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

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1 | General introduction

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.