The juvenile antisocial brain : brain imaging studies in clinically antisocial youth with nascent phychopathic traits

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CHAPTER 7

General Discussion

Summary of Main Findings

The developmental trajectory of psychopathy seemingly begins early in life and includes the presence of CU traits (e.g., deficient emotional reactivity and empathy, callous use of others) in CD youths. These youngsters with nascent psychopathic traits showcase violent and antisocial acts, respond less favorably to treatment, and as such place a substantial economic and emotional burden on society. Yet, despite these pressing concerns the pathophysiology of CU traits in these youths remains poorly understood. Neurobiological research into CD with CU traits could aid biomarker development and allow deeper insights into the developmental trajectories of psychopathy, which may ultimately hold promise for indicated preventive interventions and personalized treatments. This thesis, therefore, aimed to investigate the neurobiology underlying juvenile psychopathic traits in a forensic sample of severely antisocial CD youngsters, with a particular focus on CU traits. The remainder of this chapter will summarize the study outcomes on this topic reported in previous chapters, integrate some key results and discuss them in light of current literature. In addition, implications for clinical practice are considered, and limitations of the studies and directions for future research are outlined.

Amygdala Subregional Networks

Little is yet known of how amygdala subregional network function may contribute to callous-unemotionality in severely antisocial people. **Chapter 2** therefore examined the intrinsic functional connectivity of basolateral (BLA) and centromedial (CMA) amygdala networks in CD juvenile offenders with CU traits (CD/CU+). The analyses revealed that CD/CU+ relates to abnormally increased BLA connectivity with both dorsal and ventral portions of the anterior cingulate (ACC) and medial prefrontal (MPFC) cortices. In contrast, CD/CU+ related to diminished CMA connectivity with ventromedial/orbitofrontal regions. Critically, these connectivity changes coincided with local hypotrophy of BLA and CMA subregions, and were associated to more severe CU symptoms. These findings provide unique insights into a putative mechanism for perturbed attention-emotion interactions, which could bias salience processing and associative learning in youths with CD/CU+.

Chapter 3 focused on the same amygdala subregional parameters, though now in adolescent posttraumatic stress disorder (PTSD), a disorder believed to represent an inverse to CD/CU+ traits on some functional aspects (particularly fear/threat processing). Given the centrality of amygdalar perturbations to both PTSD and CD/CU+ traits, examining amygdala subregional connectivity and structure in relation to these phenomena could provide new insights into the neurobiology underlying their inverse association. The analyses revealed amygdalar-frontal connectivity shifts in adolescent PTSD patients that overlapped markedly with those documented in youths with CD/CU+ (Chapter 2), although the direction of effects was strikingly divergent. That is, PTSD related to BLA *hypoconnectivity* with dorsal and ventral portions of the ACC and MPFC, along with CMA *hyperconnectivity* with ventromedial/orbitofrontal regions. Of note, similar to CD/CU+ youths, BLA and CMA hypotrophy also emerged in PTSD youths, suggesting that amygdalar hypotrophy might be relevant to psychopathologies involving emotion dysregulation, be it hyper- or hypoemotionality. Collectively, these findings might partly explicate the opposing symptomatology of CD/CU+ and clinical anxiety disorders, in which distinct perturbations in largely overlapping amygdala-centered circuitries could either incite callousness and unemotionality or drive hyperemotionality and vigilance.

Chapter 4 built further upon **Chapter 2** and examined not only the association between amygdala subregional connectivity and affective (CU) psychopathic traits in CD juvenile offenders, but also its relation with interpersonal and behavioral traits of psychopathy. Though psychopathy reflects a pathological constellation of affective (e.g., callous, unemotional), interpersonal (e.g., manipulative, egocentric), and behavioral (e.g., impulsive, irresponsible) personality traits, most neurobiological research thus far has focused primarily on the affective dimension (CU). Yet, multi-dimensional models of psychopathy strongly opine that distinct dimensional features would map on discrete neural anomalies. Echoing this proposition, the analyses showed that amygdala subregional connections exhibit unique and dissociable relations with different trait dimensions of psychopathy. Adopting a multifaceted examination of psychopathy may thus allow a more nuanced apprehension of its underlying neurobiology, which otherwise is likely obscured when utilizing a categorical or unidimensional methodology.

Oxytocinergic System

Whereas oxytocin receptor gene methylation ($OXTR_{Meth}$) and its downstream neuromodulatory effects are deemed relevant to CU traits, nothing is known of how $OXTR_{Meth}$ interacts with CU to impact socioaffective brain systems in CD youngsters. **Chapter 5** therefore addressed this important knowledge gap, and assessed whether alterations in $OXTR_{Meth}$ might relate to some CU neurocognitive deficits. To this end, $OXTR_{Meth}$ x CU interactions on corticolimbic activity and amygdala subregional connections were examined during core socioaffective processes of recognizing and resonating emotions, in CD juvenile offenders versus matched healthy controls. The analyses revealed that interactions between elevated $OXTR_{Meth}$ and CU levels in CD youths predict task-related cortical hyperactivity and amygdalo-cortical disconnection. These results uniquely suggest that interactions between $OXTR_{Meth}$ and CU traits in CD youth may affect brain systems critical to decoding and integrating socioaffective information.

DSM-5 CU-Based Specifier for CD

Reflecting evidence on CU traits, the recently introduced *DSM-5* added a categorically defined CU-based specifier for the diagnosis of CD, labeled 'Limited Prosocial Emotions' (LPE), which aims to identify a more severe form of CD, plausibly predictive of chronic antisociality and adult psychopathy. Echoing prior work on CU traits, CD youths with LPE are expected to differ on neurobehavioral processing of negative emotions. Remarkably, however, no study has tested this proposition by directly contrasting CD youths with and without this LPE specifier on neurobehavioral measures of emotion processing. **Chapter 6** therefore examined how neural correlates of emotion recognition and emotional resonance might be affected in CD youths with LPE, as compared to CD youths without LPE and healthy control participants. The findings suggest that CD youths with LPE might exhibit an over-reliance on cortical neurocognitive systems when explicitly processing negative socioemotional information, which could have adverse downstream effects on relevant socioemotional functions. These data thus seem to provide novel, yet preliminary, neurobehavioral insights into potential scientific utility of the newly developed LPE specifier.

Integration of Main Findings

Functional Imbalance of Amygdala Subnuclei and CU Pathophysiology

Though subregion-specific anomalies in amygdala function and connectivity are tentatively linked to CU pathophysiology (Moul, et al., 2012; Yoder, et al., 2015b), little is yet known of how amygdala subregional network function may contribute to callous-unemotionality in severely antisocial populations. Echoing prominent neurocircuitry models of CU traits (Anderson and Kiehl, 2012; Blair, 2013a), Chapter 2 novelly revealed that CD/CU+ involves BLA *hyperconnectivity* with a network that includes dorsal and ventral portions of the ACC and MPFC (Aghajani, et al., 2016c). Dorsal segments of ACC and MPFC connect primarily to cognitive brain regions such as lateral frontal, posterior cingulate, and sensory associative cortices, forming a frontoparietal network tightly coupled with the BLA during cognitive control of attention and emotion (Arnsten and Rubia, 2012; Etkin, et al., 2011; Luckmann, et al., 2014; Pessoa, 2011). Ventral segments of ACC and MPFC, on the other hand, connect directly and reciprocally to affective brain regions such as the BLA and hippocampus, forming a frontolimbic network serving automatic emotion regulation and associative learning (Arnsten and Rubia, 2012; Barbas, 2000; Etkin, et al., 2011; Myers-Schulz and Koenigs, 2012). Ventral ACC/MPFC projections onto the BLA are deemed particularly critical in dampening the acquisition and expression of fear, as they compete with the BLA-to-CMA fear circuit (Milad and Quirk, 2002; Peters, et al., 2009; Vidal-Gonzalez, et al., 2006). Presumably, excitatory projections from these ventrofrontal regions onto inhibitory interneurons and intercalated cell masses within and around BLA tend to provide control over BLA output cells, thus effectively reducing downstream affective outputs of BLA (Asede, et al., 2015; Duvarci and Pare, 2014; Ehrlich, et al., 2009; Janak and Tye, 2015).

Exaggerated BLA connectivity with frontoparietal and frontolimbic regulatory systems as reported here, could thus speculatively allude to excessive top-down control of BLA output neurons, possibly to suppress the impact of negative emotional salience. In support of this tentative notion, BLA hyperconnectivity with these systems in our CD/CU+ group related to more severe CU traits, which include lack of negative emotionality as a cardinal feature (Frick and Viding, 2009). Increased BLA-frontoparietal coupling was recently shown in relation to CU traits (Yoder, et al., 2015b), while excessive frontopari-

etal control of BLA function, potentially via the frontolimbic regulatory pathway, is tentatively theorized in CU pathogenesis (Blair, 2010; Blair, 2013b; Blair and Mitchell, 2009; Larson, et al., 2013). This excessive BLA downregulation supposedly impairs the affective encoding of stimuli and subsequent shift of attention, thus impeding affective reactivity (particularly to fear) and emotional learning (Moul, et al., 2012).

Chapter 2 further provided initial evidence that CD/CU+ also involves CMA *hypoconnectivity* with the ventral/orbital MPFC, a region consistently implicated in psychopathy and antisocial behavior (Blair, 2013a; Koenigs, 2012). This decrease in CMA connectivity additionally related to higher callousness scores in CD/CU+ youths, further supporting the importance of amygdala-prefrontal interactions in CU symptomatology (Blair, 2013a; Koenigs, 2012). The ventral/orbital MPFC region plays a crucial role in behavioral and physiological aspects of emotion processing and associative learning by modulating CMA activity (Ghashghaei and Barbas, 2002a). Excitatory (i.e., glutamatergic) projections from the orbital MPFC target the lateral CMA neurons, which send inhibitory (i.e., GABAergic) projections to the medial CMA neurons (Ciocchi, et al., 2010b; Ghashghaei and Barbas, 2002a; Marek, et al., 2013; McDonald, et al., 1999). This prompts medial CMA neurons to reduce their output to central autonomic structures (e.g., brainstem and hypothalamus), thus lowering the behavioral and physiological expression of emotions and arousal (Ciocchi, et al., 2010b; Marek, et al., 2013). Diminished orbital MPFC input, as reflected by CMA-orbitofrontal hypoconnectivity, may thus impede lateral CMA inhibition of medial CMA output neurons (i.e., medial CMA disinhibition), possibly engendering abnormal emotion processing and behavioral dysregulation. Consistent with this notion, recent models link certain behavioral and emotional deficits seen in individuals with psychopathic traits to hyperactivity of CMA output neurons (Moul, et al., 2012). This CMA hyperactivity, together with an underactive BLA, allegedly perturbs attention-emotion integration, and causes a learning style driven by the general valence of an outcome (e.g., punishment/reward) rather than its precise value (e.g., magnitude of punishment/reward) (Moul, et al., 2012). Seemingly, this exaggerated CMA output also mediates the unusually amplified fear responses in psychopaths when they explicitly focus on relevant features of fearful stimuli (Moul, et al., 2012; Newman, et al., 2010). The contrasting shifts in BLA and CMA connectivity reported here may thus reflect a putative mechanism driving the alleged functional imbalance of amygdalar subnuclei in CU pathophysiology (Aghajani, et al., 2016c).

Amygdalar Connectional Profiles of Hyper- and Hypoemotionality

Intriguingly, Chapter 3 provided indirect support that these connectivity shifts are specific to CD/CU+ pathophysiology, and might even underlie the strikingly opposing symptomatology of CD/CU+ versus anxiety disorders such as PTSD (e.g., low fear vs. high fear). This chapter revealed amygdalar-frontal connectivity shifts in adolescent PTSD patients that overlap markedly with those documented in youths with CD/CU+ (Chapter 2), although the direction of effects is strikingly divergent. That is, PTSD related to BLA *hypoconnectivity* with dorsal and ventral portions of the ACC and MPFC, along with CMA *hyperconnectivity* with ventral/orbital MPFC regions (Aghajani, et al., 2016e). Notably, the increased CMA connectivity additionally related to more stress and anxiety symptoms in PTSD patients, further outlining the specificity of theses amygdalar shifts to clinical anxiety. Although due to some serious methodological issues (see limitations section) PTSD and CD/CU+ could not directly be contrasted to each other, but were instead independently compared with healthy control participants, these chapters collectivity point to disease-specific pathomechanisms in the form of differentially disorganized amygdalar circuits. While these amygdalar defects seemingly incite diminished affective reactivity (particularly to fear/threat) and poor emotional learning in CD/CU+ (Aghajani, et al., 2016c), they are poised to bias attentional encoding and emotional learning towards fear-related stimuli, and spur a general state of hyperemotionality in PTSD (Aghajani, et al., 2016e; Jovanovic and Ressler, 2010). Collectively, Chapters 2 and 3 may thus provide a neurobiological basis for the contrasting symptomatology of CD/CU+ and clinical anxiety, in which distinct perturbations within largely overlapping amygdala-centered circuits could either incite callousness and unemotionality or drive hyperemotionality and vigilance.

Amygdalar Hypotrophy: Transdiagnostic Marker of Emotion Dysregulation

Of note, Chapter 3 additionally revealed that similar to CD/CU+ (Chapter 2), adolescent PTSD also involves BLA and CMA hypotrophy, suggesting that amygdalar hypotrophy might be relevant to psychopathologies involving emotion dysregulation, be it hyper- or hypoemotionality. Indeed, BLA and CMA hypotrophy is shown among psychopathic individuals (Yang, et al., 2009), as well as clinically anxious populations (Depue, et al., 2014;

Morey, et al., 2012; Veer, et al., 2015; Yang, et al., 2008), fully in line with data linking amygdala structural defects to marked socioemotional deficits (e.g., impairments in fear processing and social affiliation) (Adolphs, et al., 2005; Anderson and Phelps, 2001; Flavell and Lee, 2012; Kalin, et al., 2001; Machado and Bachevalier, 2006; Schmolck and Squire, 2001). Glucocorticoid-induced apoptosis and abnormal pruning during development seem the most likely cause of neural hypotrophy, as these processes reduce the size and number of neurons (Sandi and Haller, 2015).

Importantly, Chapters 2 and 3 revealed that these intra-amygdala deformations coincide with perturbed intrinsic connectivity of BLA and CMA subnuclei. Psychopathology does indeed involve coinciding changes in functional connectivity and structure of amygdala subnuclei (Aghajani, et al., 2016e; Etkin, et al., 2009; Qin, et al., 2014), as network communication and information processing depend heavily on structural properties of neurons (e.g., size, configuration, arrangement) (Zatorre, et al., 2012). As such, conjoint examination of connectional and morphological properties of major amygdalar subregions seems crucial for a deeper understanding of clinical emotion dysregulation. The exact mechanism by which changes in structure may impact human brain function is still poorly understood. However, animal studies suggest that cellular changes in grey and white matter, including axon sprouting, dendritic arborization and fiber organization, could impact network communication and information processing (Zatorre, et al., 2012). Future advances in imaging technology, and greater dialogue between human neuroimaging and cellular/molecular neuroscience, could further our understanding of the complex interplay between brain structure and function (Zatorre, et al., 2012).

Amygdalar Connectional Profiles of Psychopathy Trait Dimensions

Building forth upon Chapter 2, Chapter 4 revealed for the first time within a forensic sample that amygdala subregional network function is not only relevant to affective psychopathic traits (CU), but also to the interpersonal and behavioral traits of psychopathy (Aghajani, et al., 2016b). In fact, it was crucially shown that amygdalar network connectivity patterns exhibit unique and dissociable relations with different traits of psychopathy (Aghajani, et al., 2016b). Interpersonal psychopathic traits, which index a self-centered, manipulative, and reward-oriented interaction style, impacted BLA and CMA connectivity

with corticostriatal and cortical midline network assemblies supportive of reward-related and sociocognitive processes, respectively (Andrews-Hanna, et al., 2010; Haber, 2011; Li, et al., 2014; Naqvi and Bechara, 2009). In contrast, the affective psychopathic traits indicative of callousness and lack of negative emotionality, impacted CMA connectivity with a frontolimbic network serving salience processing and affective responding (Etkin et al., 2011; Pessoa, 2011; Seeley et al., 2007). Finally, behavioral psychopathic traits, which index an impulsive, irresponsible, and disinhibited profile, affected BLA connectivity with a frontoparietal cluster implicated in self-regulation and action planning (Bressler and Menon, 2010; Luckmann, et al., 2014; Menon, 2011; Seeley, et al., 2007).

These trait-specific effects on amygdalar-corticolimbic interactions could be particularly relevant to the psychopathic phenotype, as they may fuel a self-centered, emotionally cold, and behaviorally disinhibited profile (Aghajani, et al., 2016b). They additionally tend to support multi-dimensional models of psychopathy, which assert that distinct dimensional features map on discrete neural anomalies (Cohn, et al., 2015a; Philippi, et al., 2015). Along this line, it is worth mentioning that the CMA-ventrofrontal hypoconnectivity documented in Chapter 2 in CD/CU+ juveniles, largely reemerged in the multi-dimensional analyses as a function of CU traits. This is despite the fact that these latter analyses were done exclusively in CD juveniles, with no groupings based on CU scores or diagnosis, and in which shared variance with other psychopathic traits was eliminated. On the other hand, these factors may also explicate why the BLA effects documented in Chapter 2 as a function CU could not be fully reproduced in the multi-dimensional analyses. Taken as a whole, however, it seems that altered amygdala subregional network function could serve as a potential biomarker of callous-unemotionality in severely antisocial populations. For a deeper understanding of psychopathic personality and its underlying trait assemblies, it would be important to examine whether amygdala subregional network function predicts susceptibility, chronicity, and treatment response in relation to different traits of psychopathy.

Oxytocinergic Epigenetics and CU Neurocognitive Deficits

Although the work presented here and elsewhere seem to greatly advance our understanding of CU neurocognitive deficits, the genetic and molecular underpinnings of these

deficits remain rather elusive, despite the strong genetic gradient implicated in CU pathogenesis (Anderson and Kiehl, 2014; Blair, et al., 2014; Blair, 2013a; Henry, et al., 2016;Viding and McCrory, 2012). Inspired by exciting new data on oxytocinergic receptor epigenetics (Nikolova and Hariri, 2015), and its association with socioaffective neural processing and CU characteristics (Cecil, et al., 2014; Dadds, et al., 2014a; Jack, et al., 2012; Puglia, et al., 2015), Chapter 5 innovatively addressed this matter and pinpointed oxytocin receptor gene methylation ($OXTR_{Meth}$) as a potential contributor to CU neurocognitive deficits (Aghajani, et al., 2017). By contrasting CD juvenile offenders with healthy control participants during core socioaffective processes of recognizing and resonating emotions, Chapter 5 uniquely revealed that elevated $OXTR_{Meth}$ and CU levels in CD youths interactively predict task-related cortical hyperactivity and amygdalo-cortical disconnection (Aghajani et al., 2017).

Specifically, interactions between elevated $OXTR_{Meth}$ and CU in CD youths predicted hyperactivity in midcingulate and supplementary motor regions during both emotion conditions, with insular, temporoparietal, and precuneal hyperactivity additionally emerging during emotion recognition. These regions are deemed key nodes within brain's socioemotional system, allowing among other things, affective salience processing, cognitive control, and interpersonal mentalizing (Bernhardt and Singer, 2012; Menon, 2011; Zaki and Ochsner, 2012). Though oxytocin receptors are only sparsely identified in precuneal and supplementary motor regions, high-affinity binding sites for oxytocin are reported in midcingulate, insular, and temporoparietal neurons that seemingly impact socioemotional functions (Baribeau and Anagnostou, 2015; Boccia, et al., 2013; Duchemin, et al., 2017). Intriguingly, hypermethylation within the *OXTR* CpG island predicts midcingulate, insular, and temporoparietal hyperactivity when processing negative or ambiguous socioemotional content, presumably reflective of oxytocinergic imbalance and associated resource-intensive (compensatory) neural computations (Jack, et al., 2012; Puglia, et al., 2015). Hyperactivity of these regions is interestingly also reported among subjects with psychopathic tendencies when *explicitly* processing socioemotional stimuli, apparently reflecting exaggerated cognitive deliberation to compensate for intrinsic affective deficits (Anderson, et al., 2017; Contreras-Rodriguez, et al., 2014a; Decety, et al., 2013a; Decety, et al., 2015; Decety, et al., 2014; Sadeh, et al., 2013; Yoder, et al., 2015a). Notably, *OXTR*

CpG island hypermethylation has also been linked to higher levels of CU traits in antisocial youngsters, both cross-sectionally and longitudinally (Cecil, et al., 2014; Dadds, et al., 2014a). Extrapolating from these data, we thus speculate that elevated $OXTR_{Meth}$ and CU levels in CD may interact and predict compensatory cortical computations to accomplish explicit emotion processing. Yet, cautious interpretation and further investigation is warranted, for $OXTR_{Meth}$ and CU have also independently been linked to corticolimbic *hypoactivity* during more *implicit* forms of emotion processing (e.g., passive viewing, gender discrimination) (Anderson and Kiehl, 2012; Blair, et al., 2014; Blair, 2013a; Ziegler, et al., 2015), consonant with context-dependent influence of oxytocin and psychopathy on socioemotional neuroprocesses (Bartz, et al., 2011; Decety, et al., 2015; Hamilton, et al., 2015)

Chapter 5 further revealed that relative to HC youths, interactions between elevated $OXTR_{Meth}$ and CU levels in CD youths related to CMA hypoconnectivity with the ventral/orbital MPFC region during emotion recognition. As mentioned earlier, this section of the MPFC contributes heavily to behavioral and physiological aspects of emotion processing and associative learning by modulating CMA function (Barbas and Zikopoulos, 2007; John, et al., 2013). Oxytocin seems to crucially impact the internal workings of this intricate circuit, by enhancing the inhibitory abilities of lateral CMA neurons rich in oxytocin receptors, and amplifying the excitatory inputs they receive from ventrofrontal cortical zones (Pittman and Spencer, 2005; Stoop, et al., 2015). It is intriguing that antisociality and CU are also relevant to this functional circuit, as they relate to perturbed local activity and ventrofrontal disconnectivity of CMA (Aghajani, et al., 2016a; Aghajani, et al., 2016c; Hyde, et al., 2016a; Moul, et al., 2012). In fact, CMA decoupling from ventral/orbital MPFC as a function of CU traits also emerged in Chapters 2 and 4 among CD youths, suggesting CMA-ventrofrontal decoupling could be a potential biomarker of CU in antisocial populations.

Interactions between unfavorably heightened $OXTR_{Meth}$ and CU levels in CD may thus carry relevance for the integrity of this oxytocinergic-modulated frontoamygdalar network, and plausibly affect how emotions are perceived, experienced, and controlled. Increased $OXTR_{Meth}$ relates to amygdala-ventrofrontal decoupling during socioaffective processing (Puglia, et al., 2015), while adverse CU x oxytocinergic interactions are tentatively linked to perturbed functionality and large-scale connectivity of CMA neurons

(Moul, et al., 2012). Both processes additionally seem to impair cognitive-emotional and physio-behavioral functions germane to adaptive socioaffective behavior (Moul, et al., 2012; Puglia, et al., 2015). Our findings, however, warrant cautious interpretation, further investigation, and future replication, given the complexities of the oxytocinergic system and its association with CU, in modulating socioaffective tendencies and conduct.

The data further revealed that relative to HC youths, interactions between high $OXTR_{Meth}$ and CU levels in CD youths related to BLA hypoconnectivity with precuneal and temporoparietal cortices during emotional resonance. These neighboring cortical regions are increasingly theorized in brain's mentalizing network, and seemingly support self-other dichotomies and internal reflection, along with dynamic inferences about others' socioaffective state (Andrews-Hanna, et al., 2010; Bernhardt and Singer, 2012; Li, et al., 2014; Schurz, et al., 2014). Amygdalar interactions with parietal nodes of this network reported here are deemed particularly crucial for representing and resonating socioemotional states (Fang, et al., 2013; Li, et al., 2014; Lieberman, 2007; Sheline, et al., 2009), by allowing affective coloring of mentalizing operations (Andrews-Hanna, 2012; Bernhardt and Singer, 2012; Li, et al., 2014; Lieberman, 2007; Shaw, et al., 2004). Notably, focal infusion of oxytocin into BLA seems to enhance some mentalizing functions among primates, presumably by optimizing socioaffective information extraction within BLA and its associated cortical targets (Chang, et al., 2015). Accordingly, oxytocinergic imbalance as reflected by *OXTR* CpG island hypermethylation, was recently linked to amygdalar dysfunction and amygdalar decoupling from cortical nodes of the mentalizing system, during socioaffective processing (Puglia, et al., 2015). It is noteworthy that perturbations in local activity and cortical connectivity of BLA are also theorized in CU pathogenesis, and believed to impair attention-emotion integrations necessary for adaptively responding to and resonating emotions (Aghajani, et al., 2016c; Hyde, et al., 2016a; Moul, et al., 2012). Elevated $OXTR_{Meth}$ and CU levels in CD thus seem to adversely interact and predict BLA decoupling from precuneal and temporoparietal regions, which hypothetically could disintegrate emotion from social cognition, and upset interpersonal behavior. Though $OXTR_{Meth}$ and CU have independently been linked to amygdala decoupling from socioaffective neurocircuits, accompanied by ostensibly maladaptive social interactions (Contreras-Rodriguez, et al., 2014a; Mier, et al., 2014; Puglia, et al., 2015; Yoder, et al., 2015a), future studies are warranted to further explore and validate our interpretation. In sum, Chapter 5 thus seems to uniquely show how interactions between $OXTR_{Meth}$ and CU traits in CD youth may affect brain systems critical to decoding and integrating socioaffective information.

Neural Underpinnings of DSM-5 CU-Based Specifier for CD

The final empirical chapter of this thesis (Chapter 6) sought to provide novel neurobehavioral insights into the newly developed *DSM-5* CU-based specifier for CD. A widely shared concern is that CD is too heterogeneous in terms of etiology, severity, and treatment responsiveness, to be useful to researchers and clinicians (Lahey, 2014), and meaningful subtyping of CD within DSM has been consistently advocated. Hence, reflecting evidence on CU traits, the *DSM-5* added a categorically defined CU-based specifier for the diagnosis of CD, labeled 'with Limited Prosocial Emotions' (LPE) (APA, 2013). This specifier is surmised capable of identifying subgroup of CD youths at risk for developing psychopathy and chronic antisociality, most likely accompanied by specific neurocognitive deficits (APA, 2013). Yet, no study has tested this proposition by directly contrasting CD youths with and without the LPE specifier on possible relevant neurocognitive systems. Chapter 6 hence examined how neural correlates of emotion recognition and emotional resonance might be affected in CD youths with LPE (CD/LPE+), as compared to CD youths without LPE and healthy control participants. This chapter novelly suggests that CD/LPE+ youths might exhibit an over-reliance on cortical neurocognitive systems when explicitly processing negative socioemotional information, which could have adverse downstream effects on relevant socioemotional functions (Aghajani et al., Submitted).

Specifically, CD/LPE+ youths exhibited abnormally increased activity within dorsolateral, dorsomedial, and ventromedial prefrontal regions during both emotion conditions, with posterior cingulate and precuneal hyperactivity additionally emerging during emotional resonance. While dorsolateral sections of the prefrontal cortex seem to support top-down attentional control and higher order executive processes, dorsomedial and ventromedial sections are deemed crucial in response selection and cognitive control of emotion (Arnsten and Rubia, 2012). The neighboring posterior cingulate and precuneal cortices, on the other hand, are increasingly theorized in brain's mentalizing system, and seemingly support self-other dichotomies and internal reflection, along with dynamic in-

ferences about others' socioaffective state (Andrews-Hanna, et al., 2010; Bernhardt and Singer, 2012; Li, et al., 2014; Schurz, et al., 2014). Noteworthy, the hyperactive medial prefrontal territories mentioned earlier in CD/LPE+ youths during emotional resonance, are also deemed integral components of this mentalizing system (Andrews-Hanna, et al., 2010; Li, et al., 2014).

Our results may thus cautiously suggest that CD/LPE+ is characterized by an over-reliance on cognitive deliberation when explicitly processing socioemotional information, a feature increasingly documented in adults with a psychopathic personality as well (Contreras-Rodriguez, et al., 2014a; Decety, et al., 2013a; Decety, et al., 2015; Decety, et al., 2014; Decety, et al., 2013b; Sadeh, et al., 2013; Yoder, et al., 2015a). In fact, neocortical hyperactivity during *explicit* emotion processing among adults with psychopathy is surmised to reflect an over-reliance on cognitive (controlled) computations, in order to compensate for intrinsic affective deficits (Contreras-Rodriguez, et al., 2014a; Decety, et al., 2013a; Decety, et al., 2015; Decety, et al., 2014; Decety, et al., 2013b; Sadeh, et al., 2013; Yoder, et al., 2015a). Despite these compensatory computations, however, the socioemotional repertoire of these individuals is deemed essentially shallow and callous due to atypical neurovisceral processing of emotions (Bird and Viding, 2014; Marsh, et al., 2008; Yoder, et al., 2015a). It is worth mentioning that neocortical hyperactivity also emerged in Chapter 5 among CD youths while performing the same task, though as a function of CU x $OXTR_{Meth}$ interactions. These findings not only point to neocortical hyperactivity during explicit socioaffective processing as a potential biomarker of CU in antisocial populations, but also cautiously suggest that this might be partly driven by alterations in the oxytocinergic system. It should be noted, however, that during *implicit* emotion processing cortical and subcortical circuits commonly exhibit *hypoactivity* in both adults and adolescents with psychopathic tendencies (Anderson and Kiehl, 2012; Blair, et al., 2014; Blair, 2013a), consonant with recent postulates of context-dependent neurobehavioral deficits in the etiology of psychopathic traits (Decety, et al., 2015; Hamilton, et al., 2015). Hence, future work should aim to reveal whether neurobehavioral underpinnings of implicit emotion processing in CD/LPE+ are impacted as well. Chapter 6 thus seems to provide novel, yet preliminary, neurobehavioral insights into the scientific utility of the newly developed LPE specifier, which should be further explored and validated in future studies.

The preliminary nature of our findings and the need for replication should be particularly emphasized, as the instrument we used for establishing LPE really allows an *approximation* of the DSM-5 LPE specifier. The Youth Psychopathic Traits Inventory (Andershed, 2002) that we used for this purpose is a subjective self-report measure that makes no assumptions about any time frame in particular. More importantly, the YPI does not directly probe the LPE criterion 'unconcerned about performance, which may imply that this tool assesses only three of the four LPE criteria. Nonetheless, the YPI is currently the most frequently used tool in published studies on the LPE specifier among criminal justice-involved adolescents with CD, and ample evidence importantly suggests that it works equally well as tools that explicitly assess all four LPE criteria (Colins and Andershed, 2015). Of note, the clinical and conceptual relevance of the criterion "unconcerned about performance" has already been questioned, mainly because it is not sufficiently discriminating, and therefore, may overlap with other DSM-5 diagnoses (Colins, 2016; Lahey, 2014; Salekin, 2016). Also worth mentioning is that according to DSM-5, CD youth will fulfill the LPE specifier if they meet *at least two* of the four LPE criteria, rendering the YPI thus well suited to probe LPE proxies in youngsters (for details see: Colins and Andershed, 2015; Colins and Vermeiren, 2013). Our findings thus provide an interesting focus for future research into CD/LPE+, which not only should explore and validate the neural perturbations reported here, but also probe the potential impact of using different, yet closely related, classification schemes of CD/LPE+.

Along this line, it is interesting to note that Chapter 6 also revealed the LPE as specified here is capturing a specific neural signal, when compared to a commonly employed method for CU-based grouping in CD (i.e., median split on CU scores). It additionally showed that relative to this commonly employed method, the LPE *in this particular study* seems better capable of differentiating CD youth with high CU from CD with low CU levels, as well as HC youngsters, with regard to socioemotional neuroprocessing. Specifically, compared to the LPE-based analysis, the only between-groups effects that emerged following median split grouping concerned CD with high CU vs. HC youths during emotion resonance, while no group differences at all were found during emotion recognition. Further analysis revealed that this seemed largely driven by the LPE-based grouping producing a more extreme group of CD with high CU, than the median split

grouping. Given the preliminary nature of the findings, however, further investigation and future replication is warranted to gain a deeper understanding of these ostensibly diverging effects.

Potential Implications for Clinical Practice

One of the main objectives in clinical psychiatric research is providing deeper insights into psychiatric disorders and their underlying pathomechanisms, so as to inform adequate treatment strategies. The work presented in this thesis and elsewhere suggests CD with CU traits (CD/CU+) is likely characterized by unique and discernable perturbations in cognitive, emotional, and neurobiological systems. This perspective may have potential implications for the clinical approach of CD/CU+, which currently has its focus on a limited set of easily detectable and often behavioral processes. In fact, many scholars believe that this inaptly narrow focus on these often overt processes is why most treatment strategies are at best marginally effective in reducing juvenile psychopathic traits in severely antisocial youngsters (Blair, 2015; Brazil, et al., 2016). Echoing prior work (Blair, 2015; Brazil, et al., 2016), we thus tentatively speculate that CD/CU+ is perhaps best described along its specific neuropsychological profile, and ideally combated using indicated and personalized interventions aimed at specific subcomponents of this profile (i.e., cognition, emotion, neurobiology). Such approach fits nicely with the newly developed and highly anticipated Research Domain Criteria (RDoC) framework of mental illness, which advocates integrating many levels of information (i.e., from genes to neural circuits to behaviors) for better understanding, and eventually treatment, of functional disturbances at the individual level (Insel, et al., 2010; Insel, 2014).

Acknowledging that CD/CU+ is likely characterized by neuropsychological deficits may require an innovative approach to its clinical care, in which alternative strategies focused on adaptive reorganization of relevant neurocircuits could be adopted to ameliorate specific psychological deficits (Anderson and Kiehl, 2014). The data presented here and elsewhere argue for such interventions to have their focus on corticolimbic neurocircuits, in which amygdalar and frontal cortical circuits should be particularly considered

(Blair, 2013a; Koenigs, 2012; Moul, et al., 2012). An exciting new development in this area has been the use of neurofeedback as an aid for effortful selfregulation of localized brain function and plasticity, which could prove useful in normalizing corticolimbic function in CD/CU+ (Anderson and Kiehl, 2014). In fact, preliminary data on the topic shows rather promising results, with real-time fMRI and EEG neurofeedback training apparently allowing criminal psychopaths to normalize their prefrontal and insular activity (Konicar, et al., 2015; Sitaram, et al., 2014), subsequently followed by enhanced cognitive control and reduced antisocial tendencies (Konicar, et al., 2015). Another promising electrophysiological technique increasingly employed for normalizing corticolimbic functioning in psychiatric patients is Transcranial Magnetic Stimulation (TMS). This is a noninvasive method for targeted in-vivo modulation of neural activity through the induction of electric currents via a rapidly changing magnetic field that is applied onto the brain (Barker, et al., 1985; Opitz, et al., 2016). A particularly important innovation in TMS has been the use of highly realistic models of individual brains that account for inter-individual variability in morphology, accompanied by Resting-State fMRI to map individual-level functional networks, allowing personalized target selection based on connectional profiles one would like to alter (e.g., fronto-amygdalar connections) (Opitz, et al., 2016).

Finally, based on data presented here, and in light of mounting evidence linking oxytocin and its receptor epigenetics to socioaffective neural processes and psychopathic tendencies (Cecil, et al., 2014; Dadds, et al., 2014a; Nikolova and Hariri, 2015), targeting the oxytocinergic system may also prove a promising strategy. In fact, manipulating the oxytocinergic system, for instance via oxytocin administration, has attracted considerable attention as a potential remedy for psychiatric disorders characterized by severe socioaffective deficits (e.g., autism) (Bartz, et al., 2011; Lefevre and Sirigu, 2016). It is intriguing that sporadic use of oxytocin seems to enhance socioaffective processes deemed relevant to CD/CU+, such as emotion recognition, emotional learning, trust, and eye contact (Bartz, et al., 2011; Lefevre and Sirigu, 2016). These positive effects are ostensibly achieved through oxytocinergic modulation of socioaffective neural circuits, with particularly strong effects in amygdalar, striatal, and medial prefrontal territories (Bartz, et al., 2011; Kirsch, 2015; Nikolova and Hariri, 2015). Especially relevant is that oxytocin administration impacts amygdala subregional function and connectivity (Chang, et al., 2015;

Koch, et al., 2016; Pittman and Spencer, 2005; Stoop, et al., 2015), neural processes deemed to be severely perturbed in CD/CU+ (Aghajani, et al., 2016b; Aghajani, et al., 2016c; Hyde, et al., 2016a; Moul, et al., 2012). It should be mentioned though that despite their apparent merits, the methods outlined here for targeting corticolimbic circuits have also produced negative or even contradictory findings. Most often this has been due to notable differences in clinical and demographic characteristics between samples (e.g., severity of disorder, comorbidity, male/female ratio, age range), though the use of widely varying analytical and methodological approaches seems to play a crucial role as well (Lefevre and Sirigu, 2016; Opitz, et al., 2016). That said, employing these methods to target some CD/CU+ neuropsychological deficits might still be worthwhile, as none of them seem to trigger serious side effects (Lefevre and Sirigu, 2016; Opitz, et al., 2016), while the field is in desperate need of effective treatment options for CD/CU+. Perhaps more importantly, these methods could benefit from the increased neuroplasticity during adolescence and plausibly achieve adaptive neural rewiring, thereby tackling the pervasive developmental trajectory that might lead to full-blown adult psychopathy (Anderson and Kiehl, 2014).

Despite these exiting neurobiological proceedings, we express great reservations towards an utterly neurobiological approach to CD/CU+, in which important environmental factors (e.g., parenting, socioeconomic status, trauma) are disregarded. Especially as CD/CU+ etiology and symptomatology seem deeply influenced by interactions between environmental context and neurobiopsychology (Viding and McCrory, 2012). Though these interactions were not directly examined in this thesis (which is a limitation), important new data shows how the environmental context may interact with relevant neurobiopsychological substrates to predict either susceptibly or resilience to juvenile psychopathic traits. For instance, negative environmental exposure in the form of maltreatment, trauma, and adverse life events may contribute to impaired socioaffective development and CU tendencies, by altering the genetic and neurocognitive landscape (Anderson and Kiehl, 2014; Blair, et al., 2014; Blair, 2013a; Cecil, et al., 2014; Viding and McCrory, 2012). Encouragingly, however, extensive psychosocial interventions geared at positive parental care (positive reinforcement, discipline, and involvement), seem to reduce CU levels and even buffer against the biological risk for CD/CU+ characteristics in young children (Humphreys, et al., 2015; Hyde, et al., 2016b; Waller, et al., 2013). One

thing that remains to be seen, however, is whether these protective effects are maintained throughout the development, when other developmentally specific factors may kick in or take over (Viding and Pingault, 2016). These may for instance be genetic factors regulating neuromaturation of socioaffective neurocircuits, as well as environmental influences, such as peer relations and socioeconomic status (Viding and Pingault, 2016). It thus seems absolutely vital for future research to thoroughly examine bio-environmental interactions on CD/CU+ etiology and symptomatology.

Limitations and Future Directions

The findings presented in this thesis are all based on cross-sectional data, which precludes any conclusions regarding causality. Additionally, the sample of antisocial youths that were examined consisted solely of males, making generalization to females rather difficult. The modest sample size that was examined might also be a limitation, for it could increase the chance of both false positives and false negatives in some cases (Button, et al., 2013). Longitudinal MRI research in larger, possibly pooled, samples with a balanced male to female ratio, could thus tackle these shortcomings. Further, the limited age range and modest size of antisocial youths precluded a thorough examination of possible age-related effects on neural alterations that were documented. Studies with relatively larger samples and wider age range, however, do document age-related variations in corticolimbic connections (Qin, et al., 2012), as well as age x psychopathology interaction effects on corticolimbic function and structure (Tottenham and Sheridan, 2009; Weems, et al., 2015; Weems, et al., 2013). To better grasp CD/CU+ neurodevelopment, it would thus be imperative to assess how normative development of corticolimbic circuits is affected in antisocial youths with and without CU features, and how pubertal factors might be contributing to these effects. We also lacked reliable measures of stress among our antisocial participants, making it difficult to assess whether stress (both current and traumatic stress) may have influenced our findings. This could be potentially relevant, as stress (especially chronic) has not only been shown to impact corticolimbic circuits (Sandi and Haller, 2015; Tottenham and Sheridan, 2009), but also linked to dynamic regulation

of oxytocin epigenetics (e.g., $OXTR_{Meth}$) (Unternaehrer, et al., 2012), processes deemed particularly germane to CD/CU+ pathogenesis. It thus seems especially important to assess how stress may dynamically and interactively contribute to the pathophysiology of psychopathic traits in antisocial populations.

Focusing on amygdala subregional networks, Chapters 2 and 3 collectively aimed to provide novel neurobiological insights into the contrasting symptomatology of CD/CU+ and anxiety disorders such as PTSD (e.g., low fear vs. high fear). However, due to markedly different scan acquisition parameters, and strongly divergent sample characteristics (e.g., age range, gender distribution, comorbidity types, medication/substance use), CD/CU+ and PTSD youths could not be directly contrasted to each other, but were instead independently compared with representative samples of healthy control participants. Though collectively these chapters seem to pinpoint *potential* disease-specific pathomechanisms in the form of differentially disorganized amygdalar circuits (relative to healthy controls), future work should aim to directly compare these two clinically opposing populations to elucidate *truly* disease-specific vs. transdiagnostic pathomechanisms.

The connectivity data presented in Chapters 2-5 concerns functional associations between amygdala subregions and cortical and subcortical systems (i.e., targets), which were elucidated by computing Fisher's *Z* transformed partial correlations. However, these correlations do not allow for causal inferences on whether spontaneous or task-evoked amygdalar activity produced synchronous activity at target regions (or vice versa), nor do they provide explicit information on the directionality of the effects. As such, our connectivity data does not allow for definitive conclusions regarding potential excitatory or inhibitory effects. Future advances in imaging technology, and greater dialogue between human neuroimaging and cellular/molecular neuroscience, could further our understanding of the intricate workings of functional brain circuits. An exciting new development in this regard is the application of circuit-wide analysis on human neuroimaging data, which allows accurate causal modeling of inhibitory and excitatory processes, particularly within corticolimbic circuits (Mujica-Parodi, et al., 2017).

The connectivity data presented in this thesis focused specifically on the amygdaloid complex, given the centrality of this structure to the pathophysiology and symptomatology of psychopathic and antisocial traits (Blair, 2013a; Moul, et al., 2012). However,

psychopathic tendencies in clinically antisocial populations are increasingly surmised to be underpinned by more widely distributed anomalies throughout the brain (Anderson and Kiehl, 2012; Cohn, et al., 2015a; Juarez, et al., 2013; Philippi, et al., 2015), consonant with large-scale network dysfunction models of psychopathology (Menon, 2011). It thus seems absolutely vital to probe the integrity of large-scale brain networks among individuals with marked psychopathic tendencies, in order to attain deeper insights into underlying neuropathologies. A particularly suited method for such endeavor would be complex brain network analysis, which acknowledges the brain as one integrated system (which it undeniably is), and explores the full breadth of its functional and structural connections using graph theoretical models (Bullmore and Sporns, 2009; Sporns, 2013). This analytical approach allows crucial insights into relevant network properties, including efficiency of local and global information transfer, integrity and configuration of networks, and centrality of a network and its key nodes to overall brain network functioning (Bullmore and Sporns, 2009; Sporns, 2013).

Finally, the neurobiological findings described in this thesis were mainly obtained using parametric general linear models (GLM), which still are the most widely employed statistical models within the field of neuroimaging. These models essentially allow voxel-by-voxel mass univariate analyses to find group-level associations between certain predictors (e.g., diagnosis, personality traits, task performance) and individual voxel properties (e.g., time-series). Notwithstanding their evident merits (Flandin and Friston, 2016), these models have recently been portrayed as less sensitive to subtle neural effects, especially at the individual-level, and most noticeably when data is non-parametrically distributed (which often is the case in MRI data) (Iniesta, et al., 2016; Iwabuchi, et al., 2013; Marquand, et al., 2016). It is increasingly anticipated, though, that these limitations can be largely overcome using statistical learning-based models (a.k.a. machine learning), which are a natural extension of classical statistical approaches such as parametric GLM, but more flexible and less constrained by assumptions about data structure (Iniesta, et al., 2016). Within neuroimaging, these models generally aim to derive an algorithm able to *multivariatly* explore data and discover otherwise latent neural patterns across the brain that best discriminate between conditions and predict certain outcomes (Iniesta, et al., 2016; Iwabuchi, et al., 2013; Marquand, et al., 2016). Most exciting thus far have been findings on accurate individ-

ual-level classification and subtyping of psychiatric patients by applying these learning-based methods on neuroimaging data, which has allowed a more fine-grained understanding of disease-specific pathophysiological profiles (Drysdale, et al., 2017; Iwabuchi, et al., 2013; Marquand, et al., 2016; Patel, et al., 2016). Crucially, these approaches also allow the use of neuroimaging in successfully predicting course and treatment response among psychiatric patients at the individual-level (Drysdale, et al., 2017; Iwabuchi, et al., 2013; Patel, et al., 2016). These findings render the use of learning-based models thus particularly warranted in studying the pathophysiology of psychopathic and antisocial tendencies, as they provide objective, data-driven means for meaningful biology-based subtyping schemes, along with the promise of personalized care and treatment strategies (Iniesta, et al., 2016; Marquand, et al., 2016). In this sense, it thus is especially encouraging that learning-based algorithms recently revealed subtle, yet highly specific, patterns of brain network connectivity and local morphology that successfully classified and subtyped psychopathic and antisocial populations (Steele, et al., 2017; Tang, et al., 2014).

Conclusion

The work presented in this thesis provides important new clues on the neurobiology of juvenile psychopathic traits in clinically antisocial juveniles. The data specifically shows that these traits are ostensibly underpinned by highly specific corticolimbic network dysfunctions, in which amygdala subregional networks seem particularly relevant. That data additionally suggests that some of these network dysfunctions and their associated neurocognitive deficits are possibly driven by alterations in the oxytocinergic system. Interestingly, the data also provides preliminary neurobiological support for the scientific utility of using juvenile psychopathic traits to subtype the highly heterogeneous group of clinically antisocial teens. While these data may represent important new steps towards a deeper understanding of clinical youth antisociality, their significance has to be evaluated by replication studies that further explore and validate the findings presented here.