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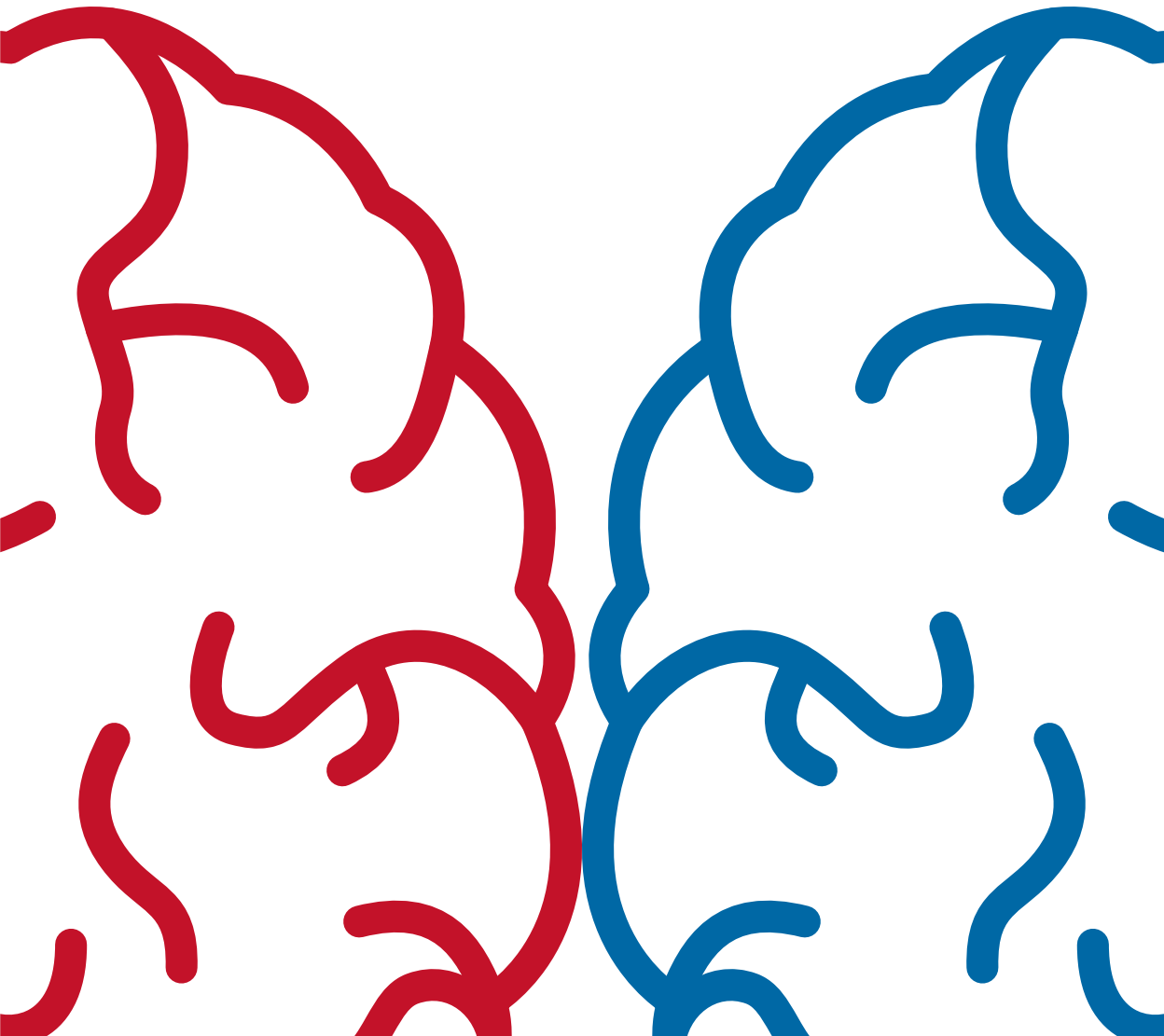

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1 General introduction

Parts of this chapter are based on:

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One of the most distinctive capacities of human beings is our ability for highly complex and flexible social interaction with other humans. From the day we are born, we humans seem to have a preference for social objects such as face-like patterns over nonsocial objects (Valenza et al., 1996) and for biological motion over random motion (Simion et al., 2008). Throughout subsequent development, a diverse array of abilities emerges and improves that enable us to successfully engage in social interaction (Frith & Frith, 2003; Happe & Frith, 2014; Tomasello et al., 2005). Although much of these abilities are used without conscious thoughts or deliberation during social interactions, they likely require vast computational demands to navigate our highly social environments (Frith & Frith, 2006). Indeed, a large proportion of the human brain is involved in social interaction and understanding other people (Blakemore, 2008).

Since adequate social functioning may seem such a natural and obvious part of human nature, all the more striking it is when someone acts socially awkward or regularly violates social norms. Not surprisingly, many psychiatric and neurological disorders are characterized by notable impairments in social functioning (Kennedy & Adolphs, 2012). A prominent disorder in which social-emotional deficits are regarded core deficits is autism spectrum disorder (ASD; American Psychiatric Association, 2013; Schultz, 2005), whereas interpersonal difficulties also characterize those with conduct disorder (CD; American Psychiatric Association, 2013; Dodge, 1993; Green et al., 2000). However, difficulties in social interactions in ASD and CD are likely underpinned by qualitatively different neurocognitive deficits (Bird & Viding, 2014; Blair, 2008). Understanding the differences and similarities underlying their social-emotional dysfunction provides more fine-grained knowledge of both disorders and of the social-emotional processes involved. This is of vital importance given the detrimental effects of the social difficulties for those individuals with the disorder themselves, their families, and society. The main goal of the current thesis is to investigate social-emotional dysfunction in both ASD and CD from a cognitive neuroscience perspective (i.e., studying cognitive mechanisms and associated neural processes and structures; Ochsner & Lieberman, 2001). First, we directly compared both groups to test the hypothesized dissociable deficits in *understanding* other's emotions in ASD

in contrast to deficits in *feeling* other's emotions in CD. Second, we examined the neural processes at the level of *social interactions* in ASD and in CD, which has been overlooked by prior work, by studying interactive decision-making in response to other's emotions. In this chapter I will give a short overview of prior work, which will form the background of the empirical studies presented in this thesis.

Social-emotional deficits in ASD and CD

ASD is a pervasive neurodevelopmental disorder characterized by difficulties in reciprocal social interactions and communication, and a restricted repertoire of behavior, activities or interests (American Psychiatric Association, 2013). Difficulties in apprehending other's emotions and behavior in ASD have been explained by impairments in the ability to represent other people's mental states (i.e., mentalizing or theory of mind) (Baron-Cohen et al., 1985; Hill & Frith, 2003; Kaland et al., 2008), by a possible deficit in the putative human mirror neuron system (Ramachandran & Oberman, 2006; but see for a critique Hamilton, 2013) and by social motivational deficits (Chevallier et al., 2012). Apart from different theoretical orientations involved, these deficits in mentalizing, emotion processing, and social motivation all seem to be associated with alterations in brain areas relevant for social-emotional functioning in ASD compared to neurotypical individuals (Di Martino et al., 2009; Dichter et al., 2012; Fishman et al., 2014; Frith, 2001; Pelphrey et al., 2011; Philip et al., 2012; White et al., 2014b).

CD is a mental disorder of childhood and adolescence in which the rights of others or basic social rules are violated. Symptoms of CD include aggression, vandalism, theft, deceitfulness, truancy, and running away from home (American Psychiatric Association, 2013). While difficulties in emotion and social processing are involved in CD generally (Dodge, 1993; Happe & Frith, 1996; Herpertz et al., 2005), social-emotional difficulties such as diminished empathy are most pronounced in a subgroup of antisocial and aggressive youths with high psychopathic traits (Blair et al., 2014; Decety & Moriguchi, 2007). This group has received

increasing attention from researchers in the past decades, with research being mostly focused on a specific component of psychopathy, namely callous-unemotional (CU) traits (e.g., lack of guilt and empathy, callous use of others for one's own gain). Antisocial adolescents with high CU traits are thought to represent a specific group within antisocial and CD youth with a distinct neurocognitive profile characterized by low levels of fear and anxiety, blunted emotional reactivity and insensitivity to punishment (Blair, 2013; Frick et al., 2014). Moreover, it is suggested that antisocial individuals with high levels of CU traits exhibit a pattern of more severe and chronic antisocial behavior than those with low levels of these traits (Frick et al., 2005). Based on this research, CU traits have been added as a specifier for CD diagnosis (labeled "with limited prosocial emotions") to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). A growing body of research indicates alterations of brain structure and function involved in social-emotional processing in CD in general (Baker et al., 2015; Decety et al., 2009; Huebner et al., 2008; Sterzer & Stadler, 2009) and CD with high CU traits specifically (Alegria et al., 2016; Blair et al., 2014).

Given the observed difficulties in understanding the emotions of others in ASD and CD (particularly in individuals with CD and CU+; henceforth CD/CU+), both disorders have been regarded as disorders of empathy (Baron-Cohen & Wheelwright, 2004; Frick & Ellis, 1999; Gillberg, 1992; Lovett & Sheffield, 2007). However, the empathy deficits in ASD and CD/CU+ are qualitatively different and opposing. Cognitive impairments in understanding others are thought to underlie social difficulties in ASD, whereas affective impairments in resonating with the feelings of others are hypothesized to underlie social difficulties in CD/CU+ (Blair, 2008; Blair, 2005; Jones et al., 2010). Support for these dissociable empathy deficits has been found in studies of ASD and CD/CU+ separately and also in the few studies that have directly compared these disorders, but no study has yet directly compared the neural mechanisms of empathic processing in these groups.

Cognitive and affective empathy in ASD and CD(CU+)

The concept of empathy rests on a rich history of theoretical and empirical attention from different research traditions.The word empathy was coined by Titchener (1909) in order to translate the German term *Einfühlung*; literally "feeling into". The German term was previously used by Lipps (1907) to describe the resonance phenomenon through which the perception of someone else's emotion directly activates the same emotion in the perceiver (Jahoda, 2005; Preston & de Waal, 2002).To give an overview of the research traditions that have subsequently studied different forms of empathy is beyond the scope of this thesis. I will only briefly summarize recent conceptualizations of the term that are relevant for the discussion of empathy in ASD and CD/CU+.

Although many definitions of empathy exist (for an overview of at least eigth "things called empathy" see Batson, 2009), in cognitive neuroscience it is broadly regarded as the ability to share and understand the feelings of other people (Bernhardt & Singer, 2012). Usually it is further divided into affective (e.g., shared affect, emotional resonance) and cognitive (e.g., emotion recognition, perspective-taking, self-other distinction) aspects (Decety & Jackson, 2004; Shamay-Tsoory et al., 2009).Affective empathy refers to a person's emotional response to the affective state of another individual and the sharing of emotions. Cognitive empathy refers to the capacity to represent what other people feel (Shamay-Tsoory et al., 2009) or more broadly to represent their mental states (Blair, 2005; Zaki & Ochsner, 2012). Closely related to cognitive empathy is theory of mind or mentalizing, especially when it refers to the capacity to attribute *emotions* to other people (Sebastian et al., 2012a; Shamay-Tsoory et al., 2010). Finally, emotion recognition is considered an important component of cognitive empathy, as some minimal recognition of other's emotions seems necessary for correctly understanding other's feelings (Bons et al., 2013; Decety & Jackson, 2004; Schulte-Ruther et al., 2014).

Lack of empathy has been considered a hallmark of ASD since the condition was first described by Kanner (1943), who proposed that autistic children were born with an inability to form affective contact with other people. Hans

Asperger, who at the same time described the disorder, also wrote being struck by "eines ausgesprochenen Gefühlsdefektes" (a distinctive emotional deficit) in children with ASD (Asperger, 1944; English translation: Asperger & Frith, 1991). Subsequently, impairments in empathy have been postulated as a characteristic of ASD by other researchers (Baron-Cohen & Wheelwright, 2004; Gillberg, 1992; Wing, 1981). However, most of the evidence suggests that problems in empathy in ASD mainly concern cognitive rather than affective aspects of empathy. Some have even suggested a more pronounced empathy imbalance in ASD characterized by excessive affective and decreased cognitive empathy, possibly leading to emotional distress when seeing other's suffering (Smith, 2009). By now, deficits, and at the least a developmental delay in cognitive empathy have been documented extensively in ASD (e.g., Baron-Cohen et al., 1985; Boucher, 2012; Castelli et al., 2002; Frith, 2001; Kaland et al., 2008; Senju et al., 2009) and many studies have reported on problems in recognizing other's emotions in ASD (Adolphs et al., 2001; Hobson, 1986; Lozier et al., 2014; Schultz, 2005; Uljarevic & Hamilton, 2013).

While there is some evidence for decreased affective empathy in ASD as measured by self-report (Lombardo et al., 2007) and by a decreased embodiment of others' pain (Minio-Paluello et al., 2009), most studies suggest affective empathy is intact in ASD (Bird et al., 2010; Blair, 1999; Dziobek et al., 2008; Fan et al., 2014; Hadjikhani et al., 2014; Rogers et al., 2007). In contrast, CU traits involve a lack of empathy characterized by more deficits in affective rather than cognitive empathy. Early descriptions of psychopathy (of which CU traits form the affective component) have emphasized the shallow affect characterizing those with psychopathic traits (Cleckley, 1976), and callousness / lack of empathy is explicitly stated in Hare's core criteria for psychopathy (Hare, 1980). Later, others hypothesized that impairments in affective empathy play a more important role than impairments in cognitive empathy in CD/CU+ (Blair, 2005), in line with the notion that feeling an aversive emotional signal in reaction to another person in distress helps to inhibit aggressive and violent behavior (Blair, 1995; Miller & Eisenberg, 1988). Thus, CU+ is likely associated with less compassion for suffering of others, resulting in the absence of a barrier to use violence and to commit crimes that result in harm to others. Studies assessing affective empathy in youth with CU+ have consistently

found behavioral and neural deficits in affective reactions towards others. Using emotional photographs and film clips and measures of vicarious responses, such as heart rate and brain activity, several studies have shown reduced self-reported and physiological responses to other's distress in CD/CU+ compared to typically developing controls (Anastassiou-Hadjicharalambous & Warden, 2008; de Wied et al., 2012; Lockwood et al., 2013b; Marsh et al., 2013). Furthermore, emotion recognition in CD/CU+ does not seem to be impaired in general, but only specifically for recognizing distress cues such as fear and sadness (Marsh & Blair, 2008).

Neural mechanisms of empathy

The neural correlates of cognitive empathy and mentalizing have been studied using a variety of tasks, ranging from classical false belief tasks to strategic use of mental state information in social interaction games (Schaafsma et al., 2014; Schurz et al., 2014). In these tasks, participants are critically required to represent the mental states and perspectives of other persons (Frith & Frith, 2003). At least two core 'social brain' regions consistently activated during mentalizing are the temporoparietal junction (TPJ) and the medial prefrontal cortex (mPFC) (Schurz et al., 2014; van Overwalle & Baetens, 2009). It is thought that the TPJ has an important role in reorienting or switching between one's own perspective and that of another person, allowing representation of other's mental states in the mPFC (Amodio & Frith, 2006; Krall et al., 2015). Neuroimaging research has revealed abnormal brain responses in ASD compared to controls in the mPFC and TPJ during cognitive empathy and mentalizing (Castelli et al., 2002; Kana et al., 2014; Lombardo et al., 2011; Pelphrey et al., 2011; Wang et al., 2007; White et al., 2014b). Furthermore, in ASD these regions also show structural alterations (DeRamus & Kana, 2015) and functional connectivity between these regions was shown to be reduced (Castelli et al., 2002; Kana et al., 2014; Kana et al., 2015). In contrast, groups with CD/CU+ were shown to activate the mPFC and TPJ normally during mentalizing (O'Nions et al., 2014; Sebastian et al., 2012b), although less activation in the TPJ has also been reported in CD during social decision-making (van den Bos et al., 2014).

Brain regions involved more specifically in emotion recognition include orbitofrontal and insular cortices and the amygdala, which are hypothesized to link perceptual representations of the face to the retrieval of knowledge about the observed emotion (Adolphs, 2002; Lindquist et al., 2012). In ASD, neuroimaging studies of emotion recognition have rather consistently showed a diminished response of the fusiform gyrus during face perception (Greimel et al., 2010; Schultz, 2005). Altered amygdala responses have also been reported frequently, mostly suggesting decreased amygdala responses in ASD in implicit emotional face tasks (e.g., Ashwin et al., 2007; Pelphrey et al., 2007; Wang et al., 2004). However, no differences in amygdala responses are usually found between ASD and control groups when participants are explicitly instructed to attend to the emotions (Harms et al., 2010; Piggot et al., 2004).

Neuroimaging studies of CD/CU+ have shown abnormalities that are consistent with the idea of an affective deficit in processing other's emotions. Affective empathy, in which one resonates with someone else's emotion, is often studied using experimental paradigms in which participants observe others in distress or pain. The rationale behind this method is that vicariously experiencing distress of others partly activates the neural networks involved in feeling pain or distress ourselves (Singer & Lamm, 2009). When assessing spontaneous neural activity to distress cues such as fear and sadness, overlap has also been shown in neural circuits involved in observing and experiencing emotions such as the insula, anterior cingulate cortex (ACC), and amygdala, suggesting other's emotions are shared via some form of simulation (de Vignemont & Singer, 2006; Goldman, 2006; Goldman & Sripada, 2005). Adolescents with CD/CU+ show reduced amygdala responses to fearful facial expressions compared to typically developing (TD) peers (Jones et al., 2009; Viding et al., 2012; White et al., 2012), as well as reduced functional and structural coupling between the amygdala and the orbitofrontal cortex (Breeden et al., 2015; Marsh et al., 2008).

Direct comparisons of ASD and CD(CU+)

As described above, the theoretical notion of ASD and CD/CU+ (and psychopathy) as disorders of cognitive and affective empathy respectively (Blair, 2008; Blair, 2005; Frith, 2012; Gray et al., 2010; Nichols, 2001) has been supported by several experimental findings in these disorders compared to controls. More robust evidence for separate empathic deficits has been derived from behavioral studies directly comparing these disorders (Jones et al., 2010; Schwenck et al., 2012) and from testing psychopathic and autistic traits in community samples (Lockwood et al., 2013a). So far, one neuroimaging study compared cognitive empathy between ASD and CD/CU+, finding that adolescents with ASD displayed reduced responses in the mPFC compared to CD/CU+ adolescents and controls, whereas no different brain responses were found between the CD/CU+ group and controls during the same task (O'Nions et al., 2014).

Thus, studies focusing on ASD and CD/CU+ separately and the few studies directly comparing these disorders have found dissociable deficits in cognitive and affective empathy and associated brain responses. However, a direct comparison between these two groups is still lacking. This is unfortunate as such a comparison will more precisely uncover both *differences* and *commonalities* in empathic processing and social understanding in ASD and CD/CU+ without relying purely on self-report. We therefore examined the neural correlates of two different processes involved in empathy in youth with ASD, youth with CD/CU+ and TD controls using an explicit empathy task (**chapter two)**. This allowed us to more precisely pinpoint differences in the neural correlates of empathy in ASD and CD/CU+ by aligning parameters that usually differ between studies, such as the experimental task, questionnaires and scanner characteristics. In addition, studies comparing ASD and CD/CU+ have thus far focused on behavior (Jones et al., 2010; Schwenck et al., 2012) and brain functioning (O'Nions et al., 2014), and not on brain structure and connectivity. Since white matter connections are crucial for linking the brain regions involved in social-emotional processes into integrated neural circuits resulting in adequate social behavior (Ameis & Catani, 2015; Kennedy & Adolphs, 2012), we also explored white matter microstructure in ASD versus CD/CU+ (**chapter three**).

The neuroscience of social interactions

Research on social-emotional functioning in developmental psychopathology has traditionally used self- and parent-reports or experiments using hypothetical scenarios. Likewise, in most of the studies conducted within the emerging field of social cognitive neuroscience participants are required to mainly observe stimuli or react upon those stimuli. For example, in the studies described in previous sections a wide range of tasks is used in which participants had to look at emotional pictures (Greimel et al., 2010; Marsh et al., 2013) and videos (Castelli et al., 2002) or had to read vignettes about social situations (Sebastian et al., 2012b; Wang et al., 2007). One of the shortcomings of these approaches is that they do not take into account the interactive nature of social exchange, which is one of the defining features of social interaction (Frith & Singer, 2008; Gummerum et al., 2008; Sharp, 2012). Furthermore, responding towards others involves different cognitive processes than merely observing others' behavior (Schilbach et al., 2013). Along similar lines, it has been argued that individual differences in empathy mainly become apparent when people are required to act in a situation in which someone else is harmed as opposed to merely observing such a situation (Will & Klapwijk, 2014). One of the approaches that has been employed to study social decision-making in an interactive context is the use of game theoretical tasks derived from experimental economics (Rilling & Sanfey, 2011). In these tasks two or more decision makers are involved and simple exchanges are made with consequences for both players. These tasks can be used to study a range of behaviors such as trust, fairness, altruism, and social norm compliance, which might in turn be influenced by individual variations in abilities to mentalize and empathize (Glimcher et al., 2009; Singer, 2009).

Economic games used to study social behavior have the advantage that they model interactive elements of social exchanges in combination with structural simplicity fitted for use in neuroimaging experiments. These games are also rather easy to understand for participants, whilst being compelling for them because of the real (monetary) consequences involved for participants (Rilling & Sanfey, 2011). For example, decisions about fairness can be studied using Dictator or

Ultimatum Games. In the Dictator Game (Kahneman et al., 1986), one player divides an amount of money between oneself and another player. The other player is forced to accept this – the dictator's – offer; hence the allocator does not need to consider whether a low offer will be rejected. Choices in this game are therefore thought to reflect pure altruistic or fairness motives (Camerer & Fehr, 2004). In the Ultimatum Game, however, sharing is also motivated by strategic motives as the allocator's offer can be accepted or rejected by the second player. In case of acceptance the stake is shared as proposed but when the second player rejects the offer both players go empty-handed (Güth et al., 1982). Studies utilizing these games to study the brain regions involved in social decisions have suggested that various psychological mechanisms are involved (Rilling & Sanfey, 2011; Ruff & Fehr, 2014). For example, fair proposals in the Ultimatum Game trigger reward related brain regions, whereas unfair proposals might lead to an emotional response associated with the insula and a regulatory response in the lateral PFC (Baumgartner et al., 2011; Güroğlu et al., 2010; Sanfey et al., 2003; Weiland et al., 2012). The involvement of the mPFC and TPJ during other economic games has further led to assume an important role for mentalizing during reciprocal exchange (Frith & Singer, 2008; McCabe et al., 2001; van den Bos et al., 2009).

Economic games have been used for studying different behaviors in various mental disorders, such as generosity in psychopathy (Koenigs et al., 2010), mentalizing in social anxiety disorder and ASD (Sally & Hill, 2006; Sripada et al., 2009) and trust in borderline personality disorder and psychosis (Fett et al., 2012; King-Casas et al., 2008). Interestingly, another line of research mainly rooted in social psychology has emphasized the importance of interpersonal effects of emotions in social exchange (Keltner & Haidt, 1999; van Kleef et al., 2010). In their most basic description, these social-functional theories hold that emotional expressions of others provide information to observers, which may influence their behavior (van Kleef, 2009). Indeed, using simple bargaining games, it has been shown in healthy populations that emotions expressed by others heavily influence social decisions (van Kleef et al., 2010). Although both ASD and CD are thought to have impairments in processing other's emotions or in integrating emotional contextual cues into their decision-making (Adolphs et al., 2001; De Martino et al., 2008;

Sebastian et al., 2012b), prior studies have not yet focused on the role of emotions in social interactions in these disorders. We therefore examined the neural processes involved in social decisions in response to other's emotions in ASD and in CD. This paradigm assesses participant's choices in a Dictator Game after receiving written emotional reactions from a peer (depicting disappointment, anger, or happiness) to a previous unfair offer. In **chapter four and five**, we report on functional magnetic resonance (fMRI) studies in which we used this paradigm in boys with CD (with high and low CU traits) and boys with ASD and compared them against TD boys.

The BESD study

The empirical studies reported in this thesis were part of the "BESD" (brain, empathy, and social decision making) study. For this study, data was collected between March 2013 and November 2014 from a total of 114 male participants between 15 and 19 years old: 54 boys with CD, 23 boys with ASD, and 37 TD boys. We recruited a higher amount of CD boys in order to be able to enroll a reasonable number of boys with CU+. Most of the previous neuroimaging research on CD has included general population boys with conduct *problems* and CU+, hence limiting the generalizability of these results to seriously antisocial adolescents with conduct *disorder*. Therefore, we took effort to recruit aggressive CD youths from a juvenile justice institution (Forensisch Centrum Teylingereind) and an outpatient forensic psychiatry clinic (Palmhuis de Jutters). Participants in the ASD group were recruited from specialized child psychiatric centers providing both inpatient and outpatient care for persons with ASD (Curium-LUMC, Centrum Autisme Rivierduinen). Only male adolescents were recruited because of the higher prevalence of males in both ASD and CD. The age range was restricted to 15-19 years old to assure that most participants had passed puberty, which also decreased the variance associated with a broader adolescent age range.

After being thoroughly screened for participation (see empirical chapters for details), main study parameters consisted of several different noninvasive

neuroimaging parameters. Scanning took place at the Leiden University Medical Center. Functional MRI was used to study neural responses during an explicit empathy task and during a repeated Dictator Game with an emotion manipulation. Using fMRI, brain activity can be measured indirectly through the local magnetic properties of the blood carried to particular brain regions. This results in differences in the blood-oxygenation-level-dependent (BOLD) signal intensity that can be measured in relation to a particular psychological process (Logothetis, 2008). Furthermore, we administered resting-state fMRI, a task-free form of fMRI in which spontaneous fluctuations in brain activity are measured to perform functional connectivity analyses (see for results in the current CD group Aghajani et al., 2016; Aghajani et al., 2017). Structural MRI was assessed by means of an anatomical high-resolution image to register the fMRI images unto. Furthermore, diffusion tensor imaging (DTI) data was collected, which permits noninvasive visualization of brain white matter architecture.

Aims and outline of the thesis

The aim of this thesis was to directly compare the 'social brains' of adolescents with either ASD or CD and to examine the neural processes involved in acting upon other's emotions in these disorders. We investigated this from multiple levels: studying brain activity during social decisions in response to emotions (separately for the clinical groups compared to controls), comparing brain activity between ASD, CD/CU+ and TD during basic emotion processing to compare cognitive and affective aspects of empathy, and comparing white matter tracts that may underlie social-emotional processing between ASD, CD/CU+ and TD.

Chapter two describes an fMRI study that compared youth with ASD, youth with CD/CU+, and TD youths on cognitive and affective aspects of empathy using an emotional face task. The study presented in **chapter three** assessed differences in connectivity reflected by white matter microstructure using diffusion tensor imaging (DTI) in boys with ASD, boys with CD/CU+, and TD boys. The following two empirical chapters describe experiments used to examine the neural mech-

anisms underlying social decisions in response to explicitly expressed emotions of others. In **chapter four**, we investigated behavioral and brain responses to communicated emotions of others in aggressive, criminal justice-involved boys with CD (regardless of CU traits) compared with TD boys. Using the same paradigm, **chapter five** describes a study comparing behavioral and brain responses to communicated emotions of others in boys with ASD and TD boys. Finally, in **chapter six**, main findings of the empirical chapters are summarized and implications and future directions are discussed.

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

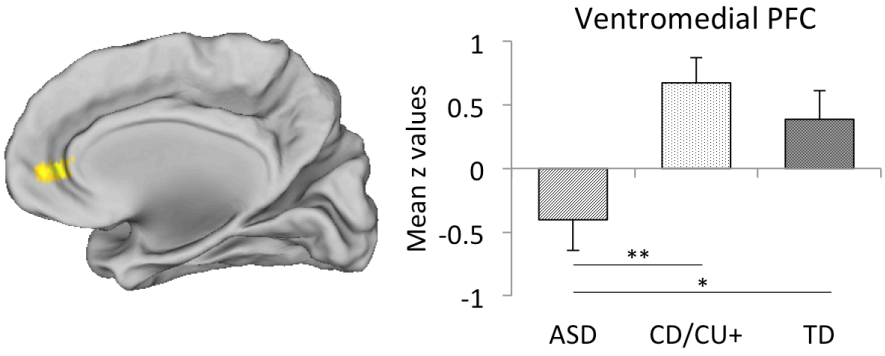

Figure 1. *Significant group differences in the ventromedial prefrontal cortex for the other > control contrast (emotion recognition) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD group showed reduced responses in this area compared to the CD/CU+ and TD groups (* = p <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

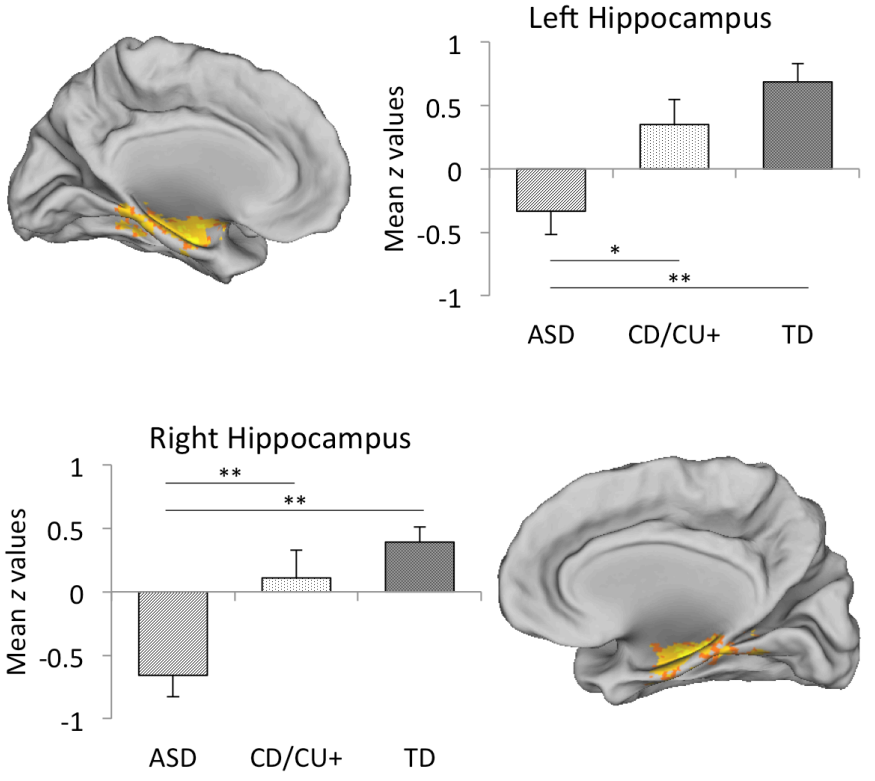

Figure 2. *Significant group differences in the left and right hippocampus for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD group showed reduced responses in these areas compared to the CD/CU+ and TD groups (* = p < .05;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

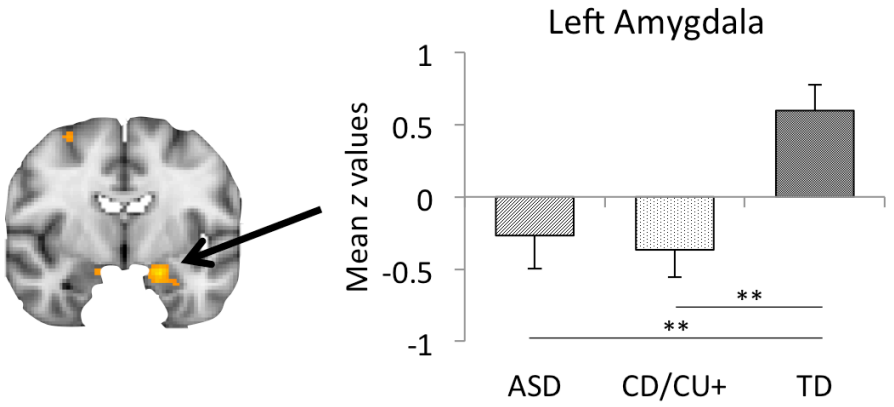

Figure 3. *Significant group differences in the left amygdala for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the ASD and CD/CU+ groups showed reduced responses in this area compared to the TD controls (* = p < .05; ** = p < .005).*

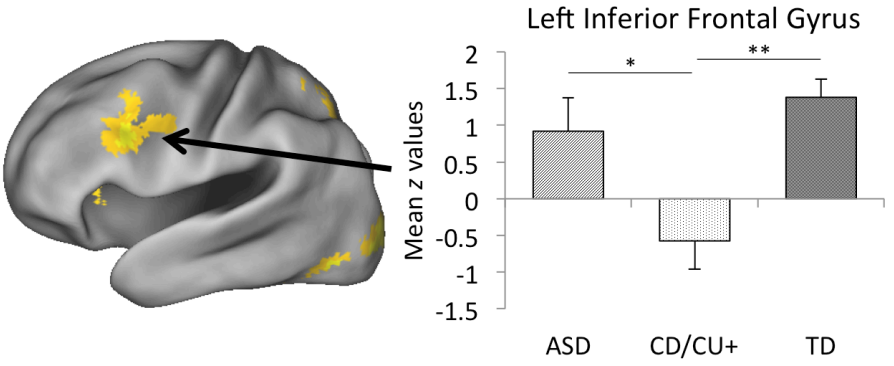

Figure 4. *Significant group differences in the left inferior frontal gyrus for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the CD/CU+ group showed reduced responses in this area compared to the ASD and TD groups (* = p < .05;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

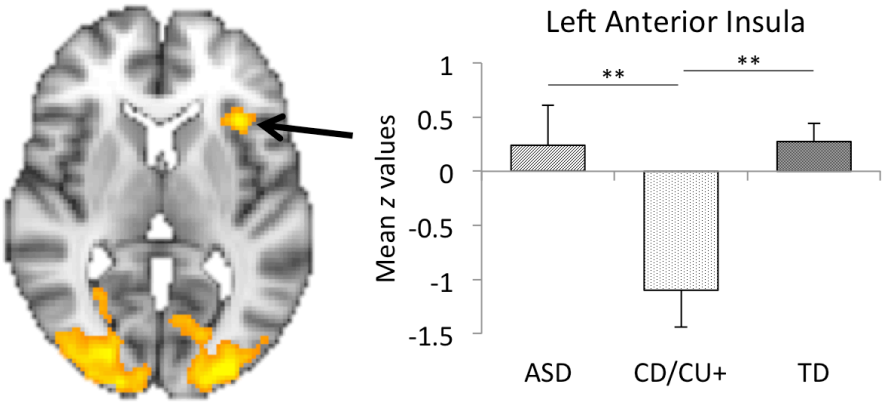

Figure S1. *Significant group differences in the left anterior insula for the self > control contrast (emotional resonance) cluster-thresholded at z > 2.3, p < .05; mean z values indicate that the CD/CU+ group showed reduced responses in this area compared to the ASD and TD groups (** = p < .005).*

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

3 Altered white matter architecture in autism versus conduct disorder

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Klapwijk, E.T., Aghajani, M., Popma, A., van Lang, N.D.J., van der Wee, N.J.A., Vermeiren, R.R.J.M., Colins, O.F. (2017) Altered white matter architecture in autism spectrum disorders versus conduct disorder and callous-unemotional traits.

Abstract

Problems in social interaction are observed in individuals with autism spectrum disorders (ASD) and in individuals with conduct disorder and co-occurring callous-unemotional traits (CD/CU+). Studies that directly compared ASD versus CD/CU+ directly suggest group differences in social-emotional reactivity and associated brain functioning. Since white matter connectivity of several tracts associated with social functioning is also altered in both conditions, for the first time we compared ASD versus CD/CU+ using diffusion tensor imaging (DTI). Tract-based spatial statistics (TBSS) was used to assess white matter microstructure in ASD (N = 22), CD/CU+ (N = 24), and typically developing (TD) male adolescents (N = 32), aged 15–19 years. Using TBSS, we examined fractional anisotropy (FA), and subsequently axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). TBSS revealed increased FA coupled with decreased MD and RD in the cingulum and corpus callosum (splenium and body) among CD/CU+ youths relative to ASD with the TD group being intermediate. These findings show disorder-specific alterations in white matter connectivity among ASD and CD/CU+ youths that may relate to social and executive dysfunctioning.

Introduction

Autism spectrum disorder (ASD) and conduct disorder (CD) are distinct mental disorders both characterized by social dysfunction. Difficulties in social interactions in these disorders, however, are likely underpinned by different neurocognitive deficits (Bird & Viding, 2014; Blair, 2008). Many studies have reported difficulties in mentalizing, or the ability to represent other people's mental states, in ASD (Baron-Cohen et al., 1985; Frith, 2001) and problems in experiencing affective reactions to other's emotions in CD, particularly in individuals with CD who display high levels of callous-unemotional traits (CU+; i.e., lack of guilt and empathy, callous use of others for one's own gain) (Jones et al., 2009; Marsh et al., 2013). In addition, neuroimaging studies show that participants with ASD have altered

hemodynamic responses in brain regions involved in mentalizing, such as the medial prefrontal cortex (MPFC) and temporoparietal junction (TPJ) ((Castelli et al., 2002; Pelphrey et al., 2011) whereas abnormal activation in the amygdala, insula and anterior cingulate cortex (ACC) accompanies diminished affective reactions to other's emotions in CD/CU+ (Blair et al., 2016; Jones et al., 2009; Lockwood et al., 2013b; Marsh et al., 2013; Marsh et al., 2008). Some studies have also directly compared groups with ASD and CD/CU+, showing mainly problems in cognitive aspects of social tasks such as mentalizing in ASD versus selective impairments in affective domains in CD/CU+ (Jones et al., 2010; Schwenck et al., 2012).

Two recent neuroimaging studies directly comparing individuals with ASD and those with CD/CU+ additionally report disorder-specific brain abnormalities during cognitive and affective emotion processing (Klapwijk et al., 2016a; O'Nions et al., 2014). We compared ASD, CD/CU+, and typically developing (TD) youths during neural processing of facial emotions (Klapwijk et al., 2016a). When participants had to cognitively label the presented emotions, the ASD group showed reduced responses compared to the other groups in the ventral MPFC. When participants had to judge their own emotional response to the presented emotions, both the CD/CU+ and ASD groups showed reduced amygdala responses compared to TD. In addition, the ASD group showed hypoactivation compared to the other groups in bilateral hippocampus and the CD/CU+ boys in the inferior frontal gyrus (IFG) and anterior insula in this condition. Along the same line, O'Nions et al. (2014) showed that ASD youths display diminished MPFC reactivity during cognitive mentalizing compared to CD/CU+ and TD groups that did not differ in this task. These studies collectivity suggest disorder-specific alterations in brain functioning in ASD and CD/CU+ during social-emotional processing, indicative of cognitive social deficits in ASD versus affective in CD/CU+.

The handful of comparative studies between ASD and CD/CU+ have thus far focused on differences in behavior and brain functioning (Jones et al., 2010; Klapwijk et al., 2016a; O'Nions et al., 2014; Schwenck et al., 2012), while overlooking possible differences in brain structure and connectivity. The current study hence addressed this important topic by comparing white matter connectivity in ASD, CD/CU+, and TD youths. White matter connections are deemed crucial

for linking distributed brain regions involved in social-emotional processes into integrated neural circuits critical to adaptive social behavior and functioning (Ameis & Catani, 2015; Kennedy & Adolphs, 2012). Especially limbic white matter tracts, as well as long-range associative and interhemispheric tracts, are thought to play an important role in processing social-emotional information (Herbet et al., 2014; Parkinson & Wheatley, 2014; Philippi et al., 2009). Several of these tracts are altered in both ASD and CD (with and without CU+) compared to TD controls (e.g., Breeden et al., 2015; Haney-Caron et al., 2014; Kumar et al., 2010; Pugliese et al., 2009), but disorder-specific alterations for ASD and CD/CU+ have yet to be elucidated.

One prominent limbic white matter tract that is implicated in both ASD and CD/CU+ is the uncinate fasciculus (UF); a tract that connects the orbitofrontal cortex to the anterior temporal lobes (including the amygdala) through a direct, bidirectional monosynaptic pathway (Von Der Heide et al., 2013). Although the exact function of the UF is still unclear, this tract has been associated with social-emotional functioning (Oishi et al., 2015; Parkinson & Wheatley, 2014) and is thought to be a likely candidate for disruption in disorders characterized by social and emotional deficits, such as ASD and CD/CU+ (Olson et al., 2015). Reduced FA of the UF has indeed been reported in children, adolescents and adults with ASD (Kumar et al., 2010; Lee et al., 2007; Pugliese et al., 2009) and a meta-analysis in which data from 14 DTI studies were pooled consistently showed reduced FA (among other tracts) in the UF in ASD (Aoki et al., 2013). In CD (regardless of CU traits), studies have reported abnormalities in the UF that was reflected in both increased (Passamonti et al., 2012; Sarkar et al., 2012) and decreased (Haney-Caron et al., 2014) FA values in the UF. Importantly, a recent study showed reduced white matter integrity in the UF in relation to CU traits in youth with conduct problems (Breeden et al., 2015), echoing previous findings of reductions in the UF in adult psychopathy (Craig et al., 2009). Previous studies have found white matter abnormalities in both ASD and CD in various other tracts that are thought to be important for social-emotional functioning such as the cingulum (Ameis & Catani, 2015; Aoki et al., 2013; Haney-Caron et al., 2014; Waller et al., 2017). This limbic white matter tract has been linked to social functioning and mentalizing (Hadland et al.,

2003; Herbet et al., 2014) and is affected in both ASD and CD/CU+ (Ameis et al., 2013; Haney-Caron et al., 2014; Pape et al., 2015; Travers et al., 2012). Despite these exciting findings, disorder-specific perturbations in white matter connectivity for ASD and CD/CU+ have yet to be elucidated. This is especially critical when searching for brain measures as potential biomarkers to aid diagnosis and treatment, as any useful biomarker should not only differentiate a specific disorder from healthy controls but must also differentiate the specific disorder from any other psychiatric disorder (Boksa, 2013).

We employed diffusion tensor imaging (DTI), to assess disorder-specific profiles of white matter integrity in ASD versus CD/CU+. We compared ASD, CD/CU+, and TD boys on white matter integrity in the UF and cingulum, using tract-based spatial statistics (TBSS; Smith et al., 2006). Additionally, whole brain analysis was performed to establish whether any other tracts might exhibit between-groups differences. We first focused on fractional anisotropy (FA) as an overall measure of white matter integrity, which measures the degree to which water molecules diffuse in a given direction and is affected by axon diameter, myelination and axonal organization (Beaulieu, 2002; Mori & Zhang, 2006). To aid interpretation of FA differences, we additionally evaluated axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) as more specific measures of white matter microstructural integrity (Aghajani et al., 2014; Alexander et al., 2007b).

Methods

Participants

Data of 22 participants with ASD, 24 with CD/CU+, and 32 TD controls were included in the current study (see Table 1 for group characteristics). All participants were males aged 15-19 years. Participants and their parents (for minors under 18 years) gave their written informed consent to participate in the study. The ethics committee of the Leiden University Medical Center approved the study protocol. 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.

Table 1. *Group characteristics*

	Autism spectrum disorders (ASD) (N = 22)		Conduct disorder and CU traits (CD/CU+) (N = 24)		Typically developing (TD) (N = 32)		Difference
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	17.0	1.3	16.6	1.0	17.1	1.2	
IQ *	107.3	10.6	94.0	4.9	96.7	8.7	ASD > CD/CU+,TD
Minority [N / %]	0	0.0	21	87.5	11	34.3	
Autistic traits [a] *	67.9	21.2	39.4	11.3	35.1	13.6	ASD > CD/CU+,TD
Callous-unemotional traits *	28.1	7.0	36.7	6.4	19.7	5.9	CD/CU+ > ASD > TD
Empathy [b]							
Cognitive empathy	34.3	4.2	34.0	6.8	36.5	5.0	
Affective empathy *	35.8	8.0	25.5	6.1	36.1	5.8	ASD,TD > CD/CU+
Aggression [c]							
Reactive aggression*	7.9	4.5	13.1	4.5	6.3	3.1	CD/CU+ > ASD,TD
Proactive aggression*	2.1	2.3	8.7	6.2	1.5	1.7	CD/CU+ > ASD,TD

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

Twenty-three participants with ASD were recruited from specialized child psychiatric centers providing both inpatient and outpatient care for persons with ASD. Data from one ASD participant was excluded due to image artifacts in the DTI data, resulting in a final sample of 22 participants with ASD. Clinical ASD diagnoses according to DSM-IV-TR criteria were autistic disorder for three participants, Asperger's syndrome for ten participants, and pervasive developmental disorder not otherwise specified (PDD-NOS) for nine participants. Three participants also

met DSM-IV-TR criteria for ADHD, two for dysthymia, and one for major depression. In addition to clinical diagnoses, we administered the Autism Diagnostic Observational Schedule-Generic (ADOS-G; Lord et al., 2000) and autism diagnostic interview-revised (ADI-R; Lord et al., 1994). Twenty 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 19 participants and all 19 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. Eleven 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 = 2 multiple medications).

Participants with CD/CU+ were recruited from a juvenile detention centre and a forensic psychiatric unit, since relatively high amounts of boys with CD are present at forensic settings (Colins et al., 2010). CD diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) Behavioral Disorders screening (Kaufman et al., 1997). First, 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 in the study (N = 54). Next, participants 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). Echoing prior work (e.g., Jones et al., 2010; Klapwijk et al., 2016a; Schwenck et al., 2012), 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. Data from two CD/CU+ participants were excluded due to image artifacts in the DTI data, resulting in a final sample of 24 participants with CD/CU+. 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.

Thirty-two TD control boys were recruited through local advertisement. They were screened using the K-SADS-PL behavioral disorders module in order

to exclude participants with behavioral disorders. 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.

DTI data acquisition

DTI data were collected at the Leiden University Medical Center using a 3T Philips Achieva MRI scanner. Prior to scanning, participants were familiarized with the scanner environment using a mock scanner. For DTI data collection, a single-shot echo–planar imaging (EPI) sequence was used with the following scan parameters: repetition time = 6600 ms, echo time = 60 ms, flip angle = 90°, b factor =1000 s/mm2, voxel dimensions = 2.3 mm isotropic, number of slices = 60, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (b=0). The DTI sequence was repeated two times and averaged to obtain stable diffusion parameters; scanning time was ~10 min.

DTI data analysis

DTI data were preprocessed and analyzed using FSL version 5.0.8 (www.fmrib.ox.ac.uk/fsl). Diffusion-weighted images were registered to the non-diffusion weighted (b = 0) image by affine transformations to minimize distortions due to eddy currents and simple head motion. Non-brain tissue and background noise was removed using the Brain Extraction Tool. The diffusion tensor model was then fitted to each voxel using the FSL Diffusion Toolbox to generate individual FA, AD, RD and MD maps for each participant. AD was defined as the largest eigenvalue ($\lambda 1$), RD was calculated as the average of the two small eigenvalues ($\lambda 2$ and $\lambda 3$), and MD was calculated as the average of the three eigenvalues ($\lambda 1$, $\lambda 2$ and $\lambda 3$). Tract-based spatial statistics (TBSS) version 1.2 was used for voxelwise analysis of the preprocessed FA data. First, all FA images were non-linearly registered to the FMRIB58_FA standard-space image using FMRIB's Non-linear Registration Tool (FNIRT). The mean FA image was calculated to create a mean FA skeleton, a representation of the centers of all tracts common to the entire group. The mean FA skeleton was then thresholded at a FA value of ≥0.35 to exclude peripheral tracts and minimize partial voluming. In a similar manner, AD, RD and MD data were

projected onto the skeleton using the FA registration and skeleton projection parameters. Finally, each participant's aligned FA, AD, RD, and MD images were projected onto the mean FA skeleton, and the resulting data were fed into voxel-wise permutation-based analysis.

To test FA alterations in specific tracts we used regions of interest (ROI) analysis in TBSS, as described previously (Aghajani et al., 2014; Westlye et al., 2011). Binary masks of the UF and cingulum (subjacent to the cingulate gyrus) were created using the Johns Hopkins University (JHU) white matter atlases provided by FSL (Mori et al., 2005). Next, the masks were applied to the mean FA skeleton in order to include only voxels comprised in the mean FA skeleton. This confines the statistical analysis exclusively to voxels from the center of the tract, thereby minimizing anatomic inter-subject variability, registration errors, and partial voluming.

Voxelwise statistical analysis of individual skeleton images of all subjects was performed between ASD, CD/CU+, and TD groups using FSL's permutation-based Randomise tool with threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009) and family-wise error (FWE) correction. Based on prior work we tested both for direct group comparisons (two-sample t-tests), as well as linear effects that cut across groups. Echoing data on *decreased* FA in the UF and cingulum in ASD vs. TD (Ameis et al., 2013) and *increased* FA in these tracts in CD youth with and without CU traits vs TD (Pape et al., 2015; Passamonti et al., 2012; Sarkar et al., 2012), we tested the following linear effect: CD/CU+ > TD > ASD (1, 0, -1). Exploratory whole-brain analysis was also performed testing both two-sample t-tests and linear effects. FA was examined in both ROIs and in the whole-brain analysis whereas AD, RD and MD were only subsequently examined in regions showing significant group differences in FA. Reverse linear effects (ASD > TD > CD/CU+; 1, 0, -1) for RD and MD were tested given that increased FA is generally coupled with decreased RD and MD and vice versa. Statistics were built up over 5000 random permutations and the statistical threshold was set to $p < 0.05$ FWE-corrected for multiple comparisons. To account for possible effects of age and IQ, these variables were included (mean-centered across groups) as covariate of no interest. We explored whether additional clinical factors, such as medication exposure or comorbidity, might have influenced the results. These analyses were

conducted with the FA values from the regions showing significant group differences in SPSS to compare participants with ASD and CD/CU+ (excluding either those with a comorbid disorder or those using medication) to TD controls.

Results

ROI analysis of the cingulum (subjacent to the cingulate gyrus) revealed a significant linear group effect, in which CD/CU+ youths exhibited increased FA relative to the ASD youths, with TD youths being intermediate (CD/CU+ > TD > ASD; see Figure 1 and Table 2). This was additionally coupled with decreased MD and RD (but no differences in AD) among CD/CU+ compared to ASD, with TD being intermediate. No group differences in AD values were found. We did not find significant FA differences between the groups for the UF.

Whole-brain TBSS analysis similarly revealed group differences in clusters in the cingulum (in its retrospenial subdivision, see Jones et al., 2013a) extending to the body of the corpus callosum, in the splenium of the corpus callosum and in the cingulum (hippocampus) (see Table 2). These group differences were found for the linear effects analysis and showed increasing FA values from ASD to TD to CD/CU+ in these tracts. We also found decreased MD and RD (but no differences in AD) in the CD/CU+ compared to the ASD group with the TD group being intermediate in these clusters. Voxelwise regression analyses did not yield any significant relationships between clinical measures of autistic (SRS) or CU traits (ICU) and mean FA, MD, or RD within affected tracts in the ASD and CD/CU+ groups. Post-hoc analyses revealed that linear trends 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 $ps < .05$).

Table 2. *MNI coordinates and cluster size for tracts showing significant different FA values between groups.*

White matter tract	MNI peak coords			Size in voxels
	x	y	z	
CD/CU+ > TD > ASD				
Cingulum ROI				
L cingulum (cingulate)	-15	-35	34	344
Whole-brain				
L cingulum (cingulate) extending to the body of the corpus callosum	-14	-34	33	118
L splenium of the corpus callosum	-21	-52	25	45
L cingulum (hippocampus)	-22	-57	21	16

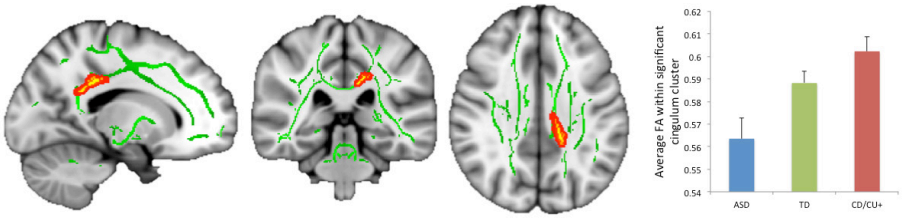

Figure 1. *Tract-based spatial statistics (TBSS) results for cingulum region of interest (ROI). Sagittal, coronal and axial sections of the white matter skeleton (in green), showing significant linear group effect (CD/CU+ > TD > ASD) of fractional anisotropy (FA) (thickened red/yellow), p < 0.05, threshold-free cluster enhancement (TFCE) and family-wise error (FWE) corrected (yellow/orange).*

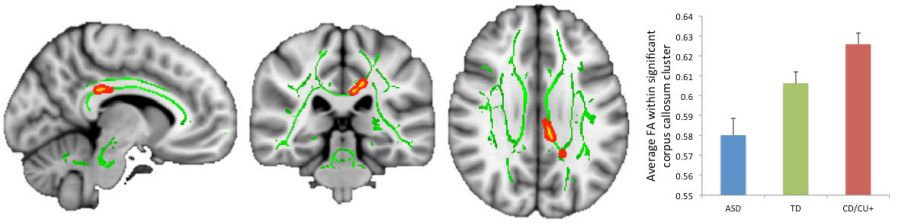

Figure 2. *Whole-brain tract-based spatial statistics (TBSS) results. Sagittal, coronal and axial sections of the white matter skeleton (in green), showing significant linear group effect (CD/CU+ > TD > ASD) of fractional anisotropy (FA) in the corpus callosum (thickened red/yellow), p < 0.05, threshold-free cluster enhancement (TFCE) and family-wise error (FWE) corrected (yellow/orange).*

Discussion

This study is the first to compare white matter microstructure between ASD and CD/CU+; two conditions characterized by social dysfunction. Our analysis revealed increased FA values coupled with decreased MD and RD values in the cingulum and the splenium and body of the corpus callosum in the CD/CU+ group compared to the ASD group with the TD group being intermediate. Contrary to our expectations, no group differences were found in the UF.

Previous studies have reported alterations in the cingulum in both ASD and CD/CU+ (e.g., Ameis et al., 2013; Kumar et al., 2010; Pape et al., 2015). In the current study, we found that the CD/CU+ group compared to the ASD group had increased FA values coupled with decreased MD and RD values in this tract with the TD group showing intermediate FA, MD and RD values. Decreased MD and RD in the CD/CU+ group suggest the increased FA results from a higher degree of myelination, whereas the opposite pattern of increased MD and RD seen in ASD suggests demyelination (Song et al., 2002). The cingulum bundle is a medial limbic tract that connects the cingulate gyrus with medial frontal, parietal, occipital and temporal lobes (Catani & Thiebaut de Schotten, 2008). This tract also seems crucial for connecting the MPFC and precuneus as part of the brain's default mode network (van den Heuvel et al., 2008), a network largely overlapping with the brain regions involved in mentalizing (Schilbach et al., 2012). Indeed, the importance of this tract for social-emotional processing was highlighted by two recent studies showing that damage to the cingulum is associated with decreased cognitive empathy and impaired mentalizing accuracy (Herbet et al., 2014; Herbet et al., 2015). Thus, decreased FA in the cingulum in the ASD group may contribute to the mentalizing deficits observed in ASD. Previously, alterations in the cingulum were also reported in ASD, such as decreased FA in the cingulum in children and adolescents with ASD (Ameis et al., 2013; Jou et al., 2011; Kumar et al., 2010; Shukla et al., 2011) and an increased number of streamlines (i.e., the lines that depict the fibers in a tract) in adults with ASD (Pugliese et al., 2009). Furthermore, density of the cingulum tract in ASD has been associated with brain activation during processing of social information, suggesting cingulum alterations may underlie impaired social behavior in ASD (Just et al., 2014).

In line with our current findings, CU traits have recently been associated with increased FA in the cingulum in at-risk antisocial youth (Pape et al., 2015). However, alterations in the cingulum in adult psychopathic offenders show the opposite effect, that is decreased FA compared to controls (Sethi et al., 2015). Such differences in the direction of FA alterations might be due to the relatively late developmental trajectory of the cingulum (Lebel et al., 2012), and may reflect accelerated maturation of white matter in the cingulum in CD/CU+ followed by marked reductions in adulthood (Fairchild et al., 2013; Passamonti et al., 2012). Interestingly, Sethi et al. (2015) discuss their finding in relation to the default mode network and conclude that abnormal cingular white matter underlying this network might contribute to social-emotional abnormalities in psychopathy (of which CU traits form the affective component). They argue that in ASD, a similar relation between the default mode network and social-emotional deficits might exist (Assaf et al., 2010; Sethi et al., 2015). The current finding of significant differences in the cingulum in a direct comparison of those with ASD with CD/CU+ do not support this suggestion. Alterations in the cingulum and the default mode network may indeed contribute to social difficulties in both disorders, while the current group differences suggest that either the pathways leading to these difficulties or their specific manifestations may be different. Additionally, decreased FA in the cingulum has also been associated with abnormal executive functioning and increased repetitive behavior in ASD (Ikuta et al., 2014; Thakkar et al., 2008), suggesting that cingulum alterations in ASD may not be restricted to social dysfunction. However, functional MRI investigations of the default mode network in ASD suggest that atypical integration of information about the self and others in this network underlies social deficits in ASD (Assaf et al., 2010; Lombardo et al., 2010; Padmanabhan et al., 2017). More speculatively, increased FA in the CD/CU+ group might be related to preserved or even enhanced mentalizing abilities in this group (Dolan & Fullam, 2004; Schwenck et al., 2012), as some data suggest that individuals with high levels of psychopathic traits have good mentalizing skills that they can use to manipulate others (Wheeler et al., 2009). However, increased FA does not necessarily have to reflect enhanced cognitive functioning, as several factors such as increased myelination, decreases in axonal diameter or reduced

neural branches may contribute to higher FA values that may also relate to poorer cognitive functioning (Beaulieu, 2002; Hoeft et al., 2007).

Our study further demonstrated increased FA values together with decreased MD and RD values in the body and splenium of the corpus callosum in the CD/CU+ versus ASD group with intermediate values in the TD group. The corpus callosum is the largest white matter bundle of the brain and crucial for interhemispheric communication, since it connects the two cerebral hemispheres. Deviating FA values of the corpus callosum might therefore impact cognitive, social, and emotional processing that is reliant on the integration of lateralized functions (Aboitiz & Montiel, 2003; Paul et al., 2007). Studies of participants with agenesis of the corpus callosum have linked callosal abnormalities to difficulties in social cognition (Symington et al., 2010). Indeed, such congenital abnormalities of the corpus callosum can yield elevated autistic symptoms comparable with those with ASD in the social and communication domains (Badaruddin et al., 2007; Paul et al., 2014). Subdivisions of the corpus callosum suggest that especially the genu and body are implicated in social processing, as the genu connects the prefrontal cortices and the body mainly connects motor, temporal and insular cortices (Hofer & Frahm, 2006; Raybaud, 2010). The splenium is the most posterior part of the corpus callosum and connects both occipital and inferior temporal areas (Catani & Thiebaut de Schotten, 2008; Hofer & Frahm, 2006), suggesting a role mainly in visual processing but probably also in social-emotional functions supported by temporal areas (Hein & Knight, 2008; Olson et al., 2007; Park et al., 2008; Pelphrey et al., 2004). Thus, the current findings of altered white matter in the body and splenium of the corpus callosum in ASD and CD/CU+ might contribute to social difficulties observed in both disorders.

Our findings are in line with previous studies showing reduced FA in the corpus callosum in ASD (Alexander et al., 2007a; Aoki et al., 2013; Jou et al., 2011; Kumar et al., 2010; Shukla et al., 2011) and elevated FA in CD (with and without CU+) (Menks et al., 2017; Pape et al., 2015; Zhang et al., 2014). Along with altered white matter microstructure, decreased size of the corpus callosum in ASD has also been reported frequently (Frazier & Hardan, 2009; but see Lefebvre et al., 2015 for a notable null finding of size differences in a large multicentre study).

Subsequently, theories of underconnectivity in ASD, which propose that decreased connectivity between cortical areas underlie the diverse set of symptoms that characterize ASD, have pointed to interhemispheric connections through the corpus callosum as one of the key underconnected components (Geschwind & Levitt, 2007; Just et al., 2012). Especially higher order cognitive functions such as language, social cognition and executive functioning that are affected in ASD could be disturbed by decreased interhemispheric communication among cortical areas (Just et al., 2007). The current findings of decreased FA in the corpus callosum in ASD converge with these previous findings and additionally suggest that these FA reductions are specific for ASD compared to CD/CU+. Previous DTI studies have found increased FA values in the body and genu of the corpus callosum to be linked with impulsivity in boys with CD (Zhang et al., 2014) and associations between higher CU traits and increased FA values in the corpus callosum in at-risk youth (Pape et al., 2015). Moreover, a DTI study in girls with CD found that compared to controls they had increased FA values coupled with decreased MD in the body of the corpus callosum (Menks et al., 2017). In addition to a broader role for the corpus callosum in higher order cognition, theoretical and empirical work suggests altered interhemispheric connectivity plays a role in aggressive behavior (Hoppenbrouwers et al., 2014; Raine et al., 2003; Schutter & Harmon-Jones, 2013). Hence, given the elevated levels of aggression in the current CD/CU+ sample, our findings of increased FA values in the corpus callosum might also be related to their impulsive and aggressive behavior.

Contrary to expectations, we did not observe significant group differences in the UF between the ASD, CD/CU+, or TD groups. Given the anatomical location of the UF, as it connects the amygdala and prefrontal cortex, many studies in ASD and CD/CU+ have focused on the UF for its alleged role in social-emotional functioning. Various studies indeed reported altered UF connectivity in ASD (Jou et al., 2011; Kumar et al., 2010; Lee et al., 2007; for meta-analysis see Aoki et al., 2013) and in CD/CU+ (Breeden et al., 2015; Haney-Caron et al., 2014; Pape et al., 2015; Sarkar et al., 2012). However, previous research both in ASD and CD/CU+ has shown inconsistencies in UF connectivity (Olson et al., 2015; Travers et al., 2012; Waller et al., 2017), suggesting alterations in the UF might not be universal to either of

these conditions. These inconsistent results may be due to differences in sample characteristics and DTI methodologies, and to relatively small sample sizes. The current study adds that no differences were found in FA values in the UF between ASD and TD (cf., Shukla et al., 2011), between CD/CU+ and TD (cf., Finger et al., 2012), but also not between both clinical groups of ASD and CD/CU+ boys.

Limitations of the current study include the cross-sectional design of the study, which prevents firm conclusions about the hypothesized developmental trajectories of white matter maturation in the cingulum and corpus callosum in both ASD and CD/CU+. Relatedly, the current adolescent sample limits the generalizability of the results to children and adults with ASD and CD/CU+. Since this sample contained boys only, we also do not know whether our results are generalizable to girls with ASD and CD/CU+. On the contrary, by selecting adolescent boys only within a limited age range, we have reduced sex- and age-related variability that might have influenced our results.

In sum, previous studies have shown differences in social-emotional task performance and associated brain functions in ASD and CD/CU+. By directly comparing white matter microstructure between ASD and CD/CU+, we add that adolescents with these disorders also differ in brain structural connectivity. The CD/CU+ group had increased FA values compared to the ASD group (with the TD group being intermediate) in the cingulum and the corpus callosum. Emerging evidence suggests that many mental disorders might share a common neural substrate (Goodkind et al., 2015; Sprooten et al., 2017), However, the observed group differences between ASD and CD/CU+ suggest that these distinctive disorders, although with superficial overlap in social dysfunction, seemingly exhibit disorder-specific alterations in white matter connectivity.

4 Fairness responses to emotions in conduct disorder

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Abstract

Research suggests that individuals with conduct disorder (CD) are marked by social impairments, such as difficulties in processing the affective reactions of others. Little is known, though, about how they make decisions during social interactions in response to emotional expressions of others. In the current study, we therefore investigated the neural mechanisms underlying fairness decisions in response to communicated emotions of others in aggressive, criminal justice-involved boys with CD (N = 32) compared to typically developing (TD) boys (N = 33), aged 15-19 years. Participants received written emotional responses (angry, disappointed or happy) from peers in response to a previous offer and then had to make fairness decisions in a version of the Dictator Game. Behavioral results showed that CD boys did not make differential fairness decisions in response to the emotions, whereas the TD boys did show a differentiation and also responded more unfair to happy reactions than the CD boys. Neuroimaging results revealed that when receiving happy versus disappointed and angry reactions, the CD boys showed less activation than the TD boys in the temporoparietal junction and supramarginal gyrus, regions involved in perspective taking and attention. These results suggest that boys with CD have difficulties with processing explicit emotional cues from others on behavioral and neural levels.

Introduction

Individuals with conduct disorder (CD) are characterized by a persistent pattern of aggressive and antisocial behavior (American Psychiatric Association, 2013), along with marked socioemotional deficits and interpersonal difficulties (Dodge, 1993; Happe & Frith, 1996; Schwenck et al., 2012). These socioemotional and interpersonal deficits are expressed in reduced responses to the distress cues of others and lack of care about others' suffering, especially in individuals with CD who

show elevated levels of callous-unemotional (CU) traits[1] (Blair, 2013; Lockwood et al., 2013b; Pardini, 2011). Studies that investigated how brain regions involved in social cognition function differently in CD (regardless of the level of CU traits) have mainly used static stimuli such as pictures of emotional faces or scenarios (e.g., Herpertz et al., 2008; Marsh et al., 2013) or stories about mental states (e.g., Sebastian et al., 2012b). Although these studies have greatly increased our understanding of the neurocognitive abnormalities in processing social stimuli in youth with CD (for a review see Blair, 2013), most do not take into account the interactive nature of social exchange, which is one of the hallmarks of social interaction. Yet social neuroscientists recently started to use simple but sophisticated tasks derived from experimental economics to study social decision-making in an interactive context (Rilling & Sanfey, 2011) and to study aberrant social decision-making in clinical populations (Hasler, 2012; Kishida et al., 2010). These tasks can be used to study a range of behaviors such as trust, fairness, altruism, and social norm compliance, which might in turn be influenced by individual variations in personality traits such as empathy.

More specifically, several studies have used economic games to examine social decision-making in relation to antisocial behavior and psychopathic traits in adults and adolescents. Neuroimaging studies showed that psychopathic traits in adults are positively related to uncooperative behavior in economic games and to weaker responses in brain regions important for processing social cues, such as the orbitofrontal cortex and the amygdala (Koenigs et al., 2010; Mokros et al., 2008; Rilling et al., 2007). One study examined the influence of reputations of others during a social exchange game and found that youths with externalizing behavior problems compared to typically developing youth show reduced differential responses within the anterior insula and caudate to the offers of a neutral relative to a kind or an aggressive partner (Sharp et al., 2011a). Another neuroimaging study showed that criminal justice-involved boys were less willing to accept lower offers from others compared to typically developing boys, even if

1 Callous-unemotional (CU) traits are a circumscribed facet of psychopathy and refer to a set of affective features characterized by deficient empathy and guilt, insensitivity to others' feelings, and shallow emotions.

they knew the other had no choice (van den Bos et al., 2014). In these criminal justice-involved boys, higher callousness scores were also related to fewer acceptances when the other had no choice compared to when the other had a fair alternative. This was accompanied by less activity in the right temporoparietal junction (rTPJ), a brain region important for social cognition and attention (Krall et al., 2015; van Overwalle & Baetens, 2009). The TPJ appears to be a site of convergence for social and attention processing streams, in which social context is extracted and synthesized in order to guide attention and decision-making (Carter & Huettel, 2013). These results suggest that the criminal justice-involved boys were mainly focused on the unfairness of the offers and less influenced by the perspective of the other player (van den Bos et al., 2014). Altogether, economic game studies show that antisocial individuals are less inclined than healthy individuals to take contextual information into account during social exchanges (Radke et al., 2013; Sharp et al., 2011b; van den Bos et al., 2014).

In contrast, evidence from healthy populations shows that contextual information in the form of emotions expressed by others heavily influence social decisions (van Kleef et al., 2010). For example, people react with more fair offers after they read disappointed compared to angry reactions, probably due to feelings of guilt caused by disappointment (Lelieveld et al., 2012, 2013b). In addition, higher psychopathic trait-scores in undergraduate students were found to be related to a lack of response to emotional feedback of happiness in an economic game (Johnston et al., 2014). To date, no study that used an interactive economic game in antisocial populations focused on the role of other's emotions in social interactions. Although individuals with CD (and especially those with high CU traits) are known to have problems with processing the affective reactions of others (Jones et al., 2009; Schwenck et al., 2012; Sebastian et al., 2012b), little is known about how they make social decisions in response to emotions in an interactive context.

In the current study, we therefore investigated the effects of other's emotions on fairness decisions and associated brain responses in boys with CD compared to typically developing (TD) controls. Participants had to allocate tokens between themselves and peers from which they received verbal emotional reactions depicting anger, disappointment, or happiness (Lelieveld et al., 2013a).

This procedure allowed us to test whether boys with CD would differentiate between various emotions and would adjust their fairness decisions accordingly. A behavioral study that used this paradigm found that typically developing adolescents took emotional reactions of others into account and reacted with more fair offers after they read disappointed reactions compared to angry and happy reactions from their peers (Klapwijk et al., 2013). In addition, in a neuroimaging study that used this paradigm healthy adults showed more activation in the rTPJ when receiving happy reactions (and they reacted with more fairness in response to both happy and disappointed reactions compared to angry reactions), suggesting increased perspective taking and attention in response to happiness (Lelieveld et al., 2013a). Based on studies pointing to problems in processing affective and contextual social signals of both negative and positive emotions in CD (de Wied et al., 2012; Fairchild et al., 2009; Herpertz et al., 2005), we expected that the CD boys would be less responsive to emotional information of others. Such low emotional responsiveness might lead to a decrease in differentiating between emotions. We expected that this lower emotional responsiveness would be reflected in less differentiation in fairness decisions between the three emotions in the CD (versus TD) boys, and by less activation in social-cognitive brain areas such as the TPJ and medial prefrontal cortex (MPFC) in the CD (versus TD) boys. Additionally, we investigated the effects of CU traits on brain and behavior in our task. Based on prior work, it was hypothesized that the CD boys with high CU traits would show even more difficulties in differentiating between negative and positive emotions than CD boys with low CU traits (de Wied et al., 2012; Fanti et al., 2016).

Method

Participants

Since CD is highly prevalent among criminally justice-involved boys (Colins et al., 2010), adolescent offenders with CD were recruited from a juvenile detention center and a forensic psychiatric facility. All had been convicted or charged for felony crimes such as assault, murder, or armed robbery. Typically developing (TD)

control adolescents were recruited through local advertisement. All participants were aged 15-19 years (see Table 1 for participant characteristics). Exclusion criteria for all participants were (central) neurological abnormalities, a history of epilepsy or seizures, head trauma, left-handedness, and IQ less than 75. Data from participants with excess motion defined by relative mean displacement > 0.5 mm were excluded from further analysis. Of note, the current task was part of a larger study and preceded by other scans (e.g., structural MRI, resting state fMRI), which might have increased the likelihood of excessive head motion during this task. 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. CU traits were measured using the Inventory of Callous-Unemotional traits (ICU; Kimonis et al., 2008).

Table 1. *Participant characteristics*

	Conduct disorder (CD) (N = 32)	Typically developing (TD) (N = 33)
Age, years (*SD*)	16.8 (1.2)	17.2 (1.2)
IQ, *M* (*SD*)	98.1 (7.0)	97.2 (8.7)
Minority, *N* (%)	27 (84.4)	9 (27.3)
Empathy scores [a]		
Cognitive empathy, *M* (*SD*)	36.3 (5.9)	38.0 (5.0)
Affective empathy, *M* (*SD*) **	28.9 (7.7)	36.1 (7.8)
Callous-unemotional traits, *M* (*SD*) *	26.0 (11.2)	20.8 (7.1)

** Significantly different at p < 0.05.*
*** Significantly different at p < 0.001.*
[a] Self-report of affective and cognitive empathy was measured using the Basic Empathy Scale (Jolliffe & Farrington, 2006).

The CD group consisted of 54 adolescent boys of which 46 completed both phases of the experimental fMRI task (see *Experimental task* section below). 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. Only boys who 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. Data from 14 CD participants were discarded due to excessive motion, leaving a final sample of 32 participants with CD. The excluded CD participants did not significantly differ from the CD participants that were included in the fMRI analysis in age, comorbidity, ICU callous-unemotionality scores, BES affective and cognitive empathy scores, or unfairness percentages in response to the three emotions in the experimental task (all ps > 0.2). The groups did differ in estimated IQ scores ($p < 0.005$), caused by lower IQ scores in the excluded (92.1) versus the included group (98.1). Eight participants with CD also met DSM-IV-TR criteria for ADHD. No other comorbid disorders were reported and none of the participants with CD took medication at the time of testing (medication history was not recorded).

Thirty-seven TD control boys were recruited through local advertisement of which 34 completed both phases of the task (see *Experimental task* section below). These participants were screened using the K-SADS-PL Behavioral Disorders module in order to exclude participants with behavioral disorders. 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. Data from one TD participant was discarded due to excessive motion, leaving a final sample of 33 TD participants. The CD group showed more head motion than the TD group and we therefore had to exclude more CD than TD participants. Importantly, in the final sample used in our paper there is no difference in relative mean displacement ($p > .19$) between the CD and TD groups.

Experimental task

We examined participants' fairness choices in the Dictator Game (Güroğlu et al., 2009; Kahneman et al., 1986) after receiving emotional reactions from others, using a procedure previously used in studies with adults and adolescents (Klapwijk et al., 2013; Lelieveld et al., 2013a). One week before participants took part in the scanning session, they first participated in a preliminary study (first phase of the experiment). This phase was used to create an interpersonal context for the emo-

tional reaction they later (second phase) received. In the first phase, participants read a scenario after which they were instructed to divide 10 tokens between themselves and another person. They could choose a 6-4 distribution in favor of themselves, an equal distribution (5-5), or a distribution in favor of the other (4-6). This negotiation scenario was intended to assure that most participants chose the 6-4 option in this phase of the study. Only participants that chose a 6-4 distribution took part in the second phase of the experiment during scanning (46 out of 54 CD boys and 34 out of 37 TD boys chose a 6-4 distribution). This was done to ensure credibility of the second phase in which emotional reactions would be directed at the 6-4 offer chosen in the first phase. In line with previous studies (Lelieveld et al., 2013a; van Kleef et al., 2010), these reactions were either angry, disappointed or happy. Using these three emotions allows for comparisons of the effects of negative and positive communicated emotions and the effects of different types of negative emotions. Additionally, although it is not uncommon to find angry and disappointed reactions in response to a 6-4 distribution because of the relative unfairness of this distribution, happy reactions should be considered acceptable since offers of around 40% of the total are mostly accepted in economic games (Falk & Fischbacher, 2006).

In the second phase of the experiment, the boys were told that their unfair offer (the 6-4 distribution chosen in the first phase) was presented to 60 peers who were given the opportunity to write out their reaction upon receiving the offer. In reality, the reactions were preprogrammed and we left at least one week between the first and second phase to increase the credibility that researchers actually collected reactions from others. During scanning (also part of the second phase), participants were paired with a different player on each trial, whose first name was provided and whose reaction to the 6-4 distribution was either angry, disappointed or happy. These preprogrammed reactions were rated to reflect the intended emotion (see also Klapwijk et al., 2013; Lelieveld et al., 2013a). Participants read the reactions of their peers and subsequently played a version of the Dictator Game with the peer who provided the reaction (see Figure 1). In this Dictator Game the participants were the allocator and had to divide 10 tokens. They could now choose between different fair and unfair distributions and

learned that the recipient had to accept any distribution they would make. The possible distributions were 5-5 versus 7-3; 6-4 versus 4-6; 3-7 versus 7-3; and 5-5 versus 6-4; and all options were presented 5 times during each emotion type. Each trial started with a jittered fixation (min. = 0.55 s, max. = 4.95 s, M = 1.54 s), after which the participants were presented with the emotional reaction for a period of three seconds plus a jittered interval (min. = 0.55 s, max. = 4.95 s, M = 1.54 s) and subsequently had six seconds to make a decision between two distributions. The 60 trials were presented in pseudo-random order divided over three blocks of four minutes each. Before the task started, participants learned that at the end of the experiment the computer would randomly select 10 trials to determine their total earnings, which would be added to the standard compensation for their participation. At the end of the session, participant's pay-off was presented, which varied between 2.5 and 6 euros. Afterwards, participants completed a post-scanning questionnaire in which they were probed for suspicion and asked to indicate their levels of guilt, anger, and fear in response to the different emotions. None of the participants expressed doubt about the set-up of the task.

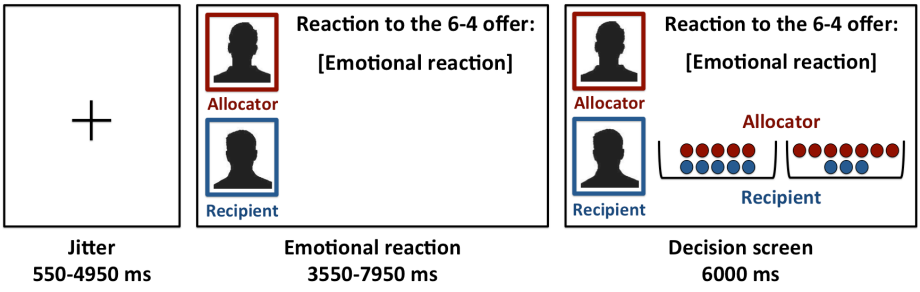

Figure 1. *Visual display and timing (in milliseconds; ms) of the task in the scanner. The emotional reaction of the recipient (here "emotional reaction") was displayed after a jittered fixation cross. Subsequently, the screen displayed two offers each containing red and blue tokens, which indicated the share for the allocator and the recipient, respectively (here 5–5 vs. 7–3). The name of the allocator was displayed in red (here "allocator") and the name of the recipient in blue (here "recipient"). If participants did not respond within 6000 ms, a screen displaying 'Too late!' was presented. After the response, the decision screen remained on the screen until 6000 ms after the onset of the decision screen.*

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. 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. 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.

fMRI data analysis

FMRI data analysis was conducted using FEAT (fMRI Expert Analysis Tool) version 6.00, part of FSL (www.fmrib.ox.ac.uk/fsl). Data pre-processing consisted of 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, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0s). Functional scans were registered to the T1-weighted images, and subsequently to the 2 mm MNI-152 standard space template. Time-series statistical analysis was performed using FILM with local autocorrelation correction. To investigate the effects of the communicated emotions, we modeled the onset of the presentation of the three different emotional reactions (i.e., anger, disappointment, happiness) as an event with zero duration 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. At first-level for each run for each participant, primary contrasts of interest were generated. Positive versus negative emotions were contrasted (happiness > [anger and disappointment]) as well as happiness against the separate negative emotions (happiness > anger; happiness > disappointment) and the negative emotions against each other (anger > disappointment). A second-level, fixed-effects analysis combined data across

the three runs for each participant. Individual participant data were then entered into a third-level group analysis using a mixed-effects design (FLAME) whole-brain analysis. The general linear model included the two groups (CD and TD) and to account for possible age effects, we included age (mean-centered) as covariate of no interest. Resulting statistical maps were corrected for multiple comparisons using cluster-based correction ($p < 0.05$, initial cluster-forming threshold $Z > 2.3$). We used Featquery and SPSS to conduct region of interest (ROI) analyses to correlate task behavior and ICU scores 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 contrasts of interest with binarized anatomical ROIs using the Harvard-Oxford structural atlases distributed with FSL. Finally, we explored whether comorbid ADHD in the CD group might have influenced the results. Extracted *z* values from the ROIs identified in the whole-brain analyses were entered into SPSS to compare only those participants with CD without comorbid ADHD to TD controls and to compare boys with and without comorbid ADHD with each other.

Results

Behavioral results

Fairness decisions after the three different emotions were compared between the groups with a 2 ×3 mixed ANOVA (group ×emotion). We found a main effect of emotion, F (1, 64) = 8.47, p = .001, caused by a higher percentage of unfair offers in response to angry (M = 56.4 %; SD = 32.9) compared to disappointed reactions (M = 48.4 %; SD = 30.0, p = .001). We found no main effect of group, F (1, 64) = 2.75, p = .102, showing that the groups did not differ on fairness levels across the emotions combined. The interaction effect was trendwise significant, F (1, 64) = 2.62, p = .081, indicating group differences in the reactions after the different emotional expressions. Analyses of the CD and TD participants separately revealed that the CD participants made no difference in fairness decisions after reading the different emotions, F (2, 64) = 1.21, p = .31, whereas the TD participants did, F (2, 66) = 11.66, $p < .001$. In line with Klapwijk et al. (2013), post hoc tests revealed that TD participants more often

chose the unfair than the fair option when dealing with angry recipients (59.5 %, SD = 33.1, $p < .001$) and happy recipients (66.8 %, SD = 27.1, $p < .05$) than when dealing with disappointed recipients (49.2 %, SD = 31.1). The percentage of unfair offers in response to happy and angry recipients ($p = .36$) did not differ in the TD group. Thus, communications of disappointment elicited relatively more fair offers than communications of anger and happiness did, but only in the TD and not in the CD group (see Figure 2). Finally, between-group comparisons showed that the TD group made more unfair offers after happy ($p = .005$) but not after angry ($p = .83$) or disappointed ($p = .45$) reactions than the CD group.

Correlations between post-scanning ratings (guilt, anger, fear) and fairness decisions revealed that self-reported guilt when reading angry reactions correlated negatively with unfair offers in response to angry reactions in the TD group ($r = -0.54, p < 0.001$), but not in the CD group ($r = -0.31, p = 0.10$), and that self-reported guilt after disappointed reactions correlated negatively with unfair offers in response to disappointment in the TD group ($r = -0.52, p < 0.005$), but not in the CD group ($r = -0.20, p = 0.30$). Fisher z-values were calculated to compare the correlations between the CD and TD groups. No significant group difference was found for the correlation between self-reported guilt and unfair offers in response to anger ($z = 1.09, p = 0.14$) and a trendwise significant difference was found for the correlation between self-reported guilt and unfair offers in response to disappointment ($z = 1.43, p = 0.076$). These results suggest that levels of guilt in the TD control were associated with individual differences in fairness decisions in reaction to disappointed reactions, whereas no significant relation was found for the CD group.

To further explore the role of CU traits in the CD group we also conducted an analysis in which we separated the CD group into a group with high CU traits (CD/CU+; N = 14) and a group with low CU traits (CD/CU-; N = 18). Participants scoring above the median ICU score of the full CD sample (N = 54; median score = 27.0) were included in the CD/CU+ group and those scoring on or under the median ICU score in the CD/CU- group. This analysis did not reveal differences between the CD/CU+ and CD/CU- group on behavior; both groups made no differences in fairness decision between the three emotions, $F(2, 28) = 0.49, p = .62$ (CD/CU+), and, $F(2, 36) = 0.66, p = .53$ (CD/CU-).

Figure 2. *Percentage of unfair offers after communication of anger, disappointment, and happiness, separate for CD and TD groups.*

fMRI results

The first set of whole-brain analyses investigated regions that showed group differences between the CD and TD groups when receiving positive relative to negative emotional reactions in general (i.e., happiness > [anger and disappointment] contrast). This analysis revealed that the CD group showed less activation than the TD group in a cluster in the rTPJ and right supramarginal gyrus (rSMG) (see Figures 3A and 3B), a cluster in the left superior parietal lobule, and a cluster in the somatosensory cortex (see Table 2). No regions were found where the CD group showed more activation than the TD group in this contrast. When analyzing the contrasts that compared happiness to a specific negative emotion (i.e., happiness > anger, and the happiness > disappointment), group differences remained in the rSMG. Furthermore, in the happiness > anger contrast, we also found less activation in the right dorsolateral prefrontal cortex (rDLPFC, see Figures 4A and 4B) in the CD compared to the TD group. Finally, when comparing the two negative emotions with each other, we found no significant group differences between the CD and TD groups when analyzing the anger > disappointment and disappointment > anger contrasts. Additionally, we re-analyzed the fMRI data using a stricter cluster-corrected threshold of $z > 3.1$, $p < .05$, after which the group differences of the whole brain comparisons were not significant anymore.

Table 2. *MNI coordinates, z values and cluster size for brain regions revealed by the whole brain pairwise comparisons of the TD control > CD groups, z > 2.3, p < .05 cluster-corrected.Activation clusters were labeled using the Harvard-Oxford structural atlases.*

Anatomical region	Max *z*	MNI peak coords			Size in voxels
		x	y	z	
happiness > [anger and disappointment]					
R supramarginal gyrus extending to the temporoparietal junction	4.26	58	-38	50	1064
Precentral gyrus	4.26	-2	-32	66	605
L superior parietal lobule	4.24	-40	-56	60	1801
happiness > anger					
L superior parietal lobule	4.40	-40	-56	60	1428
R middle frontal gyrus (DLPFC)	4.19	38	22	52	439
R supramarginal gyrus	3.75	58	-38	52	1072
happiness > disappointment					
R supramarginal gyrus	4.2	56	-36	48	750

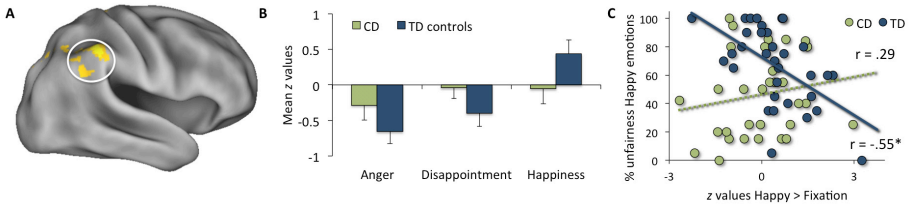

Figure 3. *(A) Right TPJ/SMG group differences in the happiness > [anger and disappointment] contrast cluster-thresholded at z > 2.3, p < .05 with (B) mean z values plotted for the three emotions and the CD and TD groups separately. (C) Activation in the rTPJ/SMG in the [happy > fixation] condition correlated negatively with the percentage unfair offers in response to happy emotions for the TD control group, but not for the CD group. Fisher z-values indicated that the correlations differed significantly between the groups (z = -3.52, p < 0.001).*

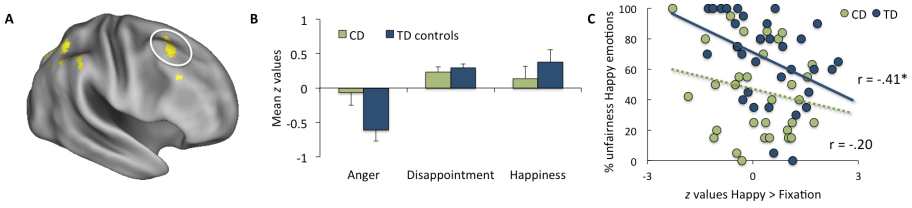

Figure 4. *(A) rDLPFC group differences in the happiness > anger contrast cluster-thresholded at z > 2.3, p < .05 with (B) mean z values plotted for the three emotions and the CD and TD groups separately. (C) Activation in the rDLPFC in the [happy > fixation] condition correlated negatively with the percentage unfair offers in response to happy emotions for the TD control group, but not for the CD group. However, Fisher z-values indicated that these correlations did not differ significantly between the groups (z = -0.89, p = 0.19).*

Relationships between fairness decisions and brain activation

Next, we conducted exploratory analyses to investigate the relation between fairness decisions and brain activity in regions identified in our whole-brain analysis. Because of the differences found in the happy condition between the CD and TD groups, these analyses focused on the behavioral and brain responses during the happy condition. We investigated the relation between the percentage of unfair offers in response to happy reactions and the activity in the rTPJ/SMG for the happy > fixation contrast. This analysis revealed a significant negative correlation between the percentage unfair offers and rTPJ/SMG activity for the TD control group ($r = -0.55$, $p < 0.001$), but not for the CD group ($r = 0.29$, $p = 0.11$, Figure 3C). Additionally, Fisher z-values were calculated which indicated that the correlations differed significantly between the groups ($z = -3.52$, $p < 0.001$). Thus, TD boys who showed higher (versus lower) levels of rTPJ/SMG activation when happiness was expressed tended to react more fair after happy reactions. This latter finding demonstrates that for the TD control group rTPJ/SMG activation is associated with individual differences in fairness decisions in reaction to happy reactions, whereas no significant relation was found for the CD group.

In addition, the relation between the percentage of unfair offers in response to happy reactions and the activity in the rDLPFC for the happy > fixation contrast revealed a significant negative correlation between the percentage unfair offers and rDLPFC activity for the TD control group ($r = -0.41$, $p < 0.05$), but not for the CD group ($r = -0.20$, $p = 0.28$, Figure 4C). However, Fisher z-values were calculated which indicated that these correlations did not differ significantly between the groups ($z = -0.89$, $p = 0.19$).

Effects of CU traits on brain activation

No significant relation between brain activation in ROIs derived from the whole brain analysis and variation of CU traits were found within the CD group or within the TD group. To further explore the role of CU traits in the CD group we also conducted analyses with the CD/CU+ (N = 14) and CD/CU- (N = 18) groups separately (see *Behavioral results*). These analyses did not reveal any significant group differences between the CD/CU+ and CD/CU- groups.

Effects of comorbidity

Post-hoc analyses revealed that all group differences remained significant when excluding CD boys with comorbid ADHD (all *p*s < .001). In addition, no significant group differences were found between CD participants with comorbid ADHD and those without (all *p*s > .3).

Discussion

The current study investigated behavioral and neural responses in reaction to other's emotions in an interactive context in CD and TD boys. Behavioral results suggest that the CD boys differentiate less between different emotions communicated by others when making fairness decisions than TD boys. In line with prior work with TD adolescents (Klapwijk et al., 2013), TD boys reacted relatively more fair in response to disappointed reactions compared to angry and happy reactions, whereas the CD boys did not show differences in fairness reactions between the three emotions. These results are in line with previous studies that suggest that individuals with CD have difficulties in processing affective stimuli (Fairchild et al., 2009; Herpertz et al., 2005), and our study contributes to the literature by showing that CD boys do not adjust their allocation behavior in response to emotional information of others. On the other hand, one might have expected that the CD boys would react more unfair in response to anger since they are more easily provoked by angry reactions and pay more attention to hostile cues (Dodge, 1993). However, we found no differences between CD boys and TD boys in fairness decision in response to angry reactions. Since hostile attributions are mostly focused on ambiguous content (de Castro et al., 2002), we might have found an influence of hostile attribution of intent in the CD boys had we used more ambiguous instead of clearly angry reactions. The current results, nevertheless, can be interpreted as a sign of insensitivity to emotions in the CD group reflected by equal amounts of fairness in response to different emotions.

The fMRI results showed that the CD boys compared to the TD boys had less activity in the right rTPJ/SMG when receiving happy compared to disappointed

and angry reactions. This is in line with a previous study using this paradigm that reported increased rTPJ activation in healthy adults in this contrast (Lelieveld et al., 2013a). The rTPJ and also the nearby-located rSMG are important regions for social cognitive abilities such as perspective taking and empathy (Frith & Frith, 2006; Krall et al., 2015; Silani et al., 2013). Thus, based on these prior studies, the decreased activation in these brain areas in the CD group might suggest that boys with CD were less inclined to take the perspective of the other person during happy compared to angry and disappointed reactions. In the current paradigm, the TPJ might support the integration of information streams to construct a social context, which may then be used to adapt behavioral decisions in response to other's emotions (cf., Carter & Huettel, 2013). Additionally, the negative correlation between right rTPJ/SMG activation and unfairness in response to happy reactions that we found only in TD controls suggests that taking the perspective of the other resulted in less unfair offers in the TD but not the CD boys. Hence, this correlational analysis supports the idea that the TD boys are more sensitive to the emotions of others than the CD boys and consequently adapt their behavior in response to others' emotions. It should be noted, however, that although activation in the rTPJ/SMG was associated with more fair offers after happiness in the TD and not the CD group, the TD group made more unfair offers in response to happiness than the CD group.

Although we hypothesized decreased activation in various brain regions involved in social processing such as the TPJ and MPFC, in the current study group differences seem to be selective for TPJ/SMG. However, we also found decreased rDLPFC activation in the CD compared to the TD group when reading happy versus angry reactions. The rDLPFC is an important region implicated in cognitive control (Miller & Cohen, 2001) and plays a role in regulating reactions and implementing norm compliance in social decision-making (Rilling & Sanfey, 2011; Spitzer et al., 2007; Steinbeis et al., 2012). Decreased activation in this area might be suggestive of less regulatory brain activation in the CD boys compared to controls. The negative association between rDLPFC activation and unfair decisions in response to happy reactions in the TD control group suggests that withholding the urge to make an unfair decision requires cognitive control. However, one may

then also expect more unfair offers in response to happiness in the CD versus TD group, which was not the case in the current study. Therefore, a likely alternative explanation is that in line with the important role of rDLPFC, rTPJ and rSMG in attentional processes (Corbetta et al., 2008; Mitchell, 2008; Ochsner et al., 2012), reduced activation in these areas might reflect reduced attention to the happy expressions in the CD versus TD boys.

Many studies have found that impaired emotional responsiveness in adolescents with conduct problems or with CD is more pronounced in those with high CU traits (Frick et al., 2014). However, current results suggest that boys with CD have difficulties in adapting their behavior in response to emotions of others irrespective of whether they show elevated levels of CU traits. This is consistent with some previous work showing nonsocial decision-making deficits in antisocial youth irrespective of CU traits (White et al., 2014a). In addition, previous studies that did find effects of CU traits on emotional responsiveness have mostly used facial emotions in which most effects were found for distress cues such as fear and sadness (but see Dawel et al., 2012 for meta-analytic evidence for more broad impairments in emotion recognition). It might be that responsiveness in the form of social decisions to written emotional reactions that depict anger, disappointment, and happiness as employed in our task might not be associated with CU traits.

Some limitations of the current study should be considered. Although the study design focused on the effects of different emotions on fairness decisions and not on fairness per se, it must be noted that although the groups did not differ on total unfairness across the three emotions, contrary to what one might expect the CD group behaved less unfair in response to happy reactions than the TD controls. However, higher unfairness in the Dictator Game in controls versus adult inmates has been reported previously and has been interpreted as a form of compensation to amend for their crimes (Gummerum & Hanoch, 2012). The criminal justice-involved CD boys might also have been motivated by a desire to please the experimenters, if they thought that despite guaranteed anonymity their behavior would be reported to authorities. Nevertheless, being more sensitive to the different emotions, the TD participants could have concluded that the happy other was satisfied with the previous unfair offer, and therefore would be content

with another unfair offer (van Kleef et al., 2010). Another possible caveat of the current study is that our design does not allow for inferences about whether the equal distributions in response to different emotions in the CD group reflect less differentiation between emotions or that this reflects that CD youth just do not use the emotional information when making fairness decisions. However, the relation between feelings of guilt (as reported after the scanning procedure) and fairness in response to disappointment in the TD controls but not in the CD group suggest that feelings of guilt did not influence fairness decisions after disappointment in the CD group. Future studies are needed in which emotion states or skin conductance are being measured directly when CD boys read the emotions in order to answer whether the differentiation is indeed being hampered as a consequence of less emotional responsiveness. Another limitation of the current study is that our group differences are reported at a cluster-corrected threshold of $z > 2.3$, $p < .05$. Notwithstanding that this is a widely used correction method, it can result in false positives and low spatial specificity (Woo et al., 2014). Using a stricter cluster-corrected threshold of $z > 3.1$, $p < .05$, as suggested by Woo et al. (2014), the group differences in the present study did not remain significant. However, when studying social-affective processes in difficult to recruit detained male adolescents, we should also be careful and avoid false negatives (see recommendations from Lieberman & Cunningham, 2009). Our study is a first step in examining how explicit emotional feedback influences brain and behavior in criminal justice-involved CD boys and future studies are needed to replicate these findings.

To conclude, the current study provides behavioral and neural evidence of interpersonal difficulties in boys with CD. The results suggest that CD (versus TD) boys do not make differential fairness decisions in response to different emotions of others, which is associated with reduced responses to others' emotions in brain regions important for social decision-making in CD (versus TD) boys.

5 Fairness responses to emotions in autism spectrum disorder

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Abstract

Little is known about how emotions expressed by others influence social decisions and associated brain responses in autism spectrum disorders (ASD). We investigated the neural mechanisms underlying fairness decisions in response to explicitly expressed emotions of others in boys with ASD and typically developing (TD) boys. Participants with ASD adjusted their allocation behavior in response to the emotions but reacted less unfair than TD controls in response to happiness. We also found reduced brain responses in the precental gyrus in the ASD versus TD group when receiving happy versus angry reactions and autistic traits were positively associated with activity in the postcentral gyrus. These results provide indications for a role of precentral and postcentral gyrus in social-affective difficulties in ASD.

Introduction

Difficulties in reciprocal social interactions and communication are among the core features of autism spectrum disorders (ASD), along with a restricted repertoire of activities and interests (American Psychiatric Association, 2013). These social deficits have been documented in numerous studies showing that individuals with ASD have impairments in the ability to represent other people's mental states (i.e., mentalizing; Baron-Cohen et al., 1985; Kaland et al., 2008) and in processing emotions of others (Adolphs et al., 2001; Hobson, 1986; Uljarevic & Hamilton, 2013). Neuroimaging studies have also revealed differences between individuals with ASD compared to typically developing (TD) individuals in brain areas relevant for social-affective functioning (Di Martino et al., 2009; Fishman et al., 2014; Frith, 2001; Pelphrey et al., 2011; Philip et al., 2012; White et al., 2014b). These studies suggest that social deficits in ASD are associated with atypical activation in brain areas involved in mentalizing, such as hypoactivation in the medial prefrontal cortex (mPFC) and temporoparietal junction (TPJ) (e.g., Castelli et al., 2002; Wang et al., 2007; Watanabe et al., 2012), as well as in brain areas relevant

for processing and resonating with others' emotions such as hypoactivation in the inferior frontal gyrus and both under- and overactivation in the amygdala (e.g., Greimel et al., 2010; Klapwijk et al., 2016a; Monk et al., 2010; Pelphrey et al., 2007; Swartz et al., 2013).

In most of the neuroimaging studies on social processing in ASD, participants are merely required to observe others or to think about their mental states (e.g., Kana et al., 2015; Schulte-Ruther et al., 2011; Vander Wyk et al., 2014). Although these studies have greatly advanced the understanding of the neurocognitive mechanisms associated with social deficits in ASD, most do not take more interactive elements of social exchange into account. Studying such elements, however, is essential, as responding towards others involves different cognitive processes than merely observing others' behavior (Schilbach et al., 2013). This is especially important because a discrepancy has been reported between potentially normative performance on explicit social tasks in ASD versus difficulties in applying social abilities during social interactions (Klin et al., 2003). For example, although adults with ASD do not spontaneously attribute mental states to others, they are able to understand mental states of others when they are explicitly encouraged to mentalize (Moran et al., 2011; Senju et al., 2009).

Paradigms inspired by behavioral economics are increasingly used to investigate social cognitive processes underlying social interactions in psychiatric populations (Hasler, 2012; Sharp et al., 2012) including ASD (Chiu et al., 2008; Sally & Hill, 2006; Yoshida et al., 2010). These paradigms not only offer simplicity and experimental control, but also have the advantage that they model interactive elements of social exchanges (King-Casas & Chiu, 2012; Rilling & Sanfey, 2011). Previous experiments using economic games suggest that people with ASD are indeed impaired in executing mentalizing abilities during interactive games. For example, adolescents with ASD show a different response in the middle cingulate cortex compared to controls when deciding to reciprocate investments in the trust game, suggesting problems with mentalizing during online social interaction (Chiu et al., 2008; Frith & Frith, 2008). In a different strategic game, the stag hunt game, players can cooperate to hunt highly valued stags or act alone and hunt rabbits of lower value. Yoshida et al. (2010) used this game to estimate participants'

representations of the other player's intentions for cooperation. They found that adults with ASD made less use of these representations than control participants when playing the game (Yoshida et al., 2010). Further evidence comes from a study in which children with ASD had to judge others' morality and subsequently played a cooperative game both with the child they judged to be morally 'nice' and 'bad'. This study showed that children with ASD (in contrast to TD children) did not distinguish between morally good and bad partners in the cooperative game but did correctly judge others' morality in basic moral judgment stories, (Li et al., 2014). These studies using economic games thus also suggest that individuals with ASD are able to make explicit inferences about others but are less effective in using this information when making interactive decisions.

Although it has been suggested that individuals with ASD are impaired in processing emotions of others (Adolphs et al., 2001; Baron-Cohen et al., 1997; Harms et al., 2010), studies using economic games among individuals with ASD did not focus on the role of emotions in social interactions. However, many studies in healthy populations have shown that emotions expressed by others during interactions can influence subsequent behavior of the observer (van Kleef et al., 2010). For example, disappointed reactions of others might lead to fairer subsequent responses in observers than angry reactions of others (Lelieveld et al., 2012, 2013b), whereas during negotiations displays of happiness might signal satisfaction leading to lower offers (van Kleef et al., 2004). Currently, evidence suggests that individuals with ASD are less likely to integrate emotional contextual cues into their decision-making (De Martino et al., 2008). Yet little is known about how they make social decisions in response to emotions during social interaction. Therefore, in the current study we examined if emotions expressed by others influence fairness decisions and associated brain responses in boys with ASD compared with TD controls. While being scanned, participants were presented with written expressions of anger, disappointment and happiness by peers in response to an earlier decision about dividing tokens, after which they were given the opportunity to divide tokens again. A previous study using this paradigm found that TD adolescents reacted with more fair allocations after they read disappointed reactions compared with angry and happy reactions from their peers (Klapwijk

et al., 2013). Neuroimaging studies that used this paradigm found that when TD participants received happy reactions they showed increased responses in the TPJ, a brain area that is important for mentalizing and attention (Klapwijk et al., 2016b; Lelieveld et al., 2013a).

Based on previous work showing that individuals with ASD made less use of social information when making decisions (Izuma et al., 2011; Li et al., 2014; Yoshida et al., 2010), we expected that they would be less likely to integrate emotional contextual information into their decision-making processes. This would be reflected in less difference in fairness decisions between the three emotions in the ASD versus TD group. Predictions for neuroimaging results were based on previous studies in ASD that revealed differences compared to controls in brain regions involved in social cognition. Whereas most previous studies used facial emotions, the current study used written emotions, and we therefore expected to find differences in frontotemporal brain regions involved both in social cognition and language processing. For example, reduced activation in the inferior frontal gyrus has been reported in ASD when presenting emotional faces (e.g., Baron-Cohen et al., 1999; Greimel et al., 2010; Holt et al., 2014) and differential activation in ASD in this region during mentalizing and social cognition has been identified in two meta-analyses (Di Martino et al., 2009; Philip et al., 2012). Furthermore, prior studies that used the same paradigm as in the current study showed that the TPJ is sensitive to happy reactions in TD controls (Klapwijk et al., 2016b; Lelieveld et al., 2013a). Given reports of reduced TPJ activation in social tasks in ASD (Castelli et al., 2002; Lombardo et al., 2011), we also expected group differences here.

Method

Participants

Male adolescents with ASD were recruited from specialized child psychiatric centers providing both inpatient and outpatient care for persons with ASD; TD control adolescents were recruited through local advertisement. All participants were aged 15-19 years (see Table 1 for participant characteristics). Exclusion cri-

teria were (central) neurological abnormalities, a history of epilepsy or seizures, head trauma, left-handedness, and IQ less than 75. Intelligence was estimated using 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 consisted of 23 adolescent boys with a clinical ASD diagnosis of whom 21 completed both phases of the task (see *Experimental task* section below). Data from two ASD participants were discarded due to excessive motion, leaving a final sample of 19 participants with ASD. Two of the 19 boys were diagnosed with autistic disorder, nine with Asperger's syndrome, and eight 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, two 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. Seventeen 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 17 participants and all 17 fulfilled the autism criteria on the ADI-R Social Interaction and Communications domains. Review of the medical charts of the other two indicated that autistic features were already present from an early age. Nine participants with ASD took medication at the time of testing (N = 1 atypical antipsychotics, N = 2 psychostimulants, N = 3 selective serotonin re-uptake inhibitors, N = 3 multiple medications). The social responsiveness scale self-report version (SRS-A) (Constantino & Gruber, 2002; Constantino & Todd, 2005) was used as a quantitative measure of autistic traits.

Thirty-seven TD control boys participated of whom 34 completed both phases of the task (see *Experimental task* section below). Data from one TD participant was discarded due to excessive motion and another 14 for group-wise matching for age and IQ, leaving a final sample of 19 TD participants. All TD par-

ticipants were screened using the SRS-A in order to exclude participants with heightened autistic traits (i.e., SRS-A *T*-score > 60). The youth self report (YSR; Achenbach, 1991) was used to assess general psychopathology; data for one participant were missing but none of the other TD boys scored in the clinical range on the YSR externalizing or internalizing scales.

Table 1. *Group characteristics*

	Autism spectrum disorders (ASD) (N = 19)	Typically developing (TD) (N = 19)	*p*-value
Age, years (*SD*)	17.1 (1.2)	16.7 (1.2)	.38
IQ, *M* (*SD*)	107.7 (11.2)	102.7 (6.2)	.10
Empathy scores [a]			
Cognitive empathy, *M* (*SD*)	34.4 (3.9)	37.3 (5.3)	.16
Affective empathy, *M* (*SD*)	34.7 (7.9)	38.1 (6.6)	.06
SRS-A autistic traits, *M* (*SD*) *	66.7 (20.0)	35.1 (14.7)	< .001
YSR DSM-oriented scales [b]			
Depressive problems, *M* (*SD*)	6.5 (5.1)	3.7 (4.9)	.09
Anxiety problems, *M* (*SD*)	3.0 (2.3)	1.7 (1.4)	.05

** Significantly different at p < 0.001.*
[a] Self-report of affective and cognitive empathy was measured using the Basic Empathy Scale (Jolliffe & Farrington, 2006).
[b] YSR is reported for N = 18 TD, due to missing data for one TD participant.

Experimental task

We examined participants' fairness choices in the Dictator Game (Kahneman et al., 1986) after receiving emotional reactions from others, using a procedure previously used in studies with adults and (conduct disordered) adolescents (Klapwijk et al., 2016b; Klapwijk et al., 2013; Lelieveld et al., 2013a). Participants first took part in a preliminary study one week before scanning (*first phase of the experiment*), where they read a scenario after which they were instructed to divide 10 tokens between themselves and another person. They could choose a 6-4 distribution in favor of themselves, an equal distribution (5-5), or a distribution in favor of the other (4-6). This negotiation scenario was intended to assure that most partici-

pants chose the 6-4 option in this phase of the study. Only participants that chose a 6-4 distribution took part in the second phase of the experiment during scanning (21 out of 23 ASD boys and 34 out of 37 TD boys chose a 6-4 distribution). Hereby we assured the credibility of the second phase in which angry, disappointed, or happy emotional reactions would be directed at the 6-4 offer chosen in the first phase. Using these three emotions allows for comparisons of the effects of negative and positive communicated emotions and the effects of different types of negative emotions (Lelieveld et al., 2013a; van Kleef et al., 2010). Additionally, although it is not uncommon to find angry and disappointed reactions in response to a 6-4 distribution because of the relative unfairness of this distribution, happy reactions should be considered acceptable since offers of around 40% of the total are mostly accepted in economic games (Falk & Fischbacher, 2006).

In the *second phase of the experiment*, the boys were told that their unfair offer (the 6-4 distribution chosen in the first phase) was presented to 60 peers who were given the opportunity to write out their reaction upon receiving the offer. In reality, the reactions were preprogrammed and we left at least one week between the first and second phase to increase the credibility that researchers actually collected reactions from others. During scanning, participants were paired with a different player on each trial, whose first name was provided and whose reaction to the 6-4 distribution was angry, disappointed, or happy. Participants read the reactions of their peers and subsequently played a version of the Dictator Game with the peer who provided the reaction (see Figure 1). In this Dictator Game the participants were the allocator and had to divide 10 tokens. They could choose between different fair and unfair distributions while the recipient had to accept any distribution they would make. Each trial started with a jittered fixation (min. = 0.55 s, max. = 4.95 s, M = 1.54 s), after which the participants were presented with the emotional reaction for a period of three seconds plus a jittered interval (min. = 0.55 s, max. = 4.95 s, M = 1.54 s) and subsequently had six seconds to make a decision between two distributions. The 60 trials were presented in pseudo-random order divided over three blocks of four minutes each. Before the task started, participants learned that at the end of the experiment the computer would randomly select 10 trials to determine their total earnings, which would be added to

the standard compensation for their participation. At the end of the session, participant's pay-off was presented, which varied between 2.5 and 6 euros. Afterwards, participants completed a questionnaire in which they were probed for suspicion. None of the participants expressed doubt about the set-up of the task.

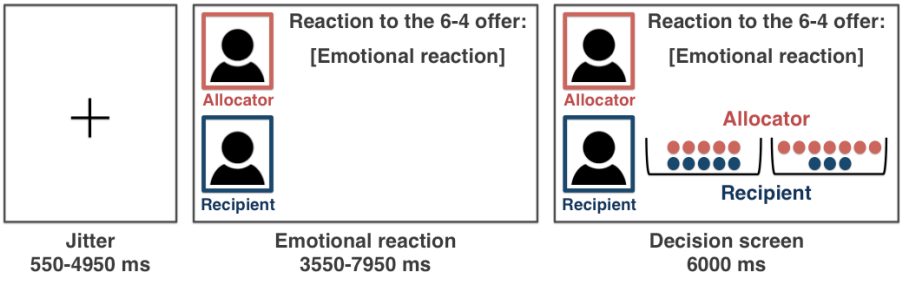

Figure 1 *Visual display and timing (in milliseconds; ms) of the task in the scanner. The emotional reaction of the recipient (here "emotional reaction") was displayed after a jittered fixation cross. Subsequently, the screen displayed two offers each containing red and blue tokens, which indicated the share for the allocator and the recipient, respectively (here 5–5 vs. 7–3). The name of the allocator was displayed in red (here "allocator") and the name of the recipient in blue (here "recipient"). If participants did not respond within 6000 ms, a screen displaying 'Too late!' was presented. After the response, the decision screen remained on the screen until 6000 ms after the onset of the decision screen*

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. 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. Data from participants with excess motion defined by relative mean displacement > 0.5 mm were excluded from further analysis (ASD N = 2; TD N = 1). 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.

fMRI data analysis

FMRI data analysis was conducted using FEAT (fMRI expert analysis tool) version 6.00, part of FSL (www.fmrib.ox.ac.uk/fsl). The following prestatistics 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, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0s). Functional scans were registered to the T1-weighted anatomical images, and subsequently to the 2 mm MNI-152 standard space template. Time-series statistical analysis was performed using FILM with local autocorrelation correction. To investigate the effects of the communicated emotions, we modeled the onset of the presentation of the three different emotional reactions (i.e., anger, disappointment, happiness) as an event with zero duration convolved with a gamma hemodynamic response function. To account for residual movement artifacts, the six realignment parameters (three for translation in mm and three for rotation in degrees) were included in the model as covariates of no interest. Note that in the final sample used in the present study there were no significant differences in the six realignment parameters (all $p > 0.05$) between the ASD and TD groups. At first-level for each run for each participant, primary contrasts of interest were generated. Positive versus negative emotions were contrasted (happiness > [anger and disappointment]) as well as happiness against the separate negative emotions (happiness > anger; happiness > disappointment) and the negative emotions against each other (anger > disappointment). A second-level, fixed-effects analysis combined data across the three runs for each participant. Individual participant data were then entered into a third-level group analysis using a mixed-effects design (FLAME) whole-brain analysis. The general linear model included the two groups (ASD and TD) and to account for possible age effects, we included age (mean-centered) as covariate of no interest. In addition, in the ASD group we analyzed the effects of autistic traits on brain responses during the different contrasts by using SRS scores as regressors of interest, adding age (mean-centered) as covariate of no interest. Resulting statistical maps were corrected for multiple comparisons using cluster-based correction ($p < 0.05$, initial

cluster-forming threshold $Z > 2.3$). We used Featquery and SPSS version 22 (IBM Corp., Armonk, NY, USA) to conduct region of interest (ROI) analyses to correlate task behavior and ASD symptom scores 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 contrasts of interest with binarized anatomical ROIs using the Harvard-Oxford structural atlases distributed with FSL. Finally, we explored whether additional clinical factors, such as medication exposure or comorbidity, might have influenced the results. Extracted z values from the ROIs identified in the whole-brain analyses were entered into SPSS to compare only those participants with ASD without a comorbid disorder, those not using medication, or both to TD controls. Additionally, we compared ASD participants with a comorbid disorder to those without and ASD participants who were on medication to those who were not. Given the high rates of anxiety reported in ASD (White et al., 2009) and the possible impact of anxiety on social decision making (Luo et al., 2014; Wu et al., 2013), we also repeated the fMRI analyses with YSR DSM-oriented Anxiety problems as a covariate of no interest to account for possible effects of anxiety. Mean group substitution was used to replace missing YSR data for one TD participant.

Results

Behavioral results

Fairness decisions after the three different emotions were compared between the groups with a 2 ×3 mixed ANOVA (group ×emotion). We found a main effect of emotion, $F(1, 37) = 4.48, p = .015$, caused by a higher percentage of unfair offers in response to angry ($M = 62.7$ %; $SD = 29.9$, $p < .001$) and happy ($M = 59.1$ %; $SD = 31.0$, $p < .05$) compared to disappointed reactions ($M = 47.5$ %; $SD = 26.0$). There was no main effect of group, $F(1, 37) = 0.18, p = .68$, showing that the groups did not differ on fairness levels across the emotions combined. We found a significant interaction effect, $F(1, 37) = 8.52, p < .001$, showing group differences in the reactions after the different emotional expressions (see Figure 2). Post hoc

tests revealed that within the ASD group, participants more often chose the unfair than the fair option when dealing with angry peers (71.8 %, SD = 22.7) than when dealing with disappointed (53.7 %, SD = 23.1, p = .001) and happy (47.9 %, SD = 31.1, p < .05) peers. No differences in fairness decisions after disappointment and happiness were found in the ASD group. Next, within the TD group, we found that participants more often chose the unfair than the fair option when dealing with angry (53.6 %, SD = 33.8, p < .01) and happy (70.3 %, SD = 27.2, p < .005) peers than when dealing with disappointed peers (41.3 %, SD = 27.8). No differences in fairness decisions after anger and happiness were found in the TD group. Finally, between-group comparisons showed that the ASD (versus TD) group made significantly less unfair offers after happy reactions (p < .05), and marginally significantly more unfair offers after angry reactions (p = .058). No significant group difference was found in unfairness after disappointed reactions (p = .14).

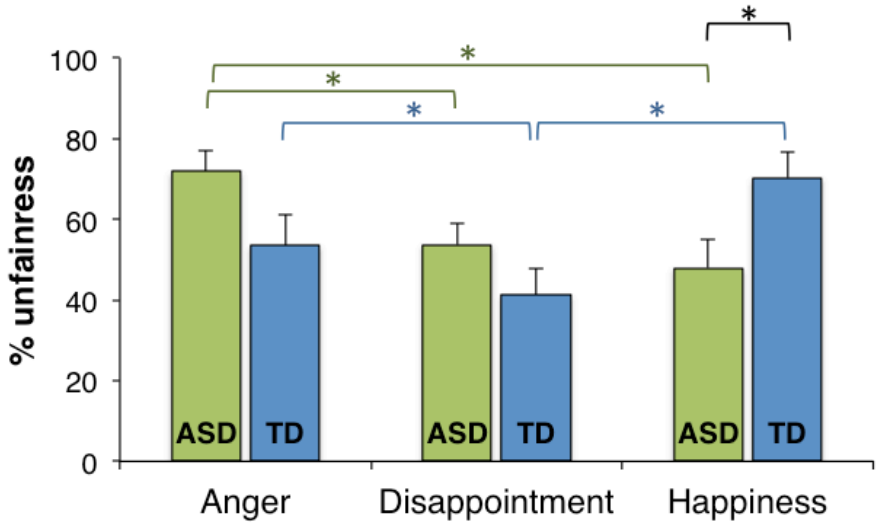

Figure 2 *Percentage of unfair offers after communication of anger, disappointment, and happiness, separate for ASD and TD groups. Asterisks indicate significant differences within groups (green = ASD; blue = TD) and between groups (in black)*

fMRI results

The first set of whole-brain analyses aimed to identify regions that differed between the ASD and TD groups when receiving positive relative to negative emotional reactions in general (i.e., happiness > [anger and disappointment] contrast). No group differences were found whilst using this contrast. When analyzing the contrasts that compared happiness to a specific negative emotion (i.e., happiness > anger, and the happiness > disappointment) we found that the ASD (versus TD) group showed less activation in the left and right precentral gyrus and right middle frontal gyrus in the happiness > anger contrast (see Table 2). Finally, when comparing the two negative emotions with each other, we found no significant group differences between the ASD and TD groups when analyzing the anger > disappointment and disappointment > anger contrasts.

We also analyzed the effects of autistic traits as measured by the SRS-A on brain responses during the different contrasts in the ASD group separately. These analyses revealed that higher activity in the left postcentral gyrus and supramarginal gyrus in the happiness > [anger and disappointment] contrast was related to higher autistic traits in the ASD group. This relation was also found between autistic traits and activity in these regions in the separate happiness > anger and happiness > disappointment contrasts. No other brain regions showed an association between autistic traits and activity in any of the contrasts. Additionally, control analyses showed no relation between autistic traits and brain activation in the TD group, suggesting the relation between autistic traits and brain activation is specific for the ASD group. We also repeated the fMRI analyses with the lowest scoring participant removed, which also showed a relation between autistic traits and activity in the left postcentral gyrus (see Supplementary materials).

Table 2. *MNI coordinates, z values and cluster sizes for brain regions revealed by the whole brain pairwise comparisons of the TD control > ASD groups, z > 2.3, p < .05 cluster-corrected. Activation clusters were labeled using the Harvard-Oxford structural atlases.*

Anatomical region	Max *z*	MNI peak coords			Size in voxels
		x	y	z	
TD > ASD					
happiness > anger					
L precentral gyrus	3.94	-44	2	46	396
R precentral gyrus	3.59	56	2	42	376
R middle frontal gyrus	3.36	54	32	26	(part of above)
Autistic traits (ASD group only)					
happiness > [anger and disappointment]					
L postcentral gyrus	3.71	-48	-32	52	1386
happiness > disappointment					
L postcentral gyrus	3.71	-48	-32	56	1056
happiness > anger					
L supramarginal gyrus	3.45	-46	-44	56	398
L postcentral gyrus	3.45	-46	-28	50	(part of above)

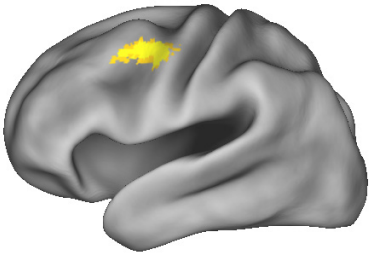

Figure 3 *Group differences in the left precentral gyrus for the happiness > anger contrast cluster-thresholded at z > 2.3, p < .05*

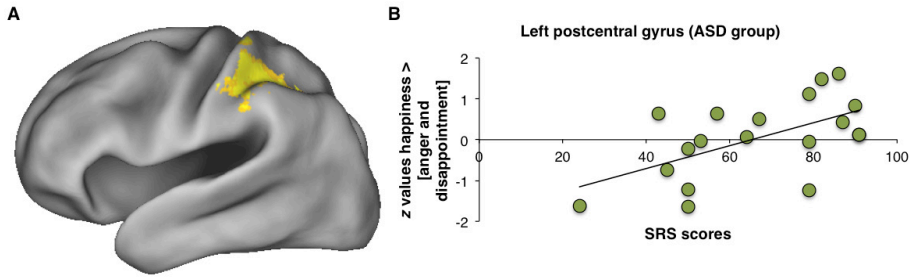

Figure 4 (A) *Higher autistic traits in the ASD group were related to higher activity in the left postcentral gyrus in the happiness > [anger and disappointment] contrast cluster-thresholded at z > 2.3, p < .05 with* **(B)** *graph showing mean z values in the postcentral gyrus as a function of SRS scores in the ASD group*

Relationships between fairness decisions and brain activation

Next, we conducted exploratory analyses to investigate the relation between fairness decisions and brain activity in regions identified in our whole-brain analysis. We investigated the relation between the percentage of unfair offers in response to happy reactions and activity in the right precentral gyrus for the happiness > anger contrast. This analysis revealed a significant negative correlation between the percentage unfair offers and left precental gyrus activity for the TD control group (r = -0.56, p < 0.5), but not for the ASD group (r = 0.08, p = 0.75). However, Fisher z-values were calculated which indicated that the difference between these correlations was not significant (z = 1.56, p = 0.58).

Effects of comorbidity and medication

Post-hoc analyses revealed that all group differences remained significant when excluding ASD participants with comorbid disorders or those using medication (all ps < .01). In addition, no significant group differences were found between ASD participants with comorbid disorders and those without (all ps > .2) or between ASD participants using medication or not (all ps > .6). The analyses with the YSR DSM-oriented Anxiety problems as a covariate did not considerably alter results. Only minor changes in size and peak coordinates of the clusters revealed in the main analysis were observed (see Supplemental Table S1).

Discussion

This is the first study focusing on the effects of emotions on fairness decisions and brain responses in ASD. Behavioral analyses showed that ASD participants were more unfair when dealing with angry compared to disappointed and happy peers, whereas TD participants more often were unfair when dealing with angry but also with happy peers compared to those that communicated disappointment. These group differences were mainly driven by differences in reactions to happy peers, as the TD group chose significantly more unfair offers after happy reactions than the ASD group. The imaging results showed reduced brain responses in the precental gyrus and middle frontal gyrus in the ASD versus TD group when receiving happy versus angry reactions. Additionally, more autistic traits in the ASD group were associated with more activity in the postcentral gyrus in the happiness versus anger and disappointment contrasts.

Although we hypothesized that the ASD group would be less likely to differentiate between the three emotions when making fairness decisions, this hypothesis was not supported as the behavioral results suggest that individuals with ASD did adjust their allocation behavior in response to the emotions of others. However, participants with ASD reacted less unfair than TD controls in response to happiness (and more unfair in response to anger compared to TD controls, although this difference failed to reach significance). The increase in unfairness in response to happiness of the TD participants is in line with findings from previous studies (Klapwijk et al., 2016b; Klapwijk et al., 2013; van Kleef et al., 2004). When receiving a happy reaction after a previous unfair offer, one could infer that the other was already satisfied and would therefore be content with another unfair offer (Cacioppo & Gardner, 1999; van Kleef et al., 2010). Possibly, our participants with ASD used different heuristics that require less such inferences about mental states since they did not choose to be more unfair in response to happiness compared to the TD participants. However, this interpretation could not be supported by altered activation in brain regions usually associated with mentalizing in the ASD group in the current study.

We did not find group differences in the specifically hypothesized brain regions that have been previously linked to atypical social-affective functioning in ASD such as the IFG and TPJ (Greimel et al., 2010; Lombardo et al., 2011). The absence of group differences in these areas might result from the specific task used in the current study, in which written emotions were presented and participants made fairness decisions subsequently. However, previous studies did report differences between ASD and TD controls in these regions in tasks using written stimuli (Lombardo et al., 2011) and the TPJ specifically has been implicated in previous studies using the same paradigm as in the current study (Klapwijk et al., 2016b; Lelieveld et al., 2013a). It might also be that individuals with ASD do not recruit these hypothesized social-affective brain regions differently from controls when making social decisions. The only other study that used fMRI to study social decisions in an economic game in ASD found group differences between individuals with ASD and controls in the middle cingulate gyrus (Chiu et al., 2008), and not in either IFG, mPFC, TPJ or amygdala. Given the sparse number of neuroimaging studies that employed economic games in ASD and the posited potential for understanding mental disorders using neuroeconomics (Hasler, 2012; King-Casas & Chiu, 2012; Kishida et al., 2010; Sharp et al., 2012), future studies are warranted to further test which brain regions are differentially recruited when making social decisions in ASD.

Interestingly, however, the reduced responses observed in the current study in the precentral gyrus and middle frontal gyrus, and also the postcentral gyrus activation related to autistic traits, align with results from recent meta-analyses of fMRI studies in ASD (Di Martino et al., 2009; Dickstein et al., 2013; Patriquin et al., 2016). Hypoactivation during social tasks in ASD versus controls was found in both the left and right precentral gyrus in the meta-analysis by Di Martino et al. (2009) and in the left precentral gyrus in the Patriquin et al. (2016) meta-analysis. Reduced responses in this area in ASD versus controls have been reported during imitation of emotional expressions and finger movements (Dapretto et al., 2006; Williams et al., 2006) and when observing fearful expressions (Deeley et al., 2007). Although the precentral gyrus is considered to be part of motor-related cortex, activity in this area has previously been associated with social-emotional

functioning. Precentral gyrus activity has been found to increase when receiving empathic responses from others (Seehausen et al., 2014; Seehausen et al., 2016) and activity in this area is also related to self-reported affective empathy in social versus nonsocial emotional scenes (Hooker et al., 2010). Furthermore, atypical functional connectivity within the precentral gyrus has been associated not only with impaired motor skills but also with social deficits in ASD (Nebel et al., 2014). In the current study, reduced activation in the precental gyrus was found in the ASD versus TD group specifically when contrasting happy versus angry reactions. This might suggest that the ASD participants process the happy emotional information differently than the TD controls in this area and therefore also responded less unfair in response to happiness than the TD group. However, future studies are needed to further clarify the role of the precentral gyrus in social-emotional functioning. For example, the current paradigm does not allow inferring whether the different response to happiness in the ASD group is the result of less responsiveness to happy emotions in general or to a different cognitive appraisal of happiness that leads to increased fairness and decreased precentral gyrus activation. Experiments in which the emotional intensity of happiness is varied could resolve whether responsiveness to happiness is related to precentral gyrus activation or not. The current findings as well as the precentral gyrus hypoactivation in ASD during social tasks in two meta-analyses (Di Martino et al., 2009; Patriquin et al., 2016) might point to a relation between precentral gyrus dysfunctions and social deficits in ASD.

The current results additionally showed a positive association between autistic traits and activity in the postcentral gyrus in the ASD group in the happiness versus anger and disappointment contrasts. The postcentral gyrus is a somatosensory region that is also not usually discussed in the context of ASD social deficits, although it has consistently been revealed as a hyperactivated region in ASD meta-analyses of social tasks (Di Martino et al., 2009; Dickstein et al., 2013; Patriquin et al., 2016) and it has also been reported as a region being structurally altered in ASD (Hyde et al., 2010). Previous studies in healthy populations have reported the involvement of primary somatosensory cortex in affective touch (Gazzola et al., 2012), in processing facial and vocal emotions (Adolphs et al., 2000; Heberlein & Atkinson, 2009) and

in affective language use (Saxbe et al., 2013). The relation between autistic traits and postcentral gyrus activation in response to happy versus angry and disappointed emotions in the current paradigm might suggest a specific relation between somatosensory processing of positive emotions and ASD symptoms.

Several limitations to this study should be noted. First, although our sample size (N=19 per group) is comparable with other task-related fMRI studies in ASD, this sample size is relatively small and may have limited the power to detect group differences in brain regions usually linked to social cognition and emotion processing. Second, since our sample contained adolescent boys only, we do not know whether our results are generalizable to girls and to children and adults with ASD. Third, the task design employed in the current study contained written preset emotions only. Future studies could further increase the amount of interaction by studying face-to-face interactions, for example by using virtual reality. Finally, it remains unclear why differences in ASD versus controls were found in the precentral gyrus, whilst a correlation with autistic traits was found in the postcentral gyrus but not in the precentral gyrus. It can be speculated that the relatively small sample size has limited the power to find a correlation between precentral gyrus activation and autistic traits. It is also possible that a correlation between autistic traits and brain activity within the ASD group does not necessarily imply group differences in the same region between the ASD and TD groups.

In conclusion, the current study provides an initial step in examining how explicit emotional feedback influences interactive decisions and associated brain responses in ASD. The results suggest that individuals with ASD do employ explicitly expressed emotional information when making social decisions, although responses towards happiness seemed atypical and were fairer than controls. The neuroimaging results might point to a possible role of precentral and postcentral gyrus in social-affective difficulties in ASD, although more research is needed to specify the neurocognitive mechanisms that are associated with these brain regions during social cognition. Future research in which the role of expressed emotions is further investigated could help to refine models for social interactions in ASD.

Supplementary materials

Table S1. *MNI coordinates, z values and cluster sizes for brain regions revealed by the whole brain pairwise comparisons of the TD control > ASD groups including YSR DSM oriented Anxiety problems as a covariate, z > 2.3, p < .05 cluster-corrected.Activation clusters were labeled using the Harvard-Oxford structural atlases.*

Anatomical region	Max *z*	MNI peak coords			Size in voxels
		x	y	z	
TD > ASD					
happiness > anger					
L precentral gyrus	3.97	-52	4	46	388
R middle frontal gyrus	3.62	52	28	34	425
R precentral gyrus	3.36	56	2	42	(part of above)
Autistic traits (ASD group only)					
happiness > [anger and disappointment]					
L postcentral gyrus	3.67	-48	-32	52	1207
happiness > disappointment					
L postcentral gyrus	3.68	-48	-32	56	918

Table S2. *MNI coordinates, z values and cluster sizes for brain regions revealed by the whole brain analysis with autistic traits as covariate with outlier removed (N = 18), z > 2.3, p < .05 cluster-corrected.Activation clusters were labeled using the Harvard-Oxford structural atlases.*

Anatomical region	Max *z*	MNI peak coords			Size in voxels
		x	y	z	
Autistic traits (ASD group only, outlier removed, *N* = 18)					
happiness > [anger and disappointment]					
L middle frontal gyrus	3.83	-28	36	44	679
L postcentral gyrus	3.52	-48	-32	52	929
Paracingulate gyrus	3.39	2	28	34	539
L precentral gyrus	3.26	-48	8	28	318
happiness > anger					
Paracingulate gyrus	3.88	4	26	34	628
L supramarginal gyrus	3.32	-46	-44	56	454
L postcentral gyrus	3.10	-46	-28	50	(part of above)

6 Summary and general Discussion

The goal of this thesis was to examine social-emotional dysfunction in autism spectrum disorder (ASD) and conduct disorder (CD) from a cognitive neuroscience perspective by directly comparing groups with ASD and CD with high callous-unemotional traits (CD/CU+) and by studying neural mechanisms underlying social decisions in response to other's emotions. Drawing on previous theoretical and empirical work on dissociable empathy deficits in ASD and CD/CU+, we compared these groups on cognitive and affective aspects of empathy during basic emotion processing using functional magnetic resonance imaging (fMRI). In order to evaluate possible disorder-specific differences between these groups in brain structure, we also compared microstructural integrity of white matter tracts that may underlie social-emotional processing in these groups. Furthermore, we combined an economic game with an emotion manipulation to elucidate the brain responses when making social decisions influenced by emotional contextual information in ASD and CD (separately compared to typically developing (TD) controls). In this final chapter, findings of these empirical studies are summarized and discussed in light of previous work and relevant recent developments. Limitations and implications are discussed, as well as future directions inspired by the work.

General summary

The first two empirical chapters of this thesis describe two studies in which adolescent boys with ASD, adolescent boys with CD/CU+, and adolescent TD boys were directly compared. In **chapter two**, an emotional face task was used during fMRI scanning to assess these three groups of boys. Participants were presented with angry and fearful faces and were asked to either infer the emotional state from the face to assess emotion recognition, or to judge their own emotional response to the face as a proxy of emotional resonance. As hypothesized, the ASD group showed altered responses in a brain region important for social cognition and cognitive empathy, demonstrated by a decreased response in the ventromedial prefrontal cortex (vmPFC) during the emotion recognition condition. Alternatively, the decreased vmPFC response might also point to problems in

regulating reactions towards angry and fearful faces in the ASD group, given the role of this brain region in emotion regulation and reports of comprised emotion regulation in ASD. Furthermore, we could only partly confirm the hypothesis concerning reduced responses in affective brain regions specifically in the CD/CU+ group, since both ASD and CD/CU+ boys showed diminished responses in the left amygdala during the emotional resonance condition compared to TD boys. Disorder-specific reductions compared to the TD controls during emotional resonance were found in bilateral hippocampus in the ASD group. Specific reductions in the inferior frontal gyrus (IFG) and anterior insula (AI) in CD/CU+ boys are consistent with previous studies suggesting that they resonate less with the feelings of others. In sum, this study showed overlap in reduced amygdala responses in ASD and CD/CU+ and specific abnormalities in the neural processing of cognitive aspects of empathy in ASD versus more problems in affective aspects in CD/CU+. These results demonstrate that ASD and CD/CU+ are not appropriately characterized by broadly defined similarities in social-emotional dysfunction, instead suggesting diagnostic instruments and interventions should be aimed at different aspects of empathic functioning in these disorders.

Chapter three was the first study to compare ASD, CD/CU+ and TD youths on underlying white matter microstructure using diffusion tensor imaging (DTI). In contrast to many previous studies that found alterations in fractional anisotropy (FA) values in the uncinate fasciculus (UF) when comparing ASD and CD with TD groups, we did not observe significant group differences in the UF between the ASD, CD/CU+, or TD groups. Our analysis did reveal microstructural alterations in the cingulum and the corpus callosum in the CD/CU+ versus ASD group, evidenced by increased FA values in these tracts in the CD/CU+ group compared to the ASD group with the TD group being intermediate. Previous studies have shown the cingulum to be important for mentalizing and cognitive empathy skills; our results of decreased FA in the ASD group in this tract may therefore be related to difficulties in social-cognitive processing in the ASD group. Additionally, the increased FA levels in the CD/CU+ may also reflect a neural mechanism underlying social difficulties, but the direction of the alterations suggest that either the pathways leading to these difficulties or their specific manifestations may be dif-

ferent in ASD and CD/CU+. The altered white matter microstructure we observed in the body and splenium of the corpus callosum in ASD and CD/CU+ might also contribute to social difficulties observed in both disorders and to aggression specifically in the CD/CU+ group. We did not find relations between white matter integrity and questionnaires of diagnostic traits, social cognition, or aggression. It remains to be investigated what cognitive or behavioral difficulties are caused by these differences in white matter integrity. For now we can conclude that ASD and CD/CU+ exhibit opposing disorder-specific alterations in white matter architecture in the cingulum and corpus callosum, suggesting alterations in these tracts may relate to specific dysfunction of brain networks in these disorders.

The first two empirical chapters showed differences between groups with ASD and CD/CU+ in processing basic emotions and in white matter tracts important for social-emotional processing. In the following chapters we were interested in how the groups acted upon the emotions of others by assessing behavioral and brain responses of fairness decisions in response to other's emotions. In **chapter four**, the group of boys with CD (with both high and low CU traits) was compared with the TD group using a paradigm in which they had to allocate money between themselves and peers while receiving written emotional reactions from a peer (depicting disappointment, anger, or happiness) to a previous unfair offer. TD individuals adjusted their fairness decisions in response to the different emotions as they reacted relatively more fair in response to disappointed reactions compared with angry and happy reactions. In contrast, the CD boys did not alter their behavior in response to the emotional feedback provided by their interaction partner. The fMRI results showed that the CD boys compared with the TD boys had less activity in the right temporoparietal junction and supramarginal gyrus (TPJ/SMG) when receiving happy compared with disappointed and angry reactions. In addition, activation in right TPJ/SMG correlated with fairness decisions after happy reactions in the TD group but not in the CD group. Given the role of the TPJ and SMG in perspective taking, these results suggest boys with CD were less inclined than the TD boys to take the perspective of the other person during happy compared with angry and disappointed reactions, which dovetails with their unresponsiveness to the other person's emotional message. We also found

decreased activation in the dorsolateral prefrontal cortex (DLPFC) in the happy versus angry contrast, suggesting less regulatory brain activation in the CD boys compared with TD boys. Taken together, these findings demonstrate decreased adjustment of decisions in response to different emotions in CD compared to TD boys, which is associated with reduced responses to others' emotions in brain regions important for perspective-taking and cognitive control. Such decreased sensitivity to emotional feedback might make it more likely that boys with CD pursue aggressive acts, as they may not adjust their hostile behavior in response to emotional signals of others.

In **chapter five**, we compared boys with ASD with TD boys using our Dictator Game with emotion manipulation. In contrast to CD boys, those with ASD did adjust their behavior in response to different emotions. Interestingly, the ASD group chose significantly less unfair offers after happy reactions than the TD controls. ASD youths reacted more unfairly when dealing with angry compared to disappointed and happy peers, whereas TD participants reacted more unfairly when dealing with angry but also with happy peers compared to disappointed peers. The neuroimaging results showed reduced brain responses in the precental gyrus in the ASD versus TD group when receiving happy versus angry reactions and autistic traits correlated with activity in the postcentral gyrus. These brain regions have previously been associated mostly with motoric and somatosensory functions, but have also been found to be hypoactivated during social tasks in ASD versus TD groups. Our results could help to refine models for social interactions in ASD, as they suggest that alterations in different brain regions are concerned when acting upon as compared to simply observing other's emotions.

Comparing ASD and CD/CU+

Our results demonstrate dissociable alterations in neural processing of facial emotions in ASD compared to CD/CU+. Thus, although both disorders are characterized by atypical processing of emotions, this seems to be underpinned by alterations in different neurocognitive systems. In ASD, decreased responses compared

to the CD/CU+ and TD group were found in the vmPFC during emotion recognition, whereas the CD/CU+ group showed decreased responses in the AI and IFG during emotional resonance. This is in line with previous studies showing atypical processing of cognitive aspects of empathy and mentalizing in the mPFC in ASD (Lombardo et al., 2010; Wang et al., 2007) compared to decreased resonance with other's feelings in the IFG and AI in CD/CU+ (Lockwood et al., 2013b; Michalska et al., 2015; Sebastian et al., 2012b). Importantly, we provide evidence for dissociable neural processing of cognitive and affective aspects of empathy by a unique direct comparison of ASD and CD/CU+. These results further corroborate theoretical and behavioral accounts of cognitive social difficulties in ASD versus affective social difficulties in CD/CU+ (Bird & Viding, 2014; Blair, 2005; Jones et al., 2010; Schwenck et al., 2012).

In addition to these dissociable patterns of brain activation we also found overlap in altered neural processing of emotions in the amygdala, as both the ASD and CD/CU+ boys showed diminished responses in the left amygdala during the emotional resonance condition compared to TD boys. At first sight, this finding can be interpreted as reflecting similar emotion processing problems in ASD and CD/CU+ in the amygdala. Indeed, previous studies have found decreased amygdala responses during emotional face processing in both disorders (e.g., Pelphrey et al., 2007; Viding et al., 2012; Wang et al., 2004; although less consistently for ASD, see for example Monk et al., 2010). Theories of amygdala dysfunction in ASD point to a disruption in directing attention to socially relevant features of emotional faces in general (Blair, 2008; Pelphrey et al., 2011), whereas in CD/CU+ this is thought to be related to impaired processing of distress cues specifically (Blair, 2008; Moul et al., 2012). Hence, future studies are needed to establish whether these mechanisms function differently in ASD and CD/CU+ by expanding direct comparisons to other emotions such as disgust and surprise while simultaneously tracking eye gaze patterns.

Following the dissociable alterations in brain responses to emotions in the ASD and CD/CU+ groups, we also found differences in white matter microstructure between the disorders. In line with previous studies that assessed ASD and CD separately, we found lower FA coupled with higher mean diffusivity (MD) and

radial diffusivity (RD) values in the cingulum and the corpus callosum in ASD compared to higher FA coupled with lower MD and RD values in these regions in the CD/CU+ group. These disorder-specific alterations in white matter microstructure are intriguing and may account for social and executive function deficits seen in ASD and CD/CU+. However, the exact functional and behavioral significance of these findings is not yet known. First, the measures of white matter architecture (FA, MD, RD) that were used probably reflect degree of myelination (Beaulieu, 2002), but the exact properties of the underlying microstructure cannot be derived using DTI (Jones et al., 2013b). Second, although we know from previous studies that the cingulum and corpus callosum are important for social cognition and executive functions, we must be careful with the reverse inference that any microstructural alteration in these tracts impacts these associated functions (cf., Poldrack, 2011). However, in line with the dissociable alterations of brain function in chapter two, our white matter results underline the importance of finding what brain measures are specific for separate disorders. This is especially critical when searching for brain measures as potential biomarkers to aid diagnosis and treatment, as any useful biomarker should not only differentiate a specific disorder from healthy controls but must also differentiate the specific disorder from any other psychiatric disorder (Boksa, 2013). Since there is large overlap in the functional and structural brain correlates of psychiatric disorders (Goodkind et al., 2015; Sprooten et al., 2017), direct comparisons between different disorders may benefit the endeavor for specific biomarkers.

The overlap and comorbidity of different disorders has also been recognized specifically for several traits and symptoms that are associated both with ASD and CD/CU+ subgroups. For example, some individuals with ASD also show elevated levels of CU traits, possibly presenting them with a combination of cognitive and affective deficits in empathy (Rogers et al., 2006). A recent study found an increase in CU traits in ASD compared with the general population, suggesting such a 'double hit' may be rather common (Carter Leno et al., 2015). Elevated levels of disruptive behaviors are also reported in ASD subsamples (Kaat & Lecavalier, 2013; Simonoff et al., 2008), but the disruptive behavior in ASD may have a distinct neural basis separable from core ASD symptoms (Yang et al., 2017). Collectively, these

studies underscore the importance of not only comparing well-separated disorder groups, but also of comparing non-comorbid groups with comorbid groups (e.g., ASD with co-occurring CD or CU+). Such comparisons can further specify what mechanisms are disorder-specific and to what extent the comorbid presentation exhibits the neurocognitive profile of the non-comorbid disorders or represents a qualitatively different, more complex disorder (Rubia, 2011).

Another area of overlap that is particularly relevant for the distinction of empathic deficits in ASD and CD/CU+ is comorbid alexithymia, a subclinical condition characterized by difficulties in describing one's own emotion states (Bird & Cook, 2013). It has been argued that a high comorbidity between alexithymic traits and ASD may explain reports of affective empathy deficits in ASD (Bird et al., 2010). Moreover, alexithymic and CU traits may be independently related to decreases in affective empathy (Lockwood et al., 2013a). Although we did not administer an alexithymia questionnaire, the normal levels of self-reported affective empathy in the ASD group suggest no elevated levels of alexithymia in the current ASD sample as a whole. Whilst self-reported affective empathy was decreased in the CD/CU+ group presented in this thesis, future studies are needed to clarify whether this is associated with increased alexithymia. The relation between alexithymia and CU traits has received relatively less attention. Research so far however suggests alexithymia does not account for affective empathy deficits in CU as seems to be the case in ASD (Lander et al., 2012; Lockwood et al., 2013a). Such studies could also shed further light on possible sub processes of affective empathy that might be affected by a reduced ability to identify one's own emotions in alexithymia and a reduced tendency to feel what others feel in those with CU+ (Lockwood et al., 2013a).

Our comparison of ASD and CD/CU+ mainly relies on rather recent theoretical accounts of the dissociation between cognitive empathy deficits in ASD versus affective empathy deficits in psychopathy / CU+ (Blair, 2008; Blair, 2005; Smith, 2006). Interest in comparing those with ASD and CD (regardless of CU traits) dates further back, as several scholars have noticed similarities in impairments in social interactions between ASD and CD earlier (Gilchrist et al., 2001; Green et al., 2000; Happe & Frith, 1996). While these studies showed similarities

in reduced social insight and everyday social functioning in ASD and CD, they also demonstrated that those with CD were less impaired in making friends, conversational responses and in mentalizing compared to ASD (Adams et al., 2002; Green et al., 2000; Happe & Frith, 1996). Furthermore, on the social and communication domains of diagnostic instruments aimed to diagnose ASD (i.e., ADI, ADOS, SRS), CD groups scored much lower than ASD groups (Cholemkery et al., 2014; Gilchrist et al., 2001). Thus, although these disorders are obviously distinct in their clinical and diagnostic description, they share some social deficits leading some to hypothesize a common neurobiological basis (Barthelemy, 2014). Yet the work in the current thesis shows that ASD and CD/CU+ are at least partly dissociable on brain responses during emotion processing and in white matter architecture, in line with qualitative differences between these disorders in social-emotional dysfunction.

Neural correlates of social decisions in ASD and CD

Most previous studies in ASD and CD have failed to incorporate the role of decision-making when studying emotion processing. Therefore, we examined how those with ASD and CD would act upon other's emotions. By assessing fairness decisions after reactions of peers during fMRI scanning, we were able to study social decisions and associated brain responses in reaction to emotions. We showed that boys with CD differentiated less between angry, disappointed, and happy reactions on behavioral and neural levels than TD boys. Differences between ASD and TD boys in this paradigm were subtler, as the ASD group did differentiate between the three emotions but reacted atypical in response to happiness. Although we did not compare the ASD and CD groups directly on this task, these results suggest more profound difficulties in processing explicit emotional cues from others during social decision-making in the CD group. Interestingly, the decreased TPJ responses in the CD compared to TD group suggest problems with cognitive social processing in this task, which is usually linked to ASD rather than CD (Blair et al., 2016; Lombardo et al., 2011). These discrepancies may be due to differences

in task conditions, such as written versus facial emotions and isolated emotion processing versus emotion manipulated decision-making. It might also be that the dissociation between cognitive and affective social processing difficulties in ASD and CD is less strict and does not generalize to situations in which it is required to act upon other's emotions. Thus, our results may suggest that uncovering the neural correlates of interacting with others might lead to refined models of social-emotional deficits in ASD and CD that are different from previous accounts based on merely observing other's emotions.

Previous studies employing economic games in those with CD and in antisocial populations had shown that compared to controls, they seem to consider less contextual cues when making social decisions (Radke et al., 2013; Sharp et al., 2011a). We add to this that boys with CD also seem to be less influenced by contextual information in the form of other's emotions, evidenced by less differentiation in behavioral fairness responses to emotions and decreased activation in TPJ and DLPFC. As noted above, altered TPJ activation points to problems with cognitive social processing, which has also been found in other studies with antisocial youth using social exchange paradigms (Bubenzer-Busch et al., 2016; van den Bos et al., 2014). Future studies are needed to settle whether atypical TPJ activation in these paradigms is indexing social cognitive or attentional abnormalities in CD, for example by manipulating attentional and social demands. Another interesting avenue for future research is to employ similar allocation paradigms to assess the influence of known peers (as opposed to unknown peers in the study in this thesis) on decision-making in CD. As studies in TD adolescents have shown, risk taking but also prosocial behavior and their associated neural processes are changed by the mere presence of peers (Chein et al., 2011; Gardner & Steinberg, 2005; Van Hoorn et al., 2016). Studies have further shown that affiliation with deviant friends is strongly associated with antisocial behavior (Heinze et al., 2004; Laird et al., 1999). Using paradigms involving real-life peers in CD could investigate how deviant or non-deviant peers have different influences on brain and behavior and whether possibly more rewarding emotional cues of known peers do lead to consideration of contextual cues in CD.

In ASD, previous studies have also suggested less usage of contextual cues and specifically of inferences about others' intentions when making social decisions (Li et al., 2014; Yoshida et al., 2010). In our study, boys with ASD did differentially adjust their behavior to emotions of others, and we found no differences in brain regions associated with mentalizing such as mPFC or TPJ. It might thus be that individuals with ASD do not recruit these mentalizing brain regions differently from controls when making social decisions (see also Chiu et al., 2008). This may also reflect type II error due to the relatively small sample size (N = 19). The atypical responses to happiness in brain and behavior do suggest that the group with ASD shows some abnormalities in social decisions in response to emotions, but many open questions remain as to how neurocognitive abnormalities observed in more basic observational social cognition tasks in ASD relate to impairments in social decision-making. Using multi-round strategic games may shed more light on how mentalizing deficits in ASD affect social decision-making, since mentalizing is important for accurately predicting future behavior of the interaction partner (Frith & Singer, 2008). For example, an emotion manipulation in a multi-round trust game could uncover whether contextual information provided by emotional cues or the evaluation of other's actual repayment behavior is used to judge other's future repayment (Franzen et al., 2011).

As argued in the general introduction of this thesis, we used a social allocation paradigm to study social behaviors that are likely closer to real-world social interactions than passive observation of social and emotional stimuli. However, this is challenging research because of the tension between the desire for experimental control versus the unstructured and complex nature of ecologically valid social interaction. In the paradigm we employed interaction was further minimized as the fairness decisions in response to emotions were not followed by further exchanges with the individuals. Hence, multi-round exchange games may be used to capture more interactive elements of social interactions. Another advantage of such games is that they allow for computational modeling analysis, which enables more insight into the cognitive mechanisms that link measurable behaviors with their neural substrates (Montague et al., 2011). For example, recent theories suggest that deficits in understanding others in ASD may result

from an overreliance on present sensory (bottom-up) information as opposed to (top-down) prior beliefs (Lawson et al., 2014; Van de Cruys et al., 2014). These theories are now being tested using computational modeling, demonstrating that an inability to integrate social information rather than an inability to process social stimuli impedes social decision-making in those with higher levels of autistic traits (Sevgi et al., 2016). Taken together, challenging further work is needed to understand how difficulties in ASD and CD arise during ecologically valid real-time social interactions, for instance by using two-person set-ups (Bolis & Schilbach, 2017; Gilam & Hendler, 2016). Our results suggest that such work should also evaluate the role of other's emotions, as we showed that both ASD and CD groups differ from TD controls in considering explicitly presented emotions when making social decisions.

Limitations

Although this thesis offers important insights into the neural mechanisms involved in ASD and CD, it is critical to consider limitations when interpreting these findings. First, due to the cross-sectional design of the study we cannot infer whether the altered neural activation and structure in the clinical groups give rise to their social-emotional deficits or that these are a consequence of the developmental histories of the ASD and CD participants. Longitudinal designs starting at an early age are needed to explore whether brain alterations could predict developmental trajectories of these disorders; studies that have recently been undertaken in infants at risk for ASD (e.g., Hazlett et al., 2017). Second, although our sample sizes are somewhat larger than many preceding neuroimaging studies in ASD and CD, our sample was still modest in size, which may have limited the power to detect individual variations in relations between clinical characteristics and brain measures. Specifically in the ASD group our sample size was not large enough to permit meaningful subgroup analyses. Given the heterogeneity of ASD, larger samples are needed to compare subgroups based for instance on alexithymia and CU+. Third, since recruitment was restricted to adolescent boys, future studies are needed to

establish whether our results are generalizable to girls and to children and adults with ASD and CD. Fourth, limitations of neuroimaging studies in general are certainly worth mentioning, although these are not specific to the current thesis. For instance, magnetic resonance imaging (MRI) as employed in this thesis provides indirect measures of neural activity and structure, requiring subjects to lie still in a noisy environment. Hopefully, continuing technical advances will lead to an increasingly sophisticated and multidimensional characterization of brain structure and function and their associations with real-life behavior.

Implications and conclusions

This thesis shows that different neural mechanisms underlie social-emotional difficulties in ASD and CD/CU+. This finding is not only interesting from a theoretical viewpoint, but also provides better insight into the neurocognitive abnormalities of both disorders. These results may guide the search for potential biomarkers, which might be especially important for empathic deficits that are difficult to differentiate based on clinical observation. Ultimately, these insights will hopefully inform which interventions might work best to improve functioning in the social domain in youth with ASD and CD/CU+. The disorder-specific nature of the social-emotional difficulties may suggest that deploying and developing interventions aimed at specific difficulties probably give better results compared to interventions aimed at social skills in general. This also implies that possible pharmacological or neuromodulatory (e.g., transcranial magnetic stimulation or neurofeedback) treatments should be tailored towards different neural targets for the two disorders. In line with more cognitive social difficulties, interventions in ASD could focus on training the recognition of emotions and mental states. Affective empathy difficulties in CD/CU+ suggest that interventions should aim at learning to vicariously experience the emotions of others. In addition to informing new treatment strategies, neuroimaging might also be useful to predict response to treatment. For example, a recent study showed that brain activity during biological motion viewing could predict behavioral treatment effectiveness in young

children with ASD (Yang et al., 2016). Potentially, such biomarkers can be used to specifically prepare those individuals who are less likely to respond to treatment with pharmacological agents such as oxytocin. Furthermore, it would be essential to gain more insight into the developmental nature of social-emotional dysfunction in both ASD and CD in order to target interventions as early as possible in development. This would require longitudinal studies that could subsequently document adaptive changes on behavioral and brain levels.

Social difficulties are a major source of impairment in ASD and CD, but the exact neurocognitive mechanisms of these difficulties are not yet fully understood. The current thesis investigated these mechanisms by studying emotion-related brain function and structure. Our results show that directly comparing groups with ASD and CD/CU+ significantly advances knowledge about disorder-specific and disorder-general social-emotional dysfunction. Results of the studies in which we examined how those with ASD and CD would act upon other's emotions provide important clues for how to gain more insight into the neuroscience of social interaction in these disorders. Further understanding the mechanisms of social interaction will be crucial for helping those who have specific difficulties in something that is so deeply human and that can be such a joy for the most of us.

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8

Nederlandse samenvatting

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Nederlandse samenvatting

Het doel van dit proefschrift was om sociaal-emotioneel disfunctioneren in jongeren met een autismespectrumstoornis (ASS) en jongeren met een normoverschrijdend-gedragsstoornis (conduct disorder; CD) te onderzoeken vanuit een cognitief neurowetenschappelijk perspectief. Hiertoe werd een groep jongens met ASS direct vergeleken met een groep jongens met CD en hoge kille-emotieloze trekken (callous-unemotional traits; CD/CU+). Tevens zijn de neurale mechanismen onderzocht die ten grondslag liggen aan sociale beslissingen in reactie op andermans emoties in deze groepen.

In de eerste twee empirische hoofdstukken worden twee studies beschreven waarin een vergelijking wordt gemaakt tussen adolescente jongens met ASS, adolescente jongens met CD/CU+ en een normatief ontwikkelende controlegroep. Voortbouwend op eerder theoretisch en empirisch werk waarin een verschillend gebrek in empathie wordt onderscheiden in ASS en CD/CU+, hebben we deze groepen in **hoofdstuk twee** vergeleken op cognitieve en affectieve aspecten van empathie gedurende basale emotieverwerking met behulp van functionele MRI. In de scanner werden boze en angstige gezichten getoond, waarop deelnemers werd gevraagd de emotie van het getoonde gezicht te benoemen (als maat voor emotieherkenning) of om hun eigen emotie in reactie op het gezicht te benoemen (als maat voor emotionele resonantie). Zoals verwacht vertoonde de ASS groep afwijkende reacties in een hersengebied belangrijk voor sociale cognitie en cognitieve empathie. Dit was te zien in een verminderde reactie in de ventromediale prefrontale cortex (vmPFC) in de emotieherkenning conditie. Deze verminderde vmPFC reactie zou ook kunnen duiden op problemen in de regulatie van reacties op boze en angstige gezichten, gezien de rol van dit hersengebied in emotieregulatie en het in eerdere studies gevonden verband tussen ASS en verminderde emotieregulatie. De hypothese dat verminderde reacties in affectieve hersengebieden specifiek zijn voor CD/CU+ kon slechts deels bevestigd worden, aangezien zowel de ASS als de CD/CU+ groep verminderde reacties in de linker amygdala vertoonden ten opzichte van de controlegroep tijdens de emotionele resonantie conditie. Stoornis-specifieke hersenactiviteit werd verder

gevonden door verminderde activiteit in de linker en rechter hippocampus in de ASS groep ten opzichte van de controle groep. De verminderde activiteit in de inferieure frontale gyrus (IFG) en anterieure insula (IA) specifiek in de CD/CU+ groep zijn in lijn met eerdere studies die opperen dat zij minder resoneren met de gevoelens van anderen. Samengevat laat deze studie overlap zien in verminderde amygdala activiteit in ASS en CD/CU+ en specifieke afwijkingen in de neurale verwerking van cognitieve aspecten van empathie in ASS en meer problemen in affectieve aspecten in CD/CU+. Deze resultaten tonen dat ASS en CD/CU+ niet juist getypeerd worden door breed gedefinieerde overeenkomsten in sociaal-emotionele disfunctie. In plaats daarvan duiden deze resultaten erop dat diagnostische instrumenten en interventies beter gericht kunnen worden op verschillende aspecten van empathisch functioneren in deze stoornissen.

Hoofdstuk drie beschrijft de eerste studie die jongeren met ASS, jongeren met CD/CU+ en een controlegroep vergelijkt op witte stof microstructuren met behulp van *diffusion tensor imaging* (DTI). In tegenstelling tot veel eerdere studies die afwijkingen vonden in witte stofverbindingen in the uncinate fasciculus (UF) wanneer ASS of CD met een controlegroep werden vergeleken, vonden wij geen significante groepsverschillen in de UF tussen ASS, CD/CU+ en de controlegroep. Onze analyse liet wel een afwijking op microstructuur zien in het cingulum en het corpus callosum in de CD/CU+ groep vergeleken met de ASS groep. In deze banen werden verhoogde fractionele anisotropie (FA) waarden gevonden in de CD/CU+ groep ten opzichte van de ASS groep met de controlegroep daartussenin. Eerdere studies hebben laten zien dat het cingulum belangrijk is voor mentaliseren en cognitieve empathie. Verminderde FA waarden in de ASS groep in deze baan zouden daarmee gerelateerd kunnen zijn aan moeilijkheden met sociaal-cognitieve verwerking in de ASS groep. Ook de verhoogde FA waarden in de CD/CU+ groep zouden op een neuraal mechanisme kunnen duiden dat ten grondslag ligt aan sociale moeilijkheden, maar de richting van de afwijkingen suggereert dat ofwel de paden die naar deze moeilijkheden leiden ofwel de stoornis-specifieke uitingen verschillend zijn in ASS en CD/CU+. Daarbij kunnen ook de afwijkende witte stof waardes in het corpus callosum in ASS en CD/CU+ bijdragen aan de sociale moeilijkheden in beide stoornissen en specifiek aan agressief gedrag in de

CD/CU+ groep. We vonden echter geen relaties tussen witte stof waardes in deze banen en vragenlijsten over diagnostische trekken, sociale cognitie of agressie. Hierdoor blijft een vraag voor verder onderzoek welke cognitieve en gedragsmatige problemen veroorzaakt zouden kunnen worden door deze verschillen in witte stof waardes. Voor nu kunnen we concluderen dat ASS en CD/CU+ tegenovergestelde en stoornis-specifieke afwijkingen laten zien in witte stof opbouw van het cingulum en corpus callosum, wat de suggestie wekt dat afwijkingen in deze banen gerelateerd zijn aan specifieke disfunctie van hersennetwerken in deze stoornissen.

De eerste twee empirische hoofdstukken lieten verschillen zien tussen groepen met ASS en CD/CU+ in basale emotieverwerking en in witte stofbanen die belangrijk zijn voor sociaal-emotionele verwerking. In de daaropvolgende hoofdstukken waren we geïnteresseerd in hoe deze groepen handelden in reactie op andermans emoties. Hiertoe werden keuzes over de verdeling van geld als reactie op andermans emoties onderzocht en de hierbij betrokken neurale processen. In **hoofdstuk vier** werd de groep jongens met CD (met zowel hoge als lage CU traits) vergeleken met een controlegroep terwijl zij geld moesten verdelen tussen zichzelf en leeftijdsgenoten. Hierbij ontvingen zij geschreven emotionele reacties van een leeftijdsgenoot (te weten teleurstelling, boosheid of blijheid) in reactie op een eerder oneerlijke verdeling. Jongens in de controlegroep pasten hun beslissingen over eerlijkheid aan in reactie op de verschillende emoties; ze reageerden relatief eerlijker in reactie op teleurgestelde berichten ten opzichte van boze en blije berichten. De CD jongens daarentegen pasten hun gedrag niet aan in reactie op de emotionele terugkoppeling van hun leeftijdgenoten. De fMRI resultaten lieten zien dat de CD jongens vergeleken met de controlegroep verminderde activiteit hadden in de rechter temporopariëtale junctie en supramarginale gyrus (TPJ/SMG) tijdens blije reacties in vergelijking met teleurgestelde en boze reactie. Daarbij correleerde, alleen in de controlegroep maar niet in de CD groep, de activiteit in de rechter TPJ/SMG met de hoeveelheid eerlijke beslissingen na blije reacties. Gezien de rol van de TPJ/SMG in perspectief nemen, doen deze resultaten vermoeden dat jongens met CD minder geneigd waren om het perspectief van de andere persoon te nemen tijdens blije reacties ten opzichte van boze en teleur-

gestelde reacties. Dit is in overeenstemming met hun verminderde gedragsmatige aanpassingen in reactie op de emotionele boodschap van de ander. Ook vonden we verminderde activatie in de dorsolaterale prefrontale cortex (DLPFC) tijdens blije versus boze emoties, wat suggereert dat de CD jongens minder regulerende hersenactivatie hadden vergeleken met de controlegroep. Samengevat tonen deze bevindingen minder aanpassing van keuzes in reactie op verschillende emoties in CD, en dat dit samenhangt met verminderde activiteit in hersengebieden die belangrijk zijn voor het nemen van perspectief en cognitieve controle. Een dergelijke afgenomen gevoeligheid voor emotionele feedback maakt het waarschijnlijker dat jongens met CD agressie vertonen, omdat ze agressief gedrag mogelijk niet afzwakken als reactie op emotionele signalen van anderen.

In **hoofdstuk vijf** vergeleken we jongens met ASS met een controlegroep met behulp van hetzelfde experiment als in hoofdstuk vier. In tegenstelling tot jongens met CD pasten de jongens met ASS hun gedrag wel aan in reactie op verschillende emoties van anderen. Wat opviel is dat in de ASS groep minder oneerlijke verdelingen werden gekozen in reactie op blije emoties dan in de controlegroep. Jongens met ASS reageerden op meer oneerlijke wijze bij het omgaan met boze in vergelijking met teleurgestelde en blije leeftijdsgenoten, terwijl de controlegroep meer oneerlijk reageerde bij het omgaan met zowel boze als blije leeftijdsgenoten in vergelijking met teleurgestelde leeftijdsgenoten. De fMRI resultaten toonden verminderde hersenactiviteit in de precentrale gyrus in de ASS groep ten opzichte van de controlegroep in reactie op blije versus boze emoties. Daarnaast werd er een correlatie gevonden tussen toegenomen autistische kenmerken en meer activiteit in de postcentrale gyrus in de ASS groep. Deze hersengebieden zijn eerder vooral in verband gebracht met motorische en somatosensorische functies, maar in andere studies ook met verhoogde activiteit tijdens sociale taken in ASS ten opzichte van controles. De huidige studie zouden kunnen bijdragen aan het verfijnen van modellen voor sociale interacties in ASS, omdat de resultaten duiden op betrokkenheid van verschillende hersengebieden die een rol spelen bij het handelen in reactie op emoties in vergelijking met hersengebieden betrokken bij het simpelweg observeren van andermans emoties.

In de discussie van dit proefschrift worden de resultaten van de beschreven studies verder afgezet tegen bestaand onderzoek en suggesties gedaan voor vervolgonderzoek. Het belang van studies zoals beschreven in hoofdstuk twee en drie waarin verschillende psychiatrische stoornissen worden vergeleken wordt benadrukt. Zeker als hersenmaten als potentiele *biomarkers* ter verbetering van diagnose en behandeling worden gezien is het van belang hun specificiteit te kunnen bepalen, aangezien een bruikbare biomarker niet alleen een specifieke stoornis van gezonde controles moet onderscheiden maar ook van specifieke andere stoornissen (Boksa, 2013). Juist omdat er grote overlap is in de functionele en structurele hersenmaten van psychiatrische stoornissen (Goodkind et al., 2015; Sprooten et al., 2017) zijn directe vergelijkingen tussen verschillende stoornissen essentieel voor de zoektocht naar specifieke biomarkers. Ook wordt het belang onderstreept van verder onderzoek naar onderliggende constructen binnen verschillende stoornissen, zoals CU traits en alexithymia bij ASS en CD. Het onderzoek naar hoe jongeren met ASS en CD handelen in reactie op andermans emoties, zoals beschreven in hoofdstuk vier en vijf, bood de mogelijkheid om de neurale mechanismen van sociaal gedrag te bestuderen dat dichter bij echte sociale interacties komt dan het geval is bij passieve observatie van sociale en emotionele stimuli. Toekomstig onderzoek kan zich richten op meer ecologisch valide sociale interacties, hoewel het een grote uitdaging zal zijn een goede afweging te maken tussen het verlangen naar experimentele controle en de ongestructureerde en complexe aard van sociale interactie. De studies in dit proefschrift suggereren dat dergelijk werk zeker de rol van andermans emoties moet meenemen, omdat we hebben aangetoond dat zowel jongens met ASS als CD verschillen van controles in het verwerken van expliciet gepresenteerde emoties bij het nemen van sociale beslissingen. Hopelijk vormt dit proefschrift een aanzet voor een beter begrip van de mechanismen van sociale interacties in ASS en CD, iets dat cruciaal is voor het helpen van hen die moeite hebben met iets dat zo diep menselijk is en dat zo veel vreugde kan geven voor de meesten van ons.

Curriculum vitae

Eduard Klapwijk was born on January 5th, 1986 in Apeldoorn, The Netherlands. He completed pre-university education at the Gereformeerde Scholengemeenschap Randstad, Rotterdam in 2004. He obtained his bachelor's degree in psychology at Leiden University in 2009. Subsequently he started a research master in developmental psychology at the same university. During his master's he completed an internship with professor Sarah-Jayne Blakemore at the Institute of Cognitive Neuroscience at University College London, United Kingdom in which he studied the relationship between pubertal hormones and brain functional connectivity during social emotion processing. For his master's thesis he conducted research to assess the effects of different relations on brain and behavior with Dr. Berna Güroğlu at Leiden University. Eduard received his master of science (research) *cum laude* in 2011.

In September 2011 he started his PhD project, of which the results are described in this thesis, at the department of child and adolescent psychiatry (Curium-Leiden University Medical Center) under supervision of prof.dr. Robert Vermeiren, prof. dr Arne Popma and dr. Olivier Colins. From January 2016 on he worked as management consultant at Purpose Management Consulting in Utrecht, after which he returned to academia in June 2017 to work as a postdoc at the Brain and Development Research Center at Leiden University. He currently examines neurodevelopmental predictors and consequences of alcohol use in adolescence in collaboration with dr. Sabine Peters and prof.dr. Eveline Crone.

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