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

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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 precentral 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 anti-social 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 (Bubbenzer-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.

