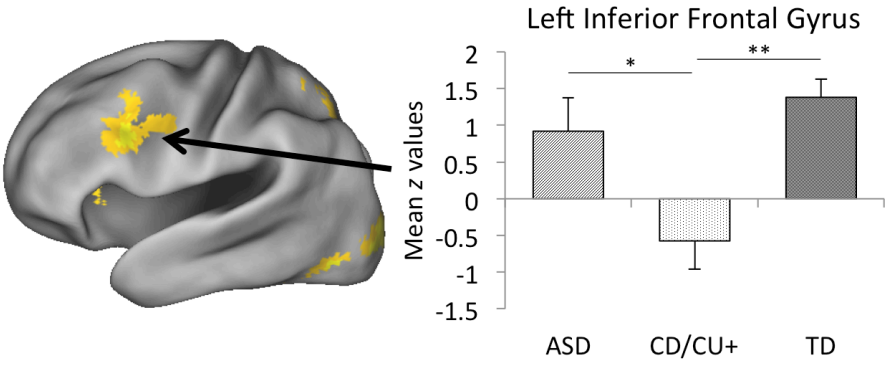

Figure 4. *Significant group differences in the left inferior frontal gyrus for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the CD/CU+ group showed reduced responses in this area compared to the ASD and TD groups (* = p < .05; ** = p < .005). Note that results were similar for the anterior insula in this cluster (see appendix Figure S1).*

Correlations with variables of interest

Correlations between brain activity in ROIs and variables of interest (autistic symptoms, CU traits, empathy scores) were conducted within the three groups separately and showed a negative correlation between CU traits as measured by the ICU and responses in the left IFG within the CD/CU+ group in the self- versus control-task, $r = -.44, p = .038$. However, this correlation was not significant anymore after correction for multiple comparisons.

Effects of IQ, medication and comorbidity

For transparency, we repeated the fMRI analyses with IQ as covariate (see for results appendix Tables S1 and S2). Furthermore, post-hoc analyses revealed that all group differences remained significant while excluding ASD boys with a comorbid disorder or ASD boys using medication, and also while excluding CD/CU+ boys with a comorbid disorder (all $ps < .05$). In addition, no significant group differences were found between ASD and CD/CU+ participants with a comorbid disorder and those without, or between ASD boys who were on medication and those who were not (all $ps > .05$).

Discussion

The purpose of this study was to compare the neural correlates of different processes involved in empathy between youth with ASD and youth with CD/CU+. The hypothesis that the ASD group would show reduced responses in social cognitive brain regions was confirmed by the decreased vmPFC response during the emotion recognition condition. However, we could only partly confirm the hypothesis concerning reduced responses in affective brain regions in the CD/CU+ group, since both ASD and CD/CU+ boys showed diminished responses in the left amygdala during the emotional resonance conditions compared to TD boys. Interestingly, there were also differences in brain responses between the ASD and CD/CU+ groups, suggesting that the neural processing of emotions has disorder specific features. During emotional resonance, ASD boys showed diminished responses in the left and right hippocampus compared to CD/CU+ and TD boys. In addition, CD/CU+ boys showed decreased responses during emotional resonance than ASD and TD boys in the left IFG and AI.

The decreased amygdala responses in ASD and CD/CU+ during emotional resonance converge with previous findings (Marsh et al., 2008; Swartz et al., 2013; Viding et al., 2012; Wang et al., 2004). At the same time, studies also have reported increased amygdala responses in ASD (e.g., Dalton et al., 2005; Monk et al., 2010). These inconsistencies may result from differences in attention to the faces.

In ASD, amygdala hypoactivation is thought to reflect a disruption in directing attention to socially relevant features of emotional faces (Pelphrey et al., 2011), whereas theories about CD/CU+ suggest that amygdala hypoactivation is related to impaired processing of and attention to distress cues, including facial expressions (Blair, 2013; Moul et al., 2012). Notwithstanding that our results are consistent with both accounts, it should be noted that reduced amygdala responses in the ASD and CD/CU+ groups were not revealed during the emotion recognition condition. This might support recent suggestions that, in this case in the amygdala, brain responses in ASD and CD/CU+ boys are normalized when being asked to attend to others' emotions (Keysers & Gazzola, 2014; Meffert et al., 2013), and disrupted when being asked to reflect on one's own emotion, whereby attention is being drawn away from the other. Similarly, adults with ASD demonstrate problems in implicit mentalizing despite the ability to perform well on explicit mentalizing tasks (Senju et al., 2009), and studies have shown impairments in spontaneous but not voluntary facial mimicry in ASD (Gillespie et al., 2014; McIntosh et al., 2006; Oberman et al., 2009). Put differently, as these authors suggest, ASD and CD/CU+ boys might have the capacity for empathy, but may be less inclined to experience empathy automatically (Keysers & Gazzola, 2014).

As expected, the CD/CU+ boys showed reduced responses in the left IFG and AI during the emotional resonance condition. The IFG and AI are crucial regions for affective empathy (Carr et al., 2003; Shamay-Tsoory et al., 2009) that are also involved in the putative human mirror neuron system (Kilner et al., 2009). Hence, the diminished IFG and AI responses in CD/CU+ boys are consistent with previous studies suggesting that they resonate less with the feelings of others (Lockwood et al., 2013b; Sebastian et al., 2012b; Sterzer et al., 2007). The fact that we found reduced IFG and AI responses solely in the CD/CU+ boys provides preliminary evidence for a disorder specific feature, although future studies are needed to replicate these findings.

During emotion recognition, the ASD boys showed diminished responses in the vmPFC. The mPFC (including its ventral part) is a core region implicated in mentalizing (Abu-Akel & Shamay-Tsoory, 2011; van Overwalle & Baetens, 2009) and previous studies have found reduced responses in this area in ASD compared

to TD and CP/CU+ groups (Bookheimer et al., 2008; Castelli et al., 2002; O'Nions et al., 2014; Wang et al., 2007; Watanabe et al., 2012). Although mentalizing is mostly associated with more dorsal regions of the mPFC, there are indications, mostly from lesion studies, that especially for cognitive empathy (i.e., affective mentalizing) more ventral parts of the mPFC are important (Leopold et al., 2012; Shamay-Tsoory et al., 2006; Shamay-Tsoory et al., 2005). In addition, vmPFC activation is critical for self-referential processing (D'Argembeau et al., 2007; Mitchell et al., 2006) and it has been argued that atypical vmPFC activation in ASD during self-reflection may partly account for their mentalizing impairments (Lombardo et al., 2010). However, the role of the vmPFC is much broader and this region may act as a 'hub' that binds information from networks involved in memory, emotion, social cognition, and reward computation (Roy et al., 2012). Specifically, many studies have shown that the regulation of emotions engages the vmPFC (Ochsner et al., 2012). Given indications that individuals with ASD have difficulties with emotion regulation strategies (Samson et al., 2012), the decreased vmPFC response in the ASD group in our study might also point to problems in regulating reactions towards angry and fearful faces. More research is needed to further understand emotion regulation processes in ASD and how this might influence responses to others' emotions (Hadjikhani et al., 2014; Mazefsky et al., 2012).

Taken together, the decreased vmPFC response in ASD is in line with theories proposing that individuals with ASD have difficulties in processing cognitive aspects of empathy and mentalizing associated with cortical midline dysfunction (Blair, 2008; Pelphrey et al., 2011), although it might also be related to emotion dysregulation in the ASD group. By contrast, as found in previous studies (O'Nions et al., 2014; Sebastian et al., 2012b), mPFC responses in the CD/CU+ boys did not differ from the TD boys in our study. This suggests that problems with processing socioemotional stimuli in CD/CU+ are limited to altered functioning of affective brain regions (Blair, 2013).

An unexpected finding was the diminished response in bilateral hippocampus in the ASD boys compared to the CD/CU+ and TD boys. The diminished response might point to problems in integrating emotional information with declarative memory in ASD. Although the hippocampus has not been a focus of

empathy and social cognition research, there is some evidence that this structure is involved in empathic processes (Schnell et al., 2011). Recently, evidence for decreased empathy in patients with hippocampal damage was found, from which the authors concluded that the role of the hippocampus in empathy might be to flexibly maintain and update information about the emotional states of self and others (Beadle et al., 2013). In addition, several studies have found structural abnormalities of the hippocampus in ASD (Groen et al., 2010; Schumann et al., 2004). Our study might further point to a relation between hippocampal abnormalities and empathy deficits in ASD.

This study has several strengths. First, to our knowledge this is the first fMRI study that directly compared ASD boys with CD/CU+ boys during specific aspects of empathy. Second, a large group of aggressive CD boys were recruited from forensic settings, thereby substantially increasing the likelihood that youth with severe antisocial behavior enrolled in the study. Third, to allow comparison with prior fMRI work among community youths with conduct problems (Lockwood et al., 2013b; O'Nions et al., 2014) and previous work that compared ASD and CD (Schwenck et al., 2012), we relied on the same tool to assess CU traits (i.e., the ICU). Evidently, the results should also be interpreted in the context of some limitations. First, the task that was used in our study measured only certain aspects of cognitive and affective empathy. Future fMRI studies are needed to compare ASD and CD/CU+ on different perspective taking and empathy for pain paradigms to further test the differences in the neural processing of empathy in these disorders. Second, no eye tracking data were collected in the present study. Therefore, we cannot test the intriguing possibility that patterns of eye gaze may have influenced decreased responses in the amygdala in either the ASD or CD/CU+ participants. Gaze fixation patterns have been associated with *increased* amygdala responses in ASD (Dalton et al., 2005) and in contrast to controls, individuals with ASD did not attend longer to pictures of intentionally caused pain than to neutral control pictures (Fan et al., 2014). Furthermore, one study in children with high levels of CU traits reported reduced eye gaze to fearful faces (Dadds et al., 2008). Future studies are needed to better characterize eye gaze deficits in CD/CU+ and how this might relate to brain responses in ASD and CD/CU+ youth. Third, due to

time constraints we did not assess the presence of all possible comorbidities with standardized diagnostic interviews in the ASD and CD/CU+ groups. Therefore, we could have underestimated the amount of comorbidities such as anxiety disorders in these groups.

In summary, the current study design gave us the unique opportunity to evaluate differences and commonalities between two disorders in a commonly affected process (i.e., empathy), and we provide for the first time direct evidence for specific abnormalities in the neural processing of cognitive and affective aspects of empathy in two important clinical groups (ASD and CD/CU+).

Appendix

Data acquisition

For fMRI, T2* weighted gradient echo, echo planar images (EPI) sensitive to BOLD contrast were obtained with the following acquisition parameters: repetition time (TR) = 2.2 s, echo time (TE) = 30 ms, flip angle = 80°, 38 axial slices, field of view (FOV) = 220 × 220 mm, 2.75 mm isotropic voxels, 0.25 mm slice gap. To allow for T1 equilibrium the first two functional volumes were automatically discarded before data collection began. A high-resolution anatomical image (T_1-weighted ultra-fast gradient-echo acquisition; TR = 9.75 ms, TE = 4.59 ms, flip angle = 8°, 140 axial slices, FOV = 224 × 224 mm, in-plane resolution 0.875 × 0.875 mm, slice thickness = 1.2 mm) was acquired for registration purposes. All anatomical scans were reviewed by a radiologist; no anomalies were found.

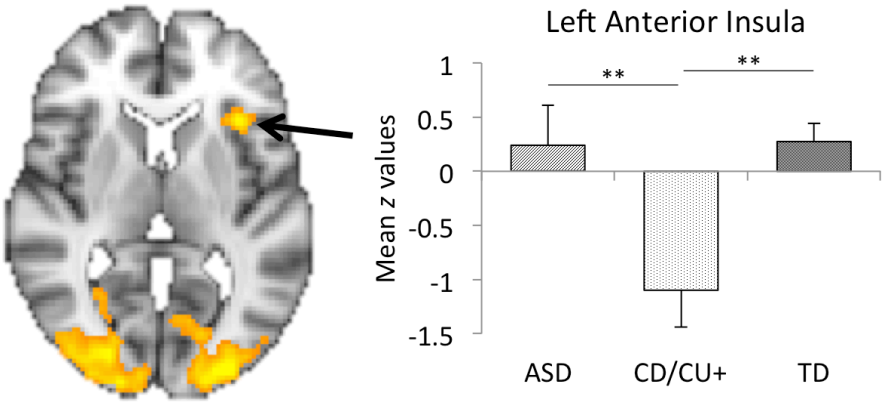

Figure S1. *Significant group differences in the left anterior insula for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the CD/CU+ group showed reduced responses in this area compared to the ASD and TD groups (** = p < .005).*

Table S1. *MNI coordinates, z values and cluster size for brain regions revealed by the whole brain pairwise comparisons of the other > control contrasts (emotion recognition) including IQ as covariate of no interest, p < .05 cluster-corrected.*

Anatomical region	**Max *z***	**MNI peak coords**			**Size in voxels**
		x	y	z	
TD >ASD					
R hippocampus	4.14	22	-10	-26	1097
R premotor cortex	4.06	38	-22	52	1011
Midcingulate cortex	3.89	-4	-12	44	764
L occipital pole	3.64	-12	-86	44	477
Anterior cingulate cortex	3.37	4	32	20	429
TD > CD/CU+					
L/R occipital cortex	4.07	-14	-74	10	2619
CD/CU+ > ASD					
R superior temporal sulcus	4.27	46	-22	-14	515
R supramarginal gyrus	4.13	66	-42	28	556
Ventromedial prefrontal cortex	3.88	12	44	-2	969

Table S2. *MNI coordinates, z values and cluster size for brain regions revealed by the whole*

brain pairwise comparisons of the self > control contrasts (emotional resonance) including IQ as covariate of no interest, p < .05 cluster-corrected.Asterisk indicates regions that are also revealed by an F test in which all three groups were compared.

Anatomical region	**Max *z***	**MNI peak coords**			**Size in voxels**
		x	y	z	
TD >ASD					
L hippocampus	4.54	-22	-46	0	1562
L amygdala	3.77	-20	-4	-18	(part of above)
R hippocampus	4.20	26	-34	-8	737
TD > CD/CU+					
R occipital cortex	4.61	40	-80	0	2296
L occipital cortex *	4.28	-30	-92	4	1598
L insula / inferior frontal gyrus *	4.03	-42	14	24	1111
L inferior parietal lobule	3.58	-48	-52	54	590
ASD > CD/CU+					
R occipital cortex *	3.95	28	-94	14	652
CD/CU+ > ASD					
R superior temporal sulcus	4.95	56	-8	-18	719
Ventromedial prefrontal cortex	4.27	-4	64	10	1198
R occipital / angular gyrus	3.69	52	-54	14	508