NeuroImage: Clinical 29 (2021) 102519

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Eye gaze patterns and functional brain responses during emotional face processing in adolescents with conduct disorder

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ARTICLE INFO

Keywords:
Conduct disorder
Neuroimaging
Emotion processing
neuropsychiatry
Eye gaze
fMRI

ABSTRACT

Background: Conduct disorder (CD) is characterized by severe aggressive and antisocial behavior. Initial evidence suggests neural deficits and aberrant eye gaze pattern during emotion processing in CD; both concepts, however, have not yet been studied simultaneously. The present study assessed the functional brain correlates of emotional face processing with and without consideration of concurrent eye gaze behavior in adolescents with CD compared to typically developing (TD) adolescents.

Methods: 58 adolescents (23CD/35TD; average age = 16 years/range = 14–19 years) underwent an implicit emotional face processing task. Neuroimaging analyses were conducted for a priori-defined regions of interest (insula, amygdala, and medial orbitofrontal cortex) and using a full-factorial design assessing the main effects of emotion (neutral, anger, fear), group and the interaction thereof (cluster-level, $p < .05$ FWE-corrected) with and without consideration of concurrent eye gaze behavior (i.e., time spent on the eye region).

Results: Adolescents with CD showed significant hypo-activations during emotional face processing in right anterior insula compared to TD adolescents, independent of the emotion presented. In-scanner eye-tracking data revealed that adolescents with CD spent significantly less time on the eye, but not mouth region. Correcting for eye gaze behavior during emotional face processing reduced group differences previously observed for right insula.

Conclusions: Atypical insula activation during emotional face processing in adolescents with CD may partly be explained by attentional mechanisms (i.e., reduced gaze allocation to the eyes, independent of the emotion presented). An increased understanding of the mechanism causal for emotion processing deficits observed in CD may ultimately aid the development of personalized intervention programs.

1. Introduction

Conduct disorder (CD) is characterized by persistent patterns of aggressive behaviors in children and adolescents that clearly deviate from age appropriate and societal norms and violate the rights of others (American Psychiatric Association, 2013). CD has a relatively high lifetime prevalence of about 9.5% (Copeland et al., 2013; Nock et al., 2006) and the consequences impact familial, academic, and occupational functioning (Fairchild et al., 2019). For example, adolescents with CD are more likely to engage in delinquencies and enter the criminal justice service, causing a tenfold increase of societal costs compared to their typically developing (TD) peers (Bardone et al., 1998; Pedersen and Mastekaasa, 2011; Scott et al., 2001). This is especially true for CD adolescents with high levels of callous-unemotional (CU) traits, who display severely reduced guilt or remorse, a lack of empathy, and shallow or deficient affect (American Psychiatric Association, 2013; Herpers et al., 2017; Rowe et al., 2010). Levels of CU traits are not only associated with behavioral severity but also with a distinct neural phenotype (Herpers et al., 2017; Rowe et al., 2010).

One of the core characteristics of adolescents with a diagnosis of CD are deficits in emotion processing and emotion recognition (Blair et al., 2014; Fairchild et al., 2019), which can be measured through tasks of

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https://doi.org/10.1016/j.nicl.2020.102519
Received 29 January 2020; Received in revised form 9 November 2020; Accepted 30 November 2020
Available online 3 December 2020

facial emotion processing (Fairchild et al., 2009). While an adequate recognition of negative emotions (e.g., sadness, anger, fear) has been proposed as a precursor for prosocial behavior, a lack thereof has been linked to aggressive and antisocial behavior (Blair, 2005; Hunnikin and van Goozen, 2019; Marsh and Blair, 2008). However, the precise mechanisms leading to deficits in emotion processing and emotion recognition in adolescents with CD, as for example displayed through facial expressions, are a continuing matter of investigation. Previous studies have suggested that either a reduced attention to the eye region or differences in appraisal (e.g., interpretation of the emotional stimuli) may be causal to the observed emotion processing and emotion recognition deficits in adolescents with antisocial behavior (Bons et al., 2013; Dadds et al., 2006, 2011). More specifically, some studies have observed that adolescents with CD focus less on the eyes during facial emotion processing tasks as measured through the number of fixations f or time spent on the eye region (Bours et al., 2018). Interestingly, adolescents with CD and high levels of CU traits have been reported to display enhanced fear recognition compared to adolescent with CD and low CU-traits (Martin-Key et al., 2018; Schwenck et al., 2014; Woodworth and Waschbusch, 2008). This is in contrast to typically developing children and adolescents scoring high on CU traits, who tend to display deficits in fear recognition and reduced attention to the eye region (Dadds et al., 2008, 2011, 2006; Martin-Key et al., 2018). Overall, results of a reduced attention to the eyes in children and adolescents with disruptive behaviors or in those with varying CU traits are not identified by all studies and thus remain a subject of investigation (Airdrie et al., 2018; Hunnikin and van Goozen, 2019). Overall, such ambiguities could be attributed to a variety of factors impacting group homogeneity including group definition or diagnosis criteria, study design, sample sizes, age differences, an unbalanced or single gender studies, the inclusion of subgroup characteristics such as CU traits, or the inclusion of further comorbidities (Raschle et al., 2015). Importantly, some studies have demonstrated that the inclusion of an instruction to focus on the eye region of faces improved emotion recognition in individuals with antisocial behavior and/or high levels of CU traits (Dadds et al., 2006; Hubble et al., 2015).

Neuroimaging studies have demonstrated that adolescents with CD have altered hemodynamic responses when processing facial emotions, particularly within the emotion-circuitries of the brain, including limbic and prefrontal brain regions (e.g., amygdala, insula, orbitofrontal cortex; (Fairchild et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014). CU traits have been shown to distinguish a relevant subgroup amongst adolescents with CD or conduct problems which may even impact the functional brain response observed (e.g., amygdala response during emotion processing). Some studies, for example, show that adolescents with conduct problems and high levels of CU traits display reduced amygdala activation when processing fearful facial expressions (Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding et al., 2012). However, other studies did not identify or report an impact of CU traits on amygdala activation during emotional face processing (Dotterer et al., 2017; Fairchild et al., 2014; Passamonti et al., 2010). Similarly, insula activity has been shown to negatively correlate with levels of CU traits in adolescent with conduct problems during empathy processing and fear conditioning (Cohn et al., 2013; Klapwijk et al., 2015; Lockwood et al., 2013). While various studies indicate that individuals with conduct problems or CD display altered functional brain responses during emotion recognition and processing tasks, to date, there is a lack of studies that have directly investigated the relationship between eye gaze behavior and brain responses during emotion processing. One study observed that redirecting attention towards the eyes of fearful faces increases brain responses in brain areas that were previously hypo-activated (e.g., amygdala, orbitofrontal cortex) in boys with conduct problems with low, but not high, levels of CU traits (Sebastian et al., 2014). Similarly, increased brain response within the amygdala was observed for typically developing adults with high levels of CU traits when processing the eye region of fearful faces as compared to the processing of fearful faces where the eyes were excluded (Han et al., 2011). These findings indicate that redirecting attention to the eye region may result in increased hemodynamic response in areas associated with emotion processing for both individuals with conduct problems and TD individuals. This may further differ, however, depending on the level of CU traits displayed. A relevant association between eye gaze behaviors and brain activation during emotional face processing has previously been reported for individuals with autism spectrum disorder (ASD; (Dalton et al., 2005)), who exhibit similar face-processing deficits as individuals with CD (Bons et al., 2013). In adolescents with a diagnosis of ASD Dalton and colleagues (2005) observed a strong positive correlation between gaze fixation to the eyes and amygdala (hyper)activation, which provided novel insight into the underlying mechanisms for the observed face-processing deficits in ASD (Dalton et al., 2005). Combining eye-tracking and functional magnetic resonance imaging (fMRI) techniques allows direct investigation of how eye movements may contribute to altered brain activity associated with emotional face-processing deficits and/or inform about attentional or avoidance mechanisms (e.g., avoidance associated with specific emotions vs. attentional mechanisms expected across emotions). Such investigations could therefore further our understanding of the mechanisms underlying emotion processing impairments in CD. Furthermore, simultaneous multi-modal data collection, i.e., eye-tracking during an fMRI paradigm, has been suggested to generate more comprehensive information than combining data modalities that were separately collected (Dalton et al., 2005). To date, no study has yet directly investigated the relationship between eye gaze behavior and brain activation patterns during emotional face processing in adolescents with CD.

Here we aim to close this gap in the literature, by investigating the functional brain correlates during emotional face processing in adolescents with CD compared to TD controls through the use of fMRI and concurrent eye-tracking. Based on prior evidence (Dadds et al., 2008; Dadds et al., 2011; Martin-Key et al., 2018), we hypothesized (**I**) to observe differences in eye gaze behavior when comparing adolescent with CD to TD peers. More specifically, a reduced focus on socially relevant facial features (e.g., the eye and mouth region) for adolescents with CD is expected, which is in line with prior eye-tracking evidence from behavioral research studies. Secondly, in line with previous evidence (Fairchild et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014; Viding et al., 2012), we (**II**) expected to observe alterations in the brain correlates during facial emotion processing in adolescents with CD compared to TD adolescents in brain regions including bilateral insula, amygdala, and orbitofrontal cortex. Thirdly, (**III**) a reduced focus on socially relevant facial features (e.g., the eye regions) was expected to be linked to reduced neuronal brain activation during facial emotion processing. Such a relation may indicate that reduced brain responses are possibly caused by an aberrant eye gaze pattern (Bons et al., 2013), which would be in line with previous studies that found improved emotion recognition after eye gaze training (Dadds et al., 2006; Hubble et al., 2015). Furthermore, emotion specificity or an effect independent of emotion will further inform about more general behavioral deficits (e.g., less attention towards relevant features) as compared to specific avoidance behavior (e.g., for negative emotions such as anger). Finally, based on prior evidence reporting a negative correlation between CU traits and eye gaze behavior in adolescents with a diagnosis of CD (Dadds et al., 2011; Jones et al., 2009; Martin-Key et al., 2018) we (**IV**) hypothesized a negative relationship between CU traits and eye gaze behavior as collected behaviorally during the facial emotion processing fMRI task conduction (i.e., through a reduced number of fixations to the eye and mouth regions during facial emotion processing) in adolescents with a diagnosis of CD.

2. Methods and materials

2.1. Participants and measures

All participants were recruited within a Swiss National Science Foundation study. We initially collected clinical interviews and psychometric testing, as well as neuroimaging and eye-tracking in 70 adolescents (age range = 14–19 years), recruited from healthcare institutions and schools. CD status and psychiatric diagnoses were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL; (Kaufman et al., 1997)). We had to exclude twelve participants from analyses due to low quality data caused by excessive eye blinks or malfunctioning of the eye-tracking system, resulting in 58 usable datasets included in the present study. All 23 participants with a diagnosis of CD (9 males, 14 females; mean age 16.7 years) fulfilled the DSM-5 criteria for CD, six had comorbidities for ADHD. All typically developing (TD) controls (10 males, 25 females; mean age 16.6 years) had no psychiatric or neurological disorders. Additional psychometric testing included a standardized battery comprising of the German version of the WISC-IV/WAIS to measure verbal, non-verbal, and total IQ (Petermann and Wechsler, 2008), the Youth Psychopathic Traits Inventory (YPI), a self-report questionnaire assessing psychopathic and callous-unemotional traits (Andershed et al., 2002), the Edinburgh Handedness Inventory (EDI; (Caplan and Mendoza, 2011)), and the Pubertal Development Scale (PDS; (Petersen et al., 1988). Clinical interviews, psychometric testing, and neuroimaging sessions with online eye-tracking were conducted on separate days, on average within 1.9 months. All participants and caretakers provided written informed consent to take part in the study as approved by the local ethics committee in Basel, Switzerland ('Ethikkommission Nordwest- und Zentralschweiz').

2.2. fMRI task:emotional face processing

We employed an adapted version of an implicit emotional face processing paradigm, which has previously been successfully implemented by different research teams (Fairchild et al., 2010; Passamonti et al., 2010). The task consisted of naturally colored photographs of neutral, anger, and fearful faces presented after each other and posed by 30 different actors from the NimStim Face Stimuli Set (50% female; (Tottenham et al., 2009)). Face stimuli were fitted to an oval field-of-view on a grey-background to remove excessive non-facial features (e.g. hair, ears) and were inflated/deflated to equalize the distance between the mouth and eyes regions for all stimuli. For stimulus presentation and feedback recording, we used Presentation® software (Neurobehavioral Systems, Inc.) and binocular video googles VisualSystem (Nordic NeuroLab, Bergen, Norway). Both the fixation event and the relaxation period consisted of a small white fixation cross positioned at the height of the nasal bridge in the exact middle of the eye and mouth region of each face stimulus. Participants were asked to relax (to prevent excessive blinking) and focus on the white cross between the stimuli to equalize the starting position of the eye-tracking data for each trial (see Fig. 1). Participants were instructed to indicate the gender of the faces presented to induce implicit processing of the emotional facial expressions. Stimuli were presented in blocks with a duration of 27.5 s, with each block containing five face trials of the same emotional expressions (neutral, anger, or fearful) displayed by different individuals. Each block was intermixed with five fixation trials, where participants had to look at the fixation cross (see Fig. 1). For each block, the stimuli were pseudo-randomized with respect to gender and trial type (face/fixation), allowing a maximum of three consecutive trials of the same trial type. Face stimuli were presented for 2 s each with 750 ms interstimulus intervals during which a blank screen with a fixation cross was presented. Twelve blocks of each facial expression (60 neutral, 60 anger, 60 fearful) were presented over the course of two subsequent runs. Eye gaze behavior (number of fixations and fixation duration) and task performance (reaction time and accuracy) were recorded and analyzed for each facial expression presented.

Eye movements from the right eye were monitored with a camera-based eye-tracker system VisualSystem (Nordic NeuroLab, Bergen, Norway) attached to the right ocular of the binocular video goggles. The real-time gaze direction of each participant was continuously tracked through pupil-location at a rate of 60 Hz with ViewPoint Software (Arrington Research®). A 12-point calibration procedure was applied and repeated until a rectilinear and well-separated calibration configuration was achieved. All participants were trained for the fMRI task and calibration procedure beforehand.

2.3. Image acquisition

Whole brain functional magnetic resonance images were obtained using a 3 T MR imaging system (Siemens Prisma, Erlangen, Germany) and a 20-channel phased-array radio frequency head coil. After high order shimming of the magnetic field, functional whole-brain volumes were acquired using a T2*-weighted echo-planar imaging (EPI) sequence [TR = 2500 ms; TE = 30 ms; flip angle = 83°; FoV = 192 mm; 41 slices; matrix size = 64 × 64; and voxel size = 3 × 3 × 2]. The first four functional time points of each run were discarded to allow a steady state magnetization before the task trials began. In addition, for anatomical reference a high-resolution T1-weighted image was acquired

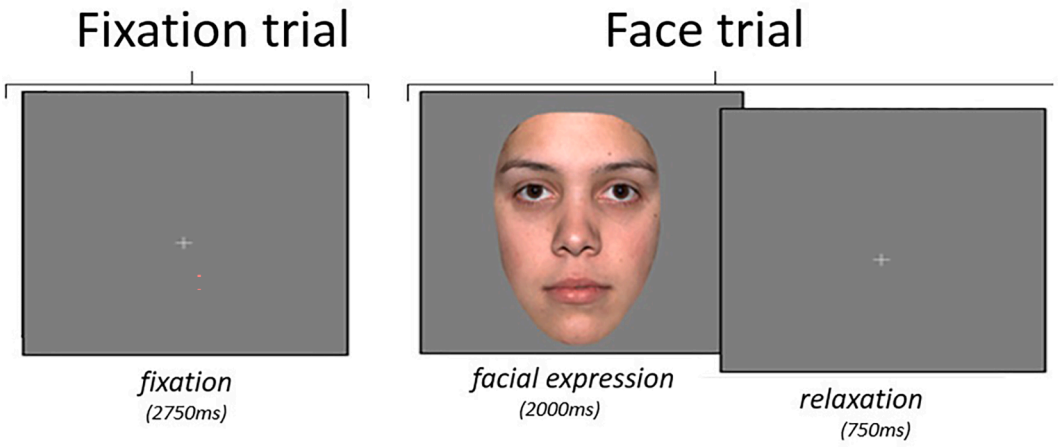

Fig. 1. An implicit emotional face processing fMRI paradigm was used to investigate emotion processing. Participants had to indicate via button press the gender of neutral, anger, and fearful facial expressions posed by 30 different actors (50% female). Stimuli were presented in blocks where 5 face trials from one emotion category (neutral, anger, or fearful) were pseudo-randomly intermixed with 5 fixation trials.

using the following sequence: TR = 1900.0 ms; TE = 3.42 ms; flip angle = 9°; FoV = 256 mm; matrix size = 256 × 256; and voxel size = 1 × 1 × 1.

2.4. Eye-tracking data analyses

All eye-tracking data were preprocessed through MATLAB and analyzed with the EyeMMV toolbox (Krassanakis et al., 2014). Preprocessing entailed the removal of blinks and correction for small head movements during each face trial. Static eye-tracking devices are sensitive to eye blinks and head movements. Such events force the eye-tracker to relocate the drifted pupil location which induces data loss. Participants were excluded from eye-tracking analyses if more than 60% of their trials had<500 ms of usable eye gaze data. Each trial was separately extracted and analyzed through the specialized fixation identification algorithm of the EyeMMV toolbox using the following parameters: fixation threshold = 150 ms, t1 = 0.05, and t2 = 0.1. The fixation output data was then further investigated through areas of interest (AOI) analyses for the mouth region and a region that surrounded the left and right eye. These AOIs were rectangle-shaped with identical dimensions and matching distance from the initial fixation cross (positioned middle on the nose bridge). For each face trial, the number of fixations and the sum of the fixation durations were extracted and calculated as the ratio between each AOI (i.e., mouth or eyes) and the remaining whole screen, to account for differences in data loss between participants due to blinking and head movement as was done in previous studies (Bours et al., 2018; Martin-Key et al., 2018). These extracted eye-tracking data were then averaged for each facial expression individually. Due to violation of normality test assumptions, a Box-Cox transformation was applied on the data to ensure a normal distribution (Box and Cox, 1964). We then performed full-factorial analyses of variance (ANOVAs) and follow-up *t*-tests using SPSSv23 (IBM Corp., Armonk, N. Y., USA).

2.5. CU traits and eye gaze behavior

CU traits are based on the callous-unemotional dimension of the YPI questionnaire. The relation between CU traits and eye gaze (i.e., the number of fixations on the eyes or mouth) for each facial expression was investigated using partial correlation analyses (Bonferroni correction for multiple comparison) within each group individually and while controlling for age, intelligence, and gender.

2.6. fMRI data analyses

Functional neuroimaging data was preprocessed and analyzed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), implemented in MATLAB (version 2014b; MathWorks). Preprocessing included data quality check, slice time correction, realignment, co-registration to the structural images, segmentation of the structural image, normalization to MNI space and smoothing (8 mm FWHM). During preprocessing, all analyses were restricted to one mask that was built from six regions of interest, namely bilateral insula, bilateral amygdala, and bilateral medial orbitofrontal cortex (mOFC), as defined using the automated anatomical labeling (aal: (Tzourio-Mazoyer et al., 2002)) atlas (Ewbank et al., 2018; Fairchild et al., 2014; Passamonti et al., 2010). In addition, a whole-brain exploratory approach is reported in order to inform about areas not previously associated with facial emotion processing.

For each participant, voxel-wise changes in BOLD response across conditions were modeled according to the general linear model and included six motion regressors to account for residual effects of movement and temporal inhomogeneities and a global regressor for each run to account for differences between runs. The model consisted of six regressors of interest: three emotional face conditions (neutral, anger, fearful; unanswered trials were removed from the regressor) and three fixation conditions (neutral fixation, anger fixation, fearful fixation). Each trial was modeled as a stick-function convolved with a canonical hemodynamic response function. Regressors were used to build the following contrasts: neutral > neutral fixation, anger > anger fixation, and fearful > fearful fixation (Fairchild et al., 2014). Finally, a full factorial analysis of covariance, including age, intelligence score, and gender as covariates of no interest was used to analyze the main effects of group, emotion, and their interaction. All results are reported using a cluster-building threshold of $p < .001$ and a cluster-level correction for multiple comparison of $p < .05$, familywise error (FWE-)corrected.

2.6.1. Consideration of eye gaze behavior

To test the influence of eye gaze behavior, the average duration of fixations on the eye regions (in ratio to duration of all fixations) was first included across all facial stimuli as covariate to the main group analyses. Secondly, eye gaze effects were directly assessed through an interaction term (eye gaze behavior by group), by adding the corresponding regressors (average duration of fixations on the eyes) per group into a follow-up full-factorial model.

3. Results

3.1. Group characteristics

The study groups did not differ significantly in regards to age ($t(56) = 0.15$, $p = .884$), pubertal status (U = 313,5$p = .244$), and handedness (U = 351.0, $p = .147$; group characteristics are reported in Table 1). Compared to controls, adolescents with a diagnosis of CD had a lower overall intelligence score ($t\_(33.3) = -2.26$, p=.031); This difference was driven by the verbal ($t(31.5) = -2.73$, p=.010) and not the performance subscale ($t(56) = -0.96$, p=.343)). The TD group had a higher female-male ratio than the CD group (U = 272.5, $p = .028$). Therefore, all neuroimaging analyses were repeated in gender-matched subgroups anew (see Figs. 5 and S3). Furthermore, the groups differed on self-reported overall psychopathic ($t(33.1) = 3.89$, $p < .001$) and callous-unemotional (CU) traits ($t(56) = 3.47$, p=.001), with participants with CD scoring higher than TD adolescents on both measures.

3.2. Eye gaze behavior

Full-factorial analyses of the corrected eye gaze data (removing

Table 1
Group characteristics and clinical assessment of adolescents with a diagnosis of conduct disorder (CD) and typically developing controls (TD).

	CD	TD	*p* value
N	23	35	
Age (years)	16.7 (1.4)	16.6 (1.4)	.884
Verbal[b]	95.9 (16.8)	106.4 (9.6)	.010
Performance IQ	102.8 (13)	105.9 (11)	.343
Total IQ[b]	99.3 (12.9)	106.1 (8.1)	.031
Gender (m/f)[b,a]	14 / 9	10 / 25	.028
PDS[a]	4.7 (0.4)	4.9 (0.3)	.244
YPI (GM)	42.4 (12.7)	36.7 (7.7)	.058
YPI (CU)[b]	32.8 (7.5)	26.8 (5.6)	.001
YPI (II)[b]	40.6 (7.7)	31.3 (5.1)	<.001
YPI (total)[b]	115.8 (23.2)	94.8 (14.3)	<.001
Handedness (R/L)[a]	22/1	29 / 6	.147
CD-Onset (child/adolescent)	5/18	–	
	ADHD	26%	–
	Alcohol-dependency	4%	–
	Drug-dependency	26%	–

For all tests, mean scores and standard deviations (SD) are reported. YPI = Youth Psychopathic Traits Inventory. GM = Grandiose Manipulative dimension; CU = Callous Unemotional dimension; II = Impulsive Irresponsible dimension. CD = conduct disorder; TD = typically developing. PDS = pubertal developmental scale.

[a] Mann-Whitney Test (2-tailed).
[b] Significant group difference (p < .05).

blinks and head motion) on the duration of fixations revealed a significant interaction effect (region (eyes versus mouth) × emotion, $F(2,56) = 330.082$, $p < .001$). Follow-up t-tests on the time spent on the eye regions revealed that adolescents with a diagnosis of CD spent less time on the eye regions than their TD peers for neutral ($t(56) = -2,07$, $p = .043$) and fearful ($t(56) = -2,20$, $p = .032$) trials, but not for anger trials ($t(56) = -1,76$, $p = .083$). In contrast, no differences between adolescents with CD and those with TD were detected regarding the time spent on the mouth region of stimuli with neutral ($t(56) = 0,820$, $p = .415$), fearful ($t(56) = 0,833$, $p = .408$) and anger ($t(56) = -0,595$, $p = .554$) facial expressions, see Fig. 2. Full-factorial analyses of the corrected eye gaze data (removing blinks and head motion) on the number of fixations revealed a significant interaction effect (region (mouth versus eye region) × emotion, $F(2,56) = 264.653$, $p < .001$). Follow-up *t*-tests indicated that adolescents with CD compared to TD fixated significantly less on the eye regions of stimuli with neutral ($t(56) = -2,36$, $p = .022$) and fearful facial expressions ($t(56) = -2,46$, $p = .017$), but not angry faces ($t(56) = -1,95$, $p = .057$). Furthermore, adolescents with CD compared to TD fixated significantly less on the mouth region of stimuli with neutral ($t(56) = -2,34$, $p = .023$) and fearful facial expressions ($t(56) = -2,38$, $p = .021$), but not angry faces ($t(56) = -1,69$, $p = .096$). These findings were in line with investigation of the raw eye-tracking data (as provided in S1).

3.3. Eye gaze behavior and CU traits

Correlation analyses indicated no significant relationship between CU traits and eye gaze patterns for TD adolescents. For the CD group, however, a positive correlation existed for CU traits and fixations on the mouth region ($r(18) = 0.613$, $p = .004$) for all emotions. Post-hoc analyses indicated this is driven by neutral facial expressions ($r(18) = 0.661$, $N = 23$, $p = .002$). A similar trend existed for anger ($r(18) = 0.560$, $p = .010$) and fearful ($r(18) = 0.504$, $p = .023$) facial expressions, but failed to survive Bonferroni correction for multiple comparisons (adjusted *p*-level $p = .008$ for the six comparison tested).

3.4. fMRI data

Our full-factorial analyses within predefined regions of interest identified a significant main effect of group for the right anterior insula. Follow-up investigations revealed that this is explained by a significantly reduced activation for adolescents with a diagnosis of CD compared to their TD peers (Fig. 3, Table 2). No main effect of emotion or an interaction effect between group and emotion were observed.

3.4.1. Consideration of eye gaze behavior

When controlling for the duration of time spent on the eye regions, the overall significant main effect of group was reduced, see Table 2. An interaction term (eye gaze behavior by group) was included into the model to test the effect of eye gaze correction on the neuronal findings

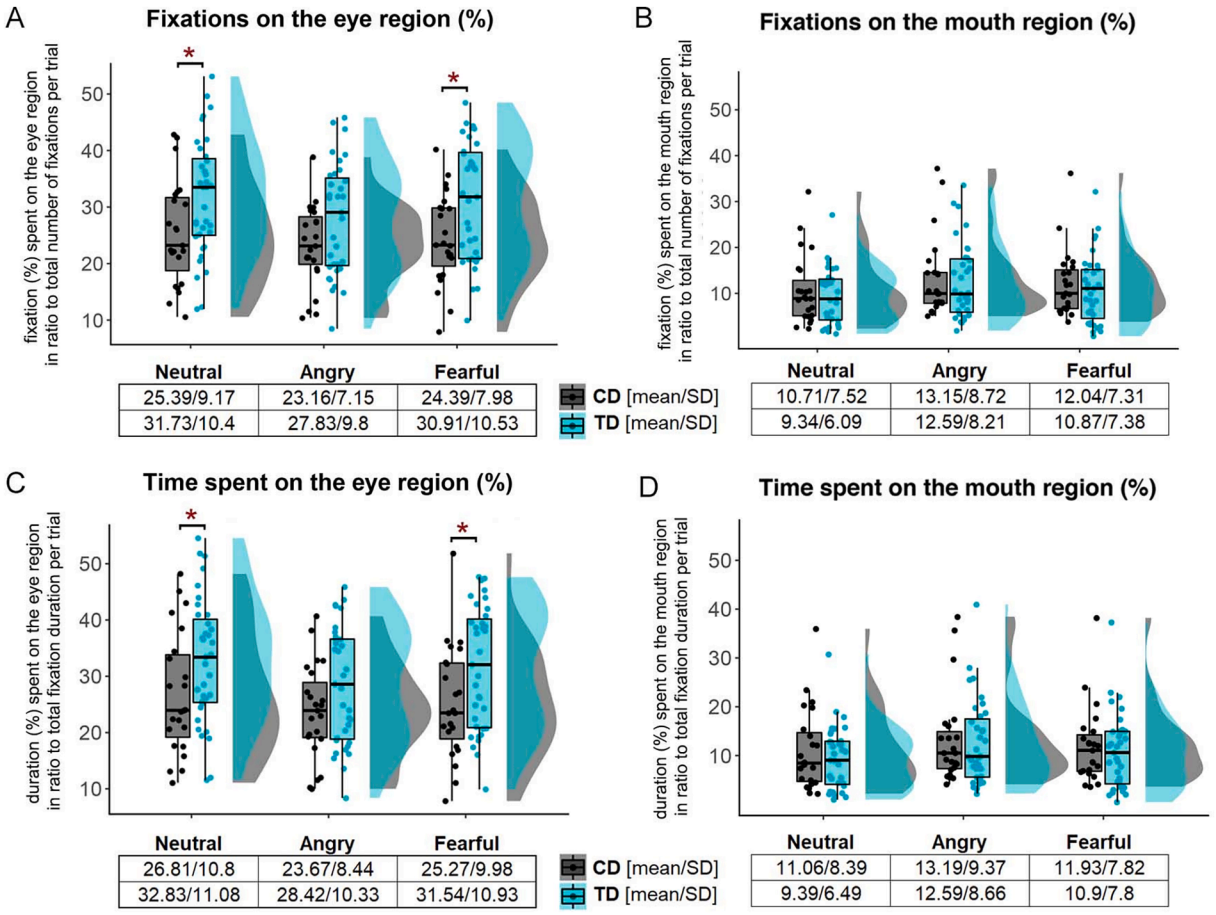

Fig. 2. Raincloud plots visualizing the eye gaze behavior of adolescents with conduct disorder (CD) and typically developing (TD) peers during functional neuroimaging (emotional face processing). Results demonstrate significant difference in the overall fixation percentage and time spent on the eyes but not the mouth region. More specifically, adolescents with a diagnosis of CD show a reduced fixation (A) and average percentage of time spent (C) on the eye region during neutral and fearful conditions when compared to TD participants. Fixations (B) and time spent (D) on the mouth region did not differ. Significant group differences are labelled with an asterisk (*).

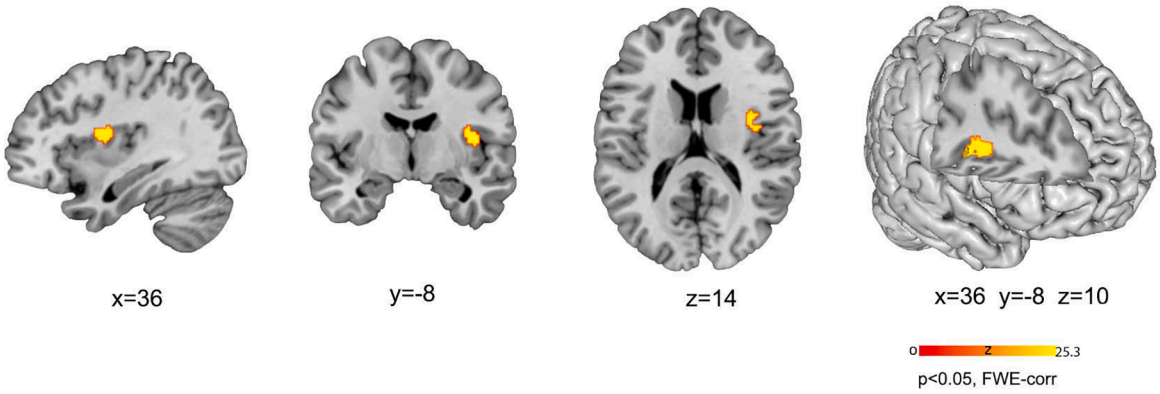

Fig. 3. Statistical parametric map (cluster-level, p < .05 FWE-corrected) displaying a main effect of group during facial emotion processing within the right insula: participants with conduct disorder (CD) had significantly reduced functional brain activation in anterior insula during emotional face processing when compared to typically developing (TD) adolescents.

Table 2
Peak activation report for emotional face processing (neutral, anger, fear) in CD and TD adolescents; with and without correcting for the fixation duration to the eye regions.

	Brain region	L/R	Vol	Local maxima			*p*-value	*F-value*	*Direction*
			(voxels)	x	y	z	(cluster-level, FWE $p < .05$)		(post-hoc)
Without correction for eye gaze behavior									
	ROI-Analysis								
	Main effect of group								
1	Insula	R	83	36	−4	16	0.030	25.33	CD < TD
	Whole-Brain Analyses								
	Main effect of group								
1	Postcentral, superior temporal gyrus, supramarginal gyrus	R	210	58	−20	18	0.040	36.60	CD < TD
2	Fusiform gyrus, hippocampus, lingual gyrus	L/R	2018	22	−48	−2	0.000	32.41	CD < TD
3	Inferior/middle occipitotemporal gyrus	L	595	−50	−76	0	0.000	30.60	CD < TD
4	Precuneus, cerebellum, lingual gyrus, posterior cingulate gyrus	L	814	−16	−50	0	0.000	25.32	CD < TD
5	Superior parietal gyrus, postcentral gyrus	R	342	44	−30	58	0.005	22.53	CD < TD
Corrected for eye gaze behavior									
	ROI-Analysis								
	Main effect of group								
1	Insula	*not significant at $p \geq 0.05$*							
		R	60	36	−4	16	0.050	21.11	CD < TD
	Whole-Brain Analyses								
	Main effect of group								
1	Fusiform gyrus, hippocampus, lingual gyrus, calcarine fissure	R	621	22	−48	−2	0.000	29.20	CD < TD
2	Inferior/middle occipitotemporal lobe	L	639	−50	−76	0	0.000	27.92	CD < TD
3	Inferior occipital lobe, lingual gyrus, calcarine fissure	L/R	393	14	−90	−6	0.002	27.90	CD < TD
4	Cerebellum	L	488	−10	−58	−4	0.001	22.77	CD < TD

All ×, y, z-coordinates represent local maxima in MNI space. TD = typically developing; CD = Conduct Disorder.

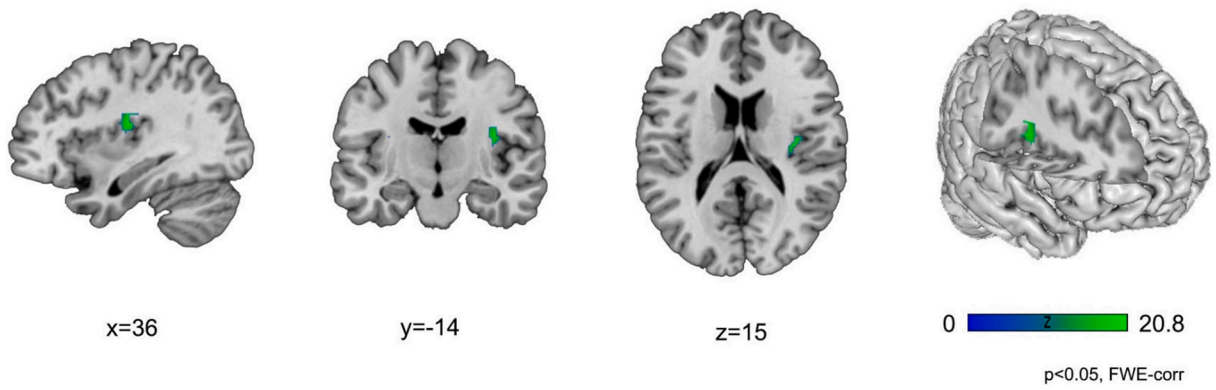

Fig. 4. Statistical parametric map (cluster-level, $p < .05$ FWE-corrected) displaying the interaction effect (eye gaze behavior by group) within the right insula.

by incorporating the corresponding regressors within the SPM design. A significant interaction effect between fixation duration on the eye regions and CD diagnosis was revealed during emotional face processing for the right insula, in line with our main group findings (Fig. 4). Follow-up analyses revealed that this effect was driven by a significant positive correlation of eye gaze behavior and neuronal activation in right anterior insula within the CD group only (see Table S2 within the supplement). To quantify the effect of eye gaze behavior on the hemodynamic response further, the averaged mean parameter estimates were extracted from the right insula cluster using the marsbar toolbox (http://marsbar.sourceforge.net). These scores were entered as a dependent variable into a stepwise multiple regression model assessing changes in R-square, with group status (TD/CD), covariates (gender, age and IQ), and fixation duration on the eye regions as independent variables (i.e., identical to the full-factorial design implemented in SPM). This analysis revealed that the overall model explained 13.4% of the variance in right insula hemodynamic response ($F(4,173) = 6.53$, $p < .001$). When adding eye gaze information, an additional 3.2% amount of variation was significantly ($p = .012$) explained, resulting in a total of 16.6% of variation explained by the new model ($F(5,173) = 6.68$, $p < .001$).

3.4.2. Post-hoc analyses: Impact of CU traits, ADHD symptoms, and CD severity.

In order to investigate the effects of CU traits, ADHD symptoms and CD severity on our findings, we extracted the averaged mean parameter estimates from the right insula cluster identified in the main effect of group using the marsbar toolbox (http://marsbar.sourceforge.net). These scores were entered as a dependent variable into a multiple regression model assessing changes in R-square for the entire group (CD and TD), with group status (TD/CD) and covariates (gender, age and IQ) identical to the main SPM model employed. However, CU traits, ADHD symptoms, and CD symptoms were now additionally added as independent variables. This analysis revealed that while group status was the most relevant factor to explain the neuronal findings (11.2% of the explained variance in insula activation; $p < .001$), CU traits explained an additional 2.5% ($p = .029$) of the variance. No significant effect of ADHD symptoms or CD severity to the model was observed. Follow-up partial correlation analyses between right anterior insula scores and CU traits in the CD and TD group individually indicated that this difference is driven by a positive correlation of CU traits and right insula scores within the CD group. More specifically, follow-up partial correlation analyses for the CD group only (including age, gender and IQ as covariates) using the right anterior insula scores as a dependent variable and CU-traits, ADHD symptoms, and CD symptoms as independent variables indicated a significant correlation between right anterior insula scores and CU traits ($r(64) = 0.347$, $p = .004$), but no significant correlations for insula scores and ADHD symptoms ($r(64) = 0.180$, $p = .149$) or CD ($r(64) = -0.061$, $p = .628$).

3.5. Exploratory analyses

3.5.1. Whole brain analysis

In addition to a priori defined ROI analyses, an exploratory whole-brain full-factorial analysis was conducted to assess novel areas previously not associated with emotional face processing. The full-factorial analysis identified five clusters of significant hypoactivation, where adolescents with a diagnosis of CD had decreased brain activation compared to their TD peers within the right postcentral/superior-temporal gyrus, right fusiform, bilateral occipital gyrus, and left cerebellum. After controlling for eye gaze behavior, one cluster (postcentral/superior temporal gyrus) no longer remained significant (Table 2).

3.5.2. Gender-matched group analysis

Previous evidence has indicated gender-specific trends for eye gaze behavior during emotional face processing in adolescents with CD (Martin-Key et al., 2018). Furthermore, gender-specific effects in the neural phenotype of CD exist (Smaragdi et al., 2017). Therefore, we further investigated a subsample of the whole group of 36 adolescents by matching for group status and gender, which (see Fig. 5 and Table S2) also resulted in a main effect of group ($p = .005$) for emotional face processing within right insula (CD < TD). When controlling for the duration of fixations on the eye regions the main effect of group no longer remained significant ($p = .207$).

4. Discussion

This study tests the functional brain correlates of emotional face processing in adolescents with conduct disorder (CD) compared to typically developing (TD) adolescents while considering concurrent in-scanner eye gaze behavior (i.e., fixation duration on the eye regions). We observed a main effect of group, based on reduced neuronal activation within the right insula during emotional face processing in adolescents with a diagnosis of CD compared to TD adolescents. There was no main effect of emotion or interaction effect between group and emotion, indicating that the brain correlates for emotional face processing were independent of the emotion presented. However, eye-tracking data revealed that adolescents with CD spent less time on the eye regions than TD adolescents for neutral and fearful facial expressions. Controlling for the time spent on the eye regions during emotional face processing attenuated the observed group differences (CD < TD) in right insula activation. Post-hoc analyses revealed that CU traits had a small, but significantly positive, effect on these insula findings, while ADHD comorbidity or CD severity did not contribute towards the observed findings.

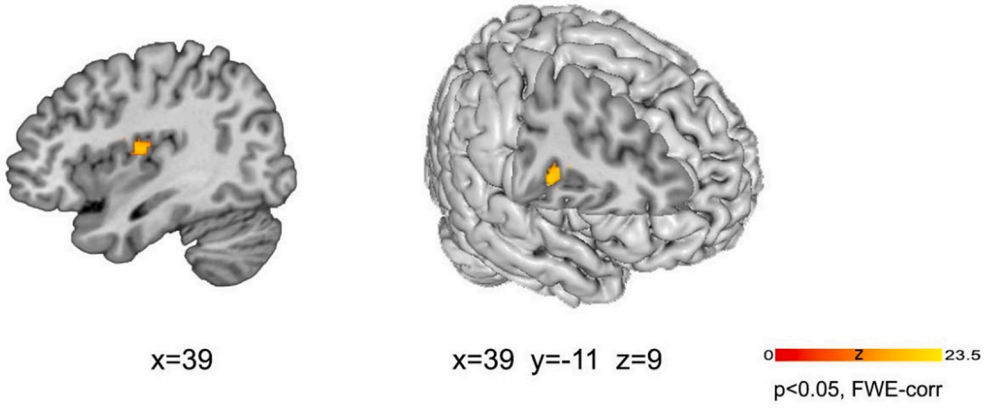

Fig. 5. Statistical parametric map (cluster-level p < .05 FWE-corrected) displaying a significant main effect of group for a gender-matched subgroup analyses. Main findings of a main effect of group within the right insula was replicated within the matched-gender subgroup.

Our main finding, insula hypo-responsivity during emotional face processing in adolescents with a diagnosis of CD, is in line with *meta*-analytical studies that reported both structural and functional insula alterations in adolescents with CD during emotion processing (Fairchild et al., 2019; Raschle et al., 2015; Rogers and De Brito, 2016; Sterzer et al., 2007). Prior studies including a similar design but targeting the insula as an a priori-defined region of interest, reported either hypo-activation within the left (Passamonti et al., 2010) or hyper-activation (Fairchild et al., 2014) within the right insula for adolescents with a diagnosis of CD. This directional discrepancy in insula findings might be caused by ADHD comorbidity. When controlling for ADHD symptoms findings of hyper-activation but not of hypo-activation diminished, suggesting that hyperactivation findings may be more strongly impacted by groups with higher ADHD scores (Fairchild et al., 2014). This further highlights the importance of controlling for ADHD comorbidity in samples with CD. The current study therefore also investigated possible ADHD effects on the observed insula findings. However, results indicated that the insula finding was largely unaffected by ADHD symptoms. Additionally, and in line with past studies (Fairchild et al., 2014; Passamonti et al., 2010), the here reported group differences in emotional face processing were independent of the emotion presented. This is in agreement with evidence suggesting that the insula is not necessarily involved in the processing of specific individual emotions (e.g., as suggested by studies indicating emotion specificity as for example (Cohn et al., 2013; Grosbras and Paus, 2006; Morris et al., 1998), but has a more general function. Since, the insula is commonly associated with social cognition, empathy and emotion processing in TD individuals it has been suggested that the insula play a generic role in the evaluation of emotional stimuli and the general production and regulation of affective states and interoceptive awareness (Craig, 2009; Fan et al., 2011; Phan et al., 2002; Phillips et al., 2003; Singer et al., 2009). Additionally, hyper-responsivity of the insula has been linked to post-traumatic stress disorder during processing of fearful and angry faces, indicating a role for exaggerated salience detection (Fitzgerald et al., 2018; Fonzo et al., 2010). The observed reduction in insula activity during emotional face processing in individuals with CD might therefore be linked to a weaker salience detection and insensitivity to affective stimuli, especially considering the insula's role in affective empathy (Fan et al., 2011). Such a model is substantiated by previous work that has linked functional and structural alterations of the insula with affective processing (Klapwijk et al., 2015; Lockwood et al., 2013; Rubia et al., 2009; Sebastian et al., 2012; Sterzer et al., 2007). More specifically, hypo-responsivity of the insula could be linked to decreased gray matter (i.e., thickness and folding), both common characteristics for adolescents with antisocial behavior within the insula (Fahim et al., 2011; Fairchild et al., 2011, 2013; Hyatt et al., 2012; Raschle et al., 2015; Rogers and De Brito, 2016; Sterzer et al., 2007), although not always observed (De Brito et al., 2009).

No differences in amygdala brain response during emotional face processing were identified in this study comparing groups of TD adolescents and adolescents with a diagnosis of CD. Amygdala dysfunction is one of the key characteristics in the symptomatology of conduct disorder (Blair, 2003; Fairchild et al., 2019; Raschle et al., 2015). The direction of amygdala response, however, differs between studies (Jones et al., 2009; Marsh et al., 2008; Passamonti et al., 2010; Sebastian et al., 2014; Viding et al., 2012; White et al., 2012), and is thought to be mediated by CU traits (Jones et al., 2009; Sebastian et al., 2014; Viding et al., 2012; White et al., 2012). Although, some studies failed to observe altered amygdala responsivity in adolescents with conduct disorder compared to TD peers during emotion processing (Fairchild et al., 2014; Lozier et al., 2014), as is in line with this study. Such discrepancies may be attributed to a variety of factors including the study designs, sample sizes, unbalanced or single gender studies, CU traits, age differences, or additional comorbidities included (Raschle et al., 2015). Nevertheless, dysfunctional amygdala has been linked to attention to the eye regions which causes impairments in facial expression recognition (Adolphs et al., 1994, 1995; Gamer and Buchel, 2009). CD adolescents included in the present analyses spent significantly less attention to the eye regions compared to the TD group, however, no differences in hemodynamic response were observed within bilateral amygdala during facial emotion processing. This was unexpected, however, two previous studies using a similar paradigm also reported no amygdala differences between adolescents with CD and their peers (Fairchild et al., 2014; Passamonti et al., 2010). However, an effect for neutral and sad faces was found when investigating each emotion separately (Passamonti et al., 2010).

4.1. Eye gaze behavior in adolescents with CD

Our analyses revealed that adolescents with CD spent less time (duration) looking at the eye regions of emotional faces (i.e., particularly on the eye regions of neutral and fearful facial expressions, but not of angry faces). In contrast, no differences between adolescents with CD and those with TD were detected regarding the time spent on the mouth region across all facial expressions. Furthermore, adolescents with CD showed significantly less numbers of fixations towards the eye and mouth regions compared to their TD peers during emotional face processing. This was particularly true for neutral and fearful facial expressions. Our findings are in line with previous behavioral studies stating a decrease of attention (e.g., shorter and less fixations) to the eyes of facial stimuli for adolescents with CD or antisocial tendencies (Bours et al., 2018; DADDS et al., 2008; Martin-Key et al., 2018). The eyes play an important role during the recognition and processing of facial expressions and are crucial in everyday social interactions. Therefore, a lack of focus on the eye region could explain the emotion recognition impairments and associated behavioral deficits (e.g., antisocial behaviors) frequently observed in adolescents with a diagnosis of CD (Fairchild et al., 2010, 2009; Martin-Key et al., 2018). This has been underscored by research demonstrating that redirecting the attention to the eye can reduce facial-expression recognition deficits, particularly for fearful expressions in antisocial adolescents (Dadds et al., 2006, 2008). Although one may hypothesize that the present findings can serve as an explanation for the observed emotion recognition impairments in adolescents with CD (Bons et al., 2013; Fairchild et al., 2009, 2019), this remains to be investigated further using paradigms that can directly link eye gaze with emotion recognition.

The present study demonstrates that controlling for the fixation duration spent on the eye region during emotional face processing diminishes differences in right insula activation when comparing adolescents with CD to their TD peers. To the best of our knowledge, this is the first study that shows a direct relation between insula activation and concurrent assessment of eye gaze behavior in a sample with CD. One study, however, found increased amygdala activation when redirecting eye gaze of adolescents with CD and low levels of CU traits to the eye region of fearful facial expressions (Sebastian et al., 2012). This is in line with a case-study of a patient with bilateral amygdala damage, where fear-recognition impairments disappeared after allocating attention to the eye region of fearful facial expressions (Adolphs et al., 2005). However, both these studies have targeted bilateral amygdala as predefined regions of interest. It is consequently unknown whether insula activation may have been altered likewise. While there is only limited evidence existing to date, our results add evidence to the hypothesis that alteration in functional brain responses in adolescents with CD during emotional face processing can partly be explained by attentional mechanism as reflected in a missing gaze allocation to the eye region.

We observed a positive correlation between CU traits and number of fixations directed to the mouth, but not the eye region. Past studies have observed fewer fixations to the eye, but not mouth, region in adolescents with CD (Bours et al., 2018; Martin-Key et al., 2018) and TD adolescents with high levels of CU- or psychopathic traits (Blair et al., 2001; Dadds et al., 2008; Stevens et al., 2001). Different types of analyses approaches (e.g., across the whole sample or subgroups only) or paradigms (e.g., implicit or explicit emotion processing) could explain these

discrepancies in CU traits effects. Implicit emotion processing tasks have the advantage of ensuring unbiased, naturalistic eye gaze behavior by avoiding an explicit focus towards the emotional content. However, such differences may explain opposing observations across studies.

5. Limitations

Several limitations should be mentioned. Firstly, the group of adolescents with CD presented with comorbid disorders including substance (26%) and alcohol (4%) dependency, as well as attention-deficit hyperactivity disorder (ADHD; 26%). This is in agreement with the most commonly reported comorbidities observed in CD samples (Fairchild et al., 2019; Loeber et al., 2000). Nevertheless, attentional mechanism may crucially impact eye gaze behavior. We employed post-hoc analyses demonstrating that ADHD symptoms did not explain any additional variance to our main group findings. This is in line with past neuroimaging studies (Airdrie et al., 2018; Passamonti et al., 2010; Sebastian et al., 2014). Secondly, adolescents with CD had a lower overall IQ, which is a key characteristic commonly reported for CD (Fairchild et al., 2013; Menks et al., 2017). In the present analyses intelligence was added as a covariate of no interest to account for this difference. Thirdly, the number of clinical cases tested is small (N = 23). Adolescents with a diagnosis of CD are challenging to recruit and test, particularly when using a combination of neuroimaging and eye-tracking methods that require participants to stay very still over a longer period of time. The resulting overall group size can is small, and results must be interpreted with caution. A larger-scale replication is recommended. Fourthly, this study has not included an emotion recognition task, therefore no direct link can be made between emotion recognition deficits and eye gaze. Nevertheless, our implicit emotion processing task allowed the measurement of natural eye gaze behavior (i.e., non-directed and unbiased attention) towards emotion face stimuli). Lastly, studies have suggested gender-specific differences in the neural correlates of CD (Fairchild et al., 2013; Smaragdi et al., 2017). Consequently, we also controlled for gender in the present study. Furthermore, additional analyses using only a subsample of all participants which was matched for gender confirmed the main findings and indicated that gender differences are unlikely to explain the observed results. However, due to the small number of individuals a direct investigation of gender was not possible and we advise that this needs to be examined in the future using larger cohorts and a higher proportion of female participants.

6. Conclusion

Our results point to a reduced anterior insula activation in adolescents with CD compared to TD peers during emotional face processing, which was attenuated when eye gaze behavior was accounted for. More specifically, adjusting for the time spent on the eye regions affected insula activation in the CD group and reduced the previously observed group differences. These findings show that eye gaze behavior affects functional brain correlates associated with emotional face processing in CD and posits a possible explanation for the emotion recognition deficits and associated socially inadequate behaviors reported in adolescents with CD (Fairchild et al., 2014, 2019). A better understanding of the mechanism underlying emotion processing deficits will aid in the development of potential intervention programs for conduct disorder (Kersten et al., 2016).

CRediT authorship contribution statement

Willeke Martine Menks: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft. **Lynn Valérie Fehlbaum:** Investigation, Project administration, Writing - review & editing. **Réka Borbás:** Investigation, Visualization, Writing - review & editing. **Philipp Sterzer:** Methodology, Writing - review & editing. **Christina Stadler:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Nora Maria Raschle:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Validation, Supervision, Funding acquisition.

Acknowledgements

We thank the adolescents, families and institutions that took part in our studies as well as the radiology team at the University Hospital in Basel.

Funding

This study was funded by the Swiss National Science Foundation (Christina Stadler; Grant No. 105314M_150282). NMR was funded by the Jacobs Foundation (Grant no. 2016 1217 13) and the University Hospital of Basel (Junior Researchers Research Fund). Preliminary data from this study were presented at the 6th Annual Flux Congress in Berlin (2018). Dr. Menks, Dr. Fehlbaum, Mrs Borbás, Prof. Sterzer, Prof. Stadler and Prof. Raschle reported no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102519.

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