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STRUCTURAL AND FUNCTIONAL BRAIN CONNECTIVITY ABNORMALITIES ASSOCIATED WITH ADOLESCENT CONDUCT DISORDER IN FEMALES

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But I was going to Tosche station to pick up some power converters!

- Luke Skywalker

ABSTRACT

Background: Antisocial behavior (ASB) in childhood and adolescence is indexed by the diagnosis of conduct disorder (CD) and is associated with high rates of comorbid mental disorders, such as anxiety, depression, alcohol and drug dependence, as well as maltreatment. Elevated levels of psychopathic traits further complicate the clinical picture of adolescents with CD. Those who persist with severe ASB into adulthood will meet criteria for antisocial personality disorder (ASPD). Others will continue to display less severe ASB, and thereby not meet the diagnostic criteria for ASPD, but will experience a wide range of adverse outcomes, including persisting comorbid mental disorders and impaired psychosocial adjustment. Many studies have explored neural abnormalities associated with ASB, yet there are several key gaps in the extant literature: (I) Females with ASB have rarely been studied. (II) There has been no study of adult women who presented CD as adolescents, but who did not progress to ASPD. (III) Past studies have typically excluded CD participants with comorbid disorders (making them unrepresentative of clinical cases) or failed to take account of these disorders when examining neural correlates of ASB. (IV) No study has taken account of childhood maltreatment. (IV) There has been no study of associations of brain connectivity and subsyndromal psychopathic traits in females.

Method: Three groups of young adult women, aged on average 24 years, completed clinical assessments and magnetic resonance imaging: women who consulted for substance misuse as adolescents and who were enrolled in a longitudinal study (n=44), sisters of ex-clients also enrolled in the longitudinal study (n=31), and newly recruited healthy women (n=24). Clinical data (diagnoses, psychopathic traits and other measures) from past waves and the current wave of data collection were used to characterize participants. Measures of brain structural connectivity (integrity of white matter tracts connecting specific regions) and functional connectivity (correlated resting-state activity between regions and Graph Theory topology) were investigated in four studies.

Results: The women who had presented CD in adolescence presented high levels of lifetime comorbid anxiety and depression disorders, alcohol and drug dependence, childhood maltreatment, higher levels of psychopathic traits than in the general population, and poor psychosocial functioning and more aggressive behavior than the healthy women. Three main findings emerged: (1) CD prior to age 15 was associated with abnormalities of white matter integrity in adulthood despite low rates of progression to ASPD (Study I and II). These abnormalities were similar to those reported in previous studies featuring male or mixed-sex samples with CD and/or ASPD. (2) Most of the differences in white matter integrity between young adult women with a history of CD and healthy peers were explained by comorbid lifetime mental disorders and maltreatment (Study I and II). (3) Psychopathic traits were associated with unique structural and functional connectivity abnormalities (Study III and IV).

Conclusions: We show for the first time that young women who presented CD as adolescents were characterized by structural connectivity abnormalities, despite not presenting ASPD but showing several indices of ASB. Even subsyndromal psychopathic traits presented by these women had unique connectivity correlates. Our findings emphasize the importance of treating CD in adolescence, as well as the comorbid mental disorders, and assessing and stopping maltreatment, so as to ensure a healthy transition to adulthood. Future studies investigating the neural correlates of CD, ASB in general, and psychopathic traits, need to take account of comorbid disorders and maltreatment.

LIST OF PUBLICATIONS

I. **Lindner P.**, Savic I., Sitnikov R., Budhiraja M., Liu Y., Jokinen J., Tiihonen J., Hodgins S. (2016). Conduct disorder in females is associated with reduced corpus callosum structural integrity independent of comorbid disorders and exposure to maltreatment. *Translational Psychiatry* 6:e714.

II. **Lindner, P.**, Flodin, P., Larm, P., Budhiraja, M., Savic, I., Jokinen, J., Tiihonen, J., Hodgins, S. (submitted manuscript). Amygdala-orbitofrontal structural and functional connectivity in females with anxiety disorders, with and without a history of conduct disorder.

III. **Lindner, P.**, Budhiraja, M., Westerman, J., Savic, I., Jokinen, J., Tiihonen, J., Hodgins, S. (2017). White matter correlates of psychopathic traits in a female community sample. *Social Cognitive and Affective Neuroscience.*

IV. **Lindner, P.**, Flodin, P., Budhiraja, M., Savic, I., Jokinen, J., Tiihonen, J., Hodgins, S. (submitted manuscript). Associations of psychopathic traits with local and global brain network topology in young adult women.

CONTENTS

LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactive Disorder
ASB	Antisocial Behavior
ASPD	Antisocial Personality Disorder
CD	Conduct Disorder
CU	Callous-Unemotional
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
fMRI	Functional Magnetic Resonance Imaging
IIT	Impaired Integration Theory (of psychopathy)
MRI	Magnetic Resonance Imaging
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PCL-R	Psychopathy Checklist Revised
PCL:SV	Psychopathy Checklist Screening Version
PFC	Prefrontal Cortex
ROI	Region Of Interest
rs-fMRI	Resting-state functional Magnetic Resonance Imaging
SUDs	Substance Use Disorders
TBSS	Tract-Based Spatial Statistics
VBM	Voxel-Based Morphometry

1 INTRODUCTION

From a behavioristic point of view, the probability of an individual engaging in a certain behavior in a certain context is the product of the probability of first appearance of that behavior, and of the subsequent reinforcing and punishing consequences perceived as contingent on that behavior. Human behaviors, both simple and complex, are thus shaped by constant, never-ending learning, which will alter not only the probabilities of reoccurrence of those behaviors, but also the opportunities to learn other behaviors. Throughout development, both internal and external contingencies will change, such that some behaviors that were previously rewarded cease being so, and vice versa. Together, these observations can accommodate the robust empirical findings that behavior patterns, such as those associated with mental disorders, typically onset early in development (childhood and adolescence), and that some will persist with this behavior pattern into adulthood, while others will not.

This is certainly the case for antisocial behavior (ASB), a term referring to any harmful, inconsiderate behavior that conflicts with contextual norms. This includes aggression, defined as an approach behavior with the intent of inflicting some kind of harm (physical or non-physical) upon another individual. Prospective, longitudinal studies conducted in several different countries show the dramatic stability of ASB. Physical aggression peaks in toddlerhood (around age 2-4) and while most children desist after that, a small group of individuals will continue to display physical aggression and other forms of ASB into adolescence and adulthood. Other children will react to behaviors being punished by engaging in functionally equivalent ones that are not punished in the same way, such as indirect aggression (Barker et al., 2007; Côté et al., 2007).

It is well recognized that among antisocial children, there are subtypes that present distinct clinical profiles, neural correlates, and outcomes (Hodgins et al., 2009a; Stadler et al., 2010). Recent evidence shows that this heterogeneity, in terms of comorbid internalizing problems and on levels of callous-unemotional traits (CU), can be identified as early as age 3 years and remains stable into adolescence (Fanti and Kimonis, 2017). This heterogeneous group of children with early-onset ASB, along with a group who presents adolescent-limited (or adolescent-delayed-onset; see below) ASB (Fontaine et al., 2009), will meet criteria for the diagnosis of conduct disorder (CD) as they grow older, and some of them will meet criteria for antisocial personality disorder (ASPD) at age 18 if this behavior persists into adulthood. CU traits are considered to be the antecedents of adult psychopathic traits. Even those who do not go on to meet ASPD criteria will continue to present indices of ASB and psychosocial maladjustment (Breslau et al., 2012; Odgers et al., 2008), but less is known about this group who are the focus of this thesis. Robust evidence shows that ASB is more common among males than females in all age groups, which is reflected in higher prevalence rates of CD and ASPD diagnoses in males. Additionally, males present higher levels of psychopathic traits than females (Strand and Belfrage, 2005). This difference in prevalence and severity is reflected in relatively little research having been devoted to antisocial females (Berkout et al., 2011).

This thesis focuses on a sample of females who met CD criteria in adolescence, yet very few of whom met ASPD criteria in adulthood. As is typical of CD, these women were characterized by elevated levels of psychopathic traits, comorbid mental disorders, and many had experienced childhood maltreatment. This thesis aimed to further understanding of neural abnormalities shown by these women and to determine whether the abnormalities were associated with prior CD, comorbid substance use disorders, anxiety and depression disorders, maltreatment, and/or psychopathic traits. The goal was to provide evidence that would inform prevention and treatment strategies.

The thesis focused on a sample of women recruited at the only clinic for adolescent substance misuse in a large Swedish urban area. Most of the women were either ex-clients or sisters of clients, who were enrolled in a follow-up study since adolescence. This sample was chosen since assessments at baseline (study entry) showed that half of the female ex-clients of the clinic presented CD (Hodgins et al., 2007). Further, studies of earlier clients of the same clinic followed to age 50 showed very negative outcomes through adulthood. One study included all n=1992 clients who consulted from 1968 to 1971. They were compared to n=1992 individuals randomly selected from the Swedish population, matched for sex, age, and birthplace. As compared to the general population women, women who had been treated at the clinic showed a seven-fold increase in risk of premature death, an almost two-fold increase in risk of physical illnesses requiring hospitalization, a six-fold increase in risk of mental disorders, a six-fold increase in the risk of schizophrenia, an 11-fold increase in the risk of substance misuse, an almost five-fold increase in the risk of a criminal conviction, and a three-fold increase in risk of poverty (Hodgins et al., 2009b, 2016). These findings, as well as those on CD, highlight the importance of investigating this population so as to prevent and treat persistent ASB and other negative outcomes.

1.1 ANTISOCIAL BEHAVIOR

1.1.1 Diagnoses of antisocial behavior

1.1.1.1 Conduct disorder

According to diagnostic criteria, CD indexes a repetitive and persistent pattern of ASB, including aggression towards people and animals, destruction of property, deceitfulness and stealing, and serious violations of age-appropriate rules and norms. Most of the scientific literature that is reviewed, and this thesis, used criteria from the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), which were unchanged in the fifth version (American Psychiatric Association, 2013), with the exception of the addition of a novel specifier (discussed below). Prevalence estimates of CD in boys are typically reported in the range of 6-16% and in girls, 2-9% (Nock et al., 2006), although numbers as low as 1-2.1% for boys and 0.5-0.8% for girls have also

been reported (Maughan et al., 2004; Wichstrøm et al., 2011). Gender ratios thus tend to fall in-between 2:1 and 4:1.

The presentation of CD differs somewhat between boys and girls. In general, females present less physical aggression than males, with trivial or no sex differences in non-physical, relational aggression (Card et al., 2008). This well-established sex difference in the prevalence of physical aggression is not specific to CD, and emerges as early as in 17 month old toddlers (Baillargeon et al., 2007). Distribution patterns of CD also differ: in boys, number of conduct problems follows a decreasing exponential distribution, while in girls, this distribution is more bimodal in nature, with larger peaks at both the low and high end (Tiet et al., 2001). Consistent with the robust sex-difference in prevalence of CD (Berkout et al., 2011) and physical aggression in general, this suggest that while CD is overall less common in girls (i.e. more cases of no or few conduct problems), the girls that do meet criteria present symptoms that are as severe as those observed among boys.

Diagnostic criteria for CD are met if three or more symptom criteria, out of a possible 15, are present within the last 12 months. The large number of criteria ensures that the population of children/adolescents with CD is heterogeneous disorder as there are 32,647 possible unique combinations of 3 to15 symptoms. However, there is of course no reason to believe that clustering of individual symptoms would occur by chance; quite the opposite. One latent class analysis performed on a large population sample revealed four clusters of CD symptoms: one less severe class characterized by rule violations, one class characterized by deceit and theft, one class by aggression, and one severe class (Breslau et al., 2012). These latent classes are strikingly similar to those reported in past research on a separate sample (Nock et al., 2006).

Diagnostically, however, no direct consideration is taken of symptom profiles, beyond an indirect severity rating based on how much harm is inflected on others. Rather, since the DSM-IV, the CD diagnosis has included a specifier based on age of onset (American Psychiatric Association, 2000). This specifier was based on research suggesting that age of onset determines developmental trajectories and outcomes: a minority present childhood-onset ASB (before age 10) which interacts with a criminogenic environment to result in life-course-persistent ASB, while the majority of antisocial individuals present adolescence-onset, often adolescence-limited ASB, caused by a temporary maturity gap and social learning from deviant peers (Moffitt, 1993). Since its release, concerns have been raised that this age-of-onset-specifier does not directly capture the presumed diversity in causal pathways (Scheepers et al., 2011). Taxometric analyses have shown that the difference between the two onset-patterns is dimensional, rather than categorical in nature (Walters, 2011) and neuroimaging studies have shown that the two subgroups are more similar than different (Fairchild et al., 2011; Passamonti et al., 2010), suggesting that other specifiers may have greater clinical utility and predictive power. The DSM-5 introduced an additional specifier of limited prosocial emotions (American Psychiatric Association, 2013). This specifier aims to capture the subgroup of youths whose ASB is associated with callousness, shallow affect,

lack of remorse, and instrumental aggression (Buitelaar et al., 2013). These traits are referred to as callous-unemotional (CU) traits, or the childhood antecedents of (affective) psychopathic traits, and are discussed in detail in section 1.1.1.3 below.

1.1.1.2 Antisocial Personality Disorder

The diagnosis of antisocial personality disorder (ASPD) can be made at age 18 or later if CD was present prior to age 15. As the name implies, ASPD is a personality disorder (DSM axis II), while CD is a clinical disorder (DSM axis I), meant to reflect the fact that if the ASB continues into adulthood, it is considered persistent enough to be categorized as a disorder of personality. ASPD is unique among personality disorders in that it includes a diagnostic criteria of there being signs of another disorder, CD, prior to age 15 (American Psychiatric Association, 2013). This requirement reflects the robust literature showing the early onset and stability of ASB. With regards to symptoms, these largely mimic those of CD, indexing a range of ASB including deception, violation of social norms and laws, and aggression. Unlike CD though, where CU/psychopathic traits are included as a specifier, the diagnosis of ASPD includes lack of remorse as a symptom. Approximately half of adolescents with CD will meet criteria for ASPD as young adults, more men than women (Loeber et al., 2002; Myers et al., 1998) and more of those with childhood-onset (Moffitt et al., 2008). Additionally, latent trajectory analyses have revealed a childhood-limited CD group which do not meet ASPD criteria as adults (Odgers et al., 2008), on which there has been very little research. Population prevalence of ASPD in the US is estimated to 6.8% among men and 0.8% in women (Swanson et al., 1994), while in Norway prevalence is estimated to 1.3% among men and 0.2% in women (Torgersen et al., 2001). In prison samples, 47% of men and 21% of women met ASPD criteria (Fazel and Danesh, 2002).

1.1.1.3 CU-traits and psychopathy

Approximately one-half of adolescents with CD present elevated CU traits, and while it is possible to score high on CU traits without meeting CD criteria, such individuals present elevated conduct problems, emotional problems and negative social impact (Rowe et al., 2010). Congruently, high CU traits in children without conduct problems have been associated with increased rates of subsequent self-reported delinquency in the years that follow (Frick et al., 2005), and criminal convictions (Hodgins et al., 2013), strengthening the case that CU traits are inherently linked to ASB. CD with CU traits is associated with earlier-onset, more severe and stable ASB (Frick and Nigg, 2012) and worst treatment outcomes in traditional treatment programs that do not specifically address CU traits (Hawes et al., 2014).

Among boys, it has been shown that conduct problems accompanied by high levels of CU traits are more genetically heritable than conduct problems without high levels of CU (Viding et al., 2005, 2008). Further, emerging evidence shows that CU traits are stable from age 3 to

mid-adolescence (Fanti and Kimonis, 2017; Klingzell et al., 2016), and that psychopathic traits measured in adolescence are stable into early adulthood (Hemphälä et al., 2015). CU traits, not CD or conduct problems, are associated with impairments in reversal learning, i.e. failure to learn from changing contingencies, resulting in persistent responses despite positive or negative punishment now being contingent on that behavior (Budhani et al., 2006). This is congruent with treatment research showing that among CD children, those with high CU traits respond equally well to reinforcement strategies (e.g. praise), but less so to punishment strategies (e.g. time-out), and had overall poorer treatment outcomes (Hawes and Dadds, 2005).

In adults, CU and interpersonal traits, along with ASB, are incorporated into the personality disorder of psychopathy, the gold standard measure of which (in psychiatric and forensic settings) is the Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). The PCL-R is a semi-structured interview, conducted by a trained clinician using a scoring checklist featuring two factors, each consisting of two facets. Factor 1 consists of the interpersonal and affective facets (corresponding to CU traits) that are unique to the psychopathy construct, and factor 2 of lifestyle and antisocial facets, which overlap with ASPD and CD criteria. The syndrome of psychopathy is defined as a total score of more than 30 points in the US. Only 10% of prisoners met criteria for the syndrome of psychopathy, while remaining prisoners are expected to have low-medium scores on the PCL (Coid et al., 2009b). However, despite psychopathy often being described as a categorical construct, each psychopathy facet is dimensional rather than categorical in nature (Guay et al., 2007) and are present at lower levels in the general population, with an estimated 1% of the household population having scores high enough to meet criteria (Coid et al., 2009a).

1.1.2 Trajectories and outcomes of antisocial behavior

Both childhood- and adolescent-onset CD has been shown to be a precursor of a wide range of problems in adulthood, including academic failure, unemployment, criminality, substance use disorders, as well as a variety of other mental disorders (Frick and Nigg, 2012; Odgers et al., 2007, 2008). Women with CD or a history of CD have children at a younger age than other women (Jaffee, 2002), and their offspring are at elevated risk for conduct problems. This results from non-optimal parenting (Jaffee et al., 2006), assortative mating (Krueger et al., 1998), and the transmission of genes that confer vulnerability for ASB (Rhee and Waldman, 2002; Viding et al., 2008).

There is evidence to suggest that ASB onset, trajectories, and outcome patterns differ somewhat between males and females, with the childhood-onset, persistent form being more prevalent in boys, and there being an adolescence-delayed-onset group in females (Fontaine et al., 2009). This latter group is characterized by risk factors common to the early-onset group (such as physical maltreatment), yet refrains from more severe ASB during childhood (presumably due to norms discouraging displays of physical aggression in females), and

experiences substantial adjustment problems as adults. Distinguishing this group from the early-onset-persistent and adolescent-limited groups is made difficult by a number of limitations of past research. Primarily, the use of global ASB measures and measures limited to physical aggression (which is overall less prevalent in females) means that ASB onset in childhood and ASB persistence in adulthood may have been under-estimated among females, obscuring sub-groups based on trajectories (Fontaine et al., 2009). This is consistent with evidence showing that even adolescents engaging in ASB who do not meet diagnostic criteria for ASPD in adulthood are likely to continue to display ASB along with poorer-than-average psychosocial functioning in adulthood (Breslau et al., 2012; Odgers et al., 2008). This evidence also suggests that neural abnormalities associated with CD in adolescence may persist into adulthood despite not progressing to ASPD.

1.1.3 Comorbid mental disorders

Almost all clinical cases of CD will meet criteria for at least one comorbid mental disorder, most prominently substance use disorders (SUDs), anxiety disorders, attention-deficit hyperactive disorder (ADHD), and depression. Findings from pooled meta-analyses of CD samples suggest comorbidity odds ratios (95% confidence intervals) of 10.7 (7.7-14.8) for comorbid ADHD, 6.6 (4.4-11.0) for comorbid depression, and 3.1 (2.2-4.6) for comorbid anxiety (Angold et al., 1999). More recent population surveys in both younger (Wichstrøm et al., 2011) and older children with CD (Costello et al., 2003) have shown similar estimates. Comorbidity rates of SUDs are even more striking, with adjusted odds ratios of 8.4 (5.4-13.9) for any substance abuse and 15 (8.6-26.2) for any substance dependence (Roberts et al., 2007).

Several studies have explored reasons for the high rate of comorbid mental disorders among children/adolescents with CD. In the case of comorbid SUDs, the evidence is converging that CD generally precedes use-onset and the onset of SUDs (Kuperman et al., 2001; Sartor et al., 2007). Both disorders have also independently been linked to certain personality traits, such as novelty seeking (Hemphälä et al., 2013). A majority will have developed a SUD by young adulthood (Kim-Cohen et al., 2003). Evidence for directionality with affective disorders is mixed, yet primarily supports an indirect association such that CD leads to psychosocial maladjustment, which leads to depression (Burke et al., 2005), or that the two disorders share common risk factors (Fergusson et al., 1996). With regards to anxiety disorders, the extant literature suggests common mechanisms. These include hyper-sensitivity to threat through hostile attention bias and autonomic hyper-arousal (Bubier and Drabick, 2009).

Not only is the prevalence of comorbid externalizing and internalizing disorders elevated among children/adolescents with CD as compared to typically developing children, but CD in childhood/adolescence is also a precursor of both externalizing and internalizing disorders in adulthood (Kim-Cohen et al., 2003), in addition to ASPD (Copeland et al., 2009). Even adults who do not progress to ASPD show increased rates of mental disorders (Goodwin and

Hamilton, 2003). CD is also a well-established precursor of schizophrenia, and this subgroup shows distinct structural and functional brain abnormalities (Schiffer et al., 2013, 2017). Thus, it is important to assess and take account of comorbid mental disorders when studying children/adolescents with CD.

1.1.4 Childhood maltreatment

There is a well-established association between CD and childhood maltreatment, with significant, adjusted odds ratios ranging from 1.6 to 2.4 compared to those without CD (Afifi et al., 2011). The traditional view held that physical abuse by parents had a causal impact on the child's cognitive development (Gould et al., 2012) and onset of ASB (Jaffee et al., 2004), the former mediated by the impact of early stress on the brain (Pechtel and Pizzagalli, 2011) and the latter mediated by social learning of the perceived necessity and rewarding consequences of violence (Dodge et al., 1995). Adolescents with CD show on average half a standard deviation lower performance IQ and almost one standard deviation lower verbal IQ than healthy peers (Isen, 2010), supporting the account that maltreatment leads to both cognitive deficits and ASB.

Recently, the view that maltreatment causes cognitive deficits has been challenged by robust evidence showing that pre-exposure deficits largely explain post-exposure deficits (Danese et al., 2016). The association between maltreatment and CD, on the other hand, appears reciprocal: not only does maltreatment increase the risk of later ASB, both ASB also increases the risk of maltreatment (Lansford et al., 2011; Pardini et al., 2008; Serbin et al., 2015; Shaffer et al., 2013). These findings emphasize the importance of not only of assessing maltreatment in youths with ASB, but also show that for research purposes, both cross-sectional designs and after-onset recruitment strategies risk confusing the directionality of findings between CD and maltreatment.

Girls with CD are at particular risk for sexual abuse. While odds of having being been sexually abused are higher among CD girls than in community girls, the odds are similar to those found in other mental disorder groups, and the directionality is unknown (Maniglio, 2014). There is however evidence to suggest that the presentation of CD increases the risk of being sexually abused by peers through involvement in high-risk situations, e.g. heavy drinking in the presence of delinquent peers (Maniglio, 2015).

1.1.5 Summary: Antisocial behavior in youths and adults

It is well recognized that antisocial children, adolescents and adults constitute a heterogeneous population, differing in age of onset and persistence of ASB, severity of psychopathic traits, and prevalence of comorbid mental disorders and experience of maltreatment (Hodgins et al., 2009a; Stadler et al., 2010). This heterogeneity makes CD and

ASPD difficult disorders to study, yet disentangling the impact of two or more concurrent conditions is often of high clinical importance. For example, disentangling adverse trajectories and outcomes specific to one of the disorders may inform clinical decisions about which condition to treat first, if no integrated treatment is available or suitable. The same is true when attempting to study neural correlates of CD/ASPD. As will become apparent below in a review of neuroimaging studies on antisocial youth and adults, the clinical heterogeneity of CD/ASPD has not been fully recognized in most of the extant neuroimaging literature. The majority of neuroimaging studies have recruited clinically unrepresentative samples with no or few comorbid disorders or not assessed comorbid disorders. Although the former approach has the advantage of increased specificity, the applicability of findings from these samples to real-world cases is questionable, limiting translational efforts. It also fails to further understanding of the mechanisms underlying each disorder or the identification of mechanisms that may be common to specific combinations of disorders.

Another aspect to bear in mind when reviewing the extant neuroimaging literature is that they exclusively included either adolescents presenting ASB, or adults whose ASB was persistent and severe enough to meet ASPD criteria or score high on psychopathy measures. There has been no study of the adults who met CD criteria but who did not progress to ASPD. This presents a key knowledge gap in the literature. Finally, there has been very little research on antisocial females.

1.2 NEUROIMAGING OF INDIVIDUALS WITH ANTISOCIAL BEHAVIOR

The hypothesis that ASB and other behaviors are associated with variations of the structure and functioning of the brain– an axiom of modern clinical neuroscience – took root in the 18th century with the development and dissemination of phrenology. An unquestionable pseudoscience by today's standards, phrenological theory was nonetheless correct in asserting that the brain has specific regions that are associated with mental phenomena and overt behaviors. The 19th century saw the case of Phineas Gage, a railroad worker who in the year 1848 survived having a one-meter tamping iron accidently shot through his skull and brain. Although the exact nature and extent of the impact has been questioned, the damage was thought to have caused changes in his personality and cognitive abilities (Van Horn et al., 2012), suddenly making Gage fitful, explosive, impulsive, emotionally labile, and socially inept.

The first neuroimaging studies of antisocial individuals were published in the late 1980s and early '90s (Bassarath, 2001). Guided by neuropsychological studies showing that damage to the prefrontal and temporal cortices and subcortical areas could induce symptoms resembling ASB – as in the case of Phineas Gage – the first studies to use magnetic resonance imaging (MRI) techniques focused on these regions. Since the first rudimentary studies studying manually segmented prefrontal cortex volumes (Raine et al., 2000), advances in image acquisition and analysis techniques, as well as more detailed, theory-driven characterization

of the imaged samples, have led to novel insights into the neural mechanisms promoting ASB.

Today, the absolute majority of neuroimaging research is conducted using magnetic resonance imaging (MRI). In brief, MRI works by using strong scanner magnets (typically 1.5 or 3 Tesla) to create a magnetic field that align otherwise randomly arranged protons of the body in one specific direction. Radiofrequency currents are then applied in pulses, causing the protons to spin out of equilibrium and emitting a specific radio frequency. Protons in different types of tissues (e.g. bone, gray matter, white matter and cerebrospinal fluid) will have different relaxation times, meaning that these different tissues can be distinguished on the resulting image. MRI provides excellent anatomical contrast, is non-invasive, and does not require any costly, burdensome and toxic radioactive agents. Still, scanner availability, operators training requirements, constraints inherent to the scanner environment, logistic challenges and scanning costs mean that MRI is far from a ubiquitous research tool.

For these reasons, neuroimaging studies of individuals presenting mental disorders have historically, and still are, plagued by a reliance on small and often extreme samples (Schnack and Kahn, 2016). The fact that participant variance exists both within studies (overlooked characteristics) and between studies (different homogenous samples), along with the multitude of analysis options available, are some of the reasons why the neuroimaging literature on children/adolescents with CD and adults with ASB is inconsistent, and at times, contradictory (Hodgins et al., 2009a). The scarcity of detailed, theory-driven analyses has arguably amplified this problem in the field of ASB. The following section detailing past neuroimaging research on ASB therefore begins by focusing on robust findings from meta-analyses of grey matter structure and function, and discusses in detail the few studies that have focused on disentangling the impact of comorbid conditions and sex differences.

1.2.1 Morphometric studies

There are more than 50 studies investigating structural brain abnormalities observed in individuals presenting ASB, using techniques such as automated Voxel-Based Morphometry (VBM) (Ashburner and Friston, 2000) and cortical thickness analysis (Fischl and Dale, 2000). An early meta-analysis of results of VBM studies of individuals with ASB of all ages, with and without psychopathic traits, revealed that compared to healthy peers, individuals presenting ASB (87% males) displayed reduced gray matter volumes in the right lentiform nucleus (putamen and globus pallidus), left insula, left frontopolar cortex, as well as increased volumes of the right fusiform gyrus, right inferior and superior parietal lobule, right cingulate and right postcentral gyrus (Aoki et al., 2014). A later meta-analysis (Rogers and Brito, 2015) of studies that used VBM contrasting youth with conduct problems (83% males) to typically developing peers revealed reduced gray matter volumes in the left amygdala, insula, inferior frontal gyrus, anterior cingulate cortex (ACC), and temporal pole, of which the volume

reduction in the left insula-amygdala cluster was specific to childhood-onset CD. Post-hoc analyses revealed that severity of CU traits was associated with lower reductions of amygdala volumes, a higher proportion of males was associated with decreased amygdala volumes, and a wider sample age range was associated with greater amygdala volume reductions (Rogers and Brito, 2015).

Meta-analyses are pivotal in making sense of the large variation in findings across multiple studies. This is especially the case in the study of ASB: as detailed above, among both adult and adolescents, comorbid mental disorders and childhood maltreatment are more common than among healthy peers. Minor changes in recruitment practices regarding these factors can have a large impact on results since these conditions are independently associated with structural abnormalities of gray matter. For example, meta-analyses have revealed robustly reduced volumes of the inferior frontal gyrus associated with depression (Zhao et al., 2014), stimulant dependence (Ersche et al., 2013), childhood maltreatment (Lim et al., 2014), and anxiety (Shang et al., 2014). Amygdala reductions are associated with childhood maltreatment (Lim et al., 2014), comorbid depression and anxiety (Bora et al., 2012) and depression (Zhao et al., 2014). ACC reductions are associated with alcohol dependence (Xiao et al., 2015), stimulant dependence (Ersche et al., 2013), anxiety (Radua et al., 2010; Shang et al., 2014), and depression (Bora et al., 2012; Du et al., 2012). Insula reductions are associated with childhood maltreatment (Lim et al., 2014), alcohol dependence (Xiao et al., 2015), stimulant dependence (Ersche et al., 2013), and anxiety (Shang et al., 2014).

These findings emphasize the importance of considering comorbid mental disorders and history of maltreatment when studying the neural correlates of ASB. Failure to do so may result in neural abnormalities being incorrectly associated with a specific disorders. The samples included in the above-mentioned meta-analysis of volumetric abnormalities in CD were often recruited so as to present no (Fahim et al., 2011), or few comorbid disorders (Dalwani et al., 2011; Fairchild et al., 2011, 2013; Huebner et al., 2008; Olvera et al., 2014; Sterzer et al., 2007; Stevens and Haney-Caron, 2012). Typically, these studies either statistically adjusted the group comparison for the cofounder of interest (Dalwani et al., 2011; Fairchild et al., 2011, 2013; Michalska et al., 2015), or ran post-hoc analyses to investigate if the confounders were independently associated with brain volumes, either across the brain (Huebner et al., 2008), or confined to the regions implicated in the group comparison (Sterzer et al., 2007). In the volumetric studies on CD, ADHD has been the primary confounder of interest. There is strong evidence to suggest that these two disorders, despite often being pooled under the common flag of externalizing disorders, have very different neural correlates, with ADHD being a disorder of the "cool" cognitive circuitry and CD being a disorder of the "hot" affective circuitry (Rubia, 2011). Unsurprisingly, most findings on volumetric abnormalities associated with CD remained significant after adjusting for ADHD symptoms, and in the mentioned meta-analysis, comorbid ADHD was not associated with brain volumes (Rogers and Brito, 2015). Little research has investigated the confounding effects of other common comorbid mental disorders. None of the studies included in the meta-analysis measured maltreatment.

Arguably, the strongest evidence for the impact of confounders comes from studies that recruited 2 × 2 groups that differed on both ASB and a confounder, allowing investigations of both main effects of each condition, and interaction effects. One such study compared four groups of men: violent offenders with and without SUDs and non-offenders with and without SUDs. The violent offenders compared with non-offenders, presented larger gray matter volumes in the amygdala bilaterally, the left nucleus accumbens, and the right caudate head and with less gray matter in the left insula. By contrast, the men with SUDs exhibited less gray matter in the orbitofrontal cortex, ventromedial prefrontal cortex, and premotor cortex than did men without SUDs, but there were no regional interaction effects (Schiffer et al., 2011). These results are consistent with a recent VBM study, performed on the same larger female sample as the studies in this thesis, that used multiple regression to statistically adjust for comorbid disorders and found that volumetric abnormalities of the superior temporal gyrus, lingual gyrus, hippocampus and ACC, in women with a history of CD compared to healthy women, could be explained by comorbid disorders and history of maltreatment (Budhiraja et al., 2017).

These findings highlight the importance of considering the heterogeneity of the population presenting ASB and disentangling the neural correlates of comorbid disorders and maltreatment. In addition to comorbid mental disorders and maltreatment, ASB population heterogeneity also stems from differences in levels of CU traits in children and adolescents and interpersonal-affective psychopathic traits in adults. Earlier studies typically first ran between-group comparisons to find clusters distinguishing antisocial from comparison groups, and then investigated psychopathy correlates of these clusters (Craig et al., 2009; Hoppenbrouwers et al., 2013; Sundram et al., 2012). While informative, this is obviously not an optimal way to disentangle subgroups since analyses are restricted to regions already shown to be common to any potential subgroup. Here too can the recruitment of 2 × 2 groups, differing both on ASB and the confounder, provide valuable information on the impact of heterogeneity. For example, one VBM study divided male violent offenders with ASPD into subgroups with and without the syndrome of psychopathy. Results showed that the OFC and temporal pole volume reductions were specific to the offenders with psychopathy, and that the offenders with ASPD and not the syndrome of psychopathy did not differ from healthy peers (Gregory et al., 2012). Intriguingly, a later neuropsychological study on the same sample revealed that the two groups of violent offenders with ASPD showed similar impairments in verbal working memory and reversal learning compared to the healthy non-offenders (De Brito et al., 2013), suggesting that the same subgroup-specific patterns of abnormalities cannot be assumed across brain and behavior.

Additional evidence emphasizing the importance of considering psychopathic traits derives from studies investigating volumetric correlates of specific facets and factors of psychopathy among both offenders and community samples. In a mixed-sex sample of young healthy adults, boldness traits were positively associated with insula volumes, meanness traits positively associated with lateral OFC and striatum volumes, and negatively associated with amygdala volume, as was disinhibition (Vieira et al., 2014). In a mixed-sex adult sample of

individuals in treatment for substance misuse, PCL-R antisocial and lifestyle facet scores correlated negatively with volume in the middle temporal gyrus and insula, affective facet scores correlated negatively with superior temporal gyrus volumes and claustrum, interpersonal score correlated negatively with volumes of the middle temporal gyrus, middle occipital gyrus and lingual gyrus. ACC volume was positively associated with both interpersonal and antisocial facet scores, putamen and temperoparietal junction volumes were positively associated with affective facet scores, and precuneus volumes were positively associated with antisocial facet scores (Cope et al., 2012). In a sample of adolescent offenders, the interaction between CD symptoms and CU trait scores were associated with insula abnormalities, such that there was a significant positive association between volume and CU traits only in adolescents low on CD symptoms. Amygdala volumes were positively associated with CD symptoms and negatively associated with CU traits when modeled simultaneously (Cohn et al., 2016).

Another source of heterogeneity in the extant literature is sex. There is a striking scarcity of neuroimaging studies investigating structural abnormalities in antisocial females, or sex × ASB interaction effects (the latter showing that the difference between healthy and individuals with ASB are different between sexes). There are some exceptions. For example, one study first compared female adolescents with CD with healthy females and observed reduced volumes in the insula and striatum, as well as in the OFC and precuneus and increased volumes in the OFC at a less stringent statistical threshold, among those with CD. Next, the samples of females and males with CD and the samples with healthy females and males were combined and the CD and healthy participants were compared. Sex × CD interaction effects were found in the insula, such that males with CD presented increased insula volumes compared to healthy males, while females with CD presented decreased insula volumes compared to healthy teenage girls. A main effect of sex on striatal, ACC, OFC and amygdala volumes emphasizes the importance of studying sex × CD interaction effects, rather than simply comparing males and females with CD (Fairchild et al., 2013). Sex × ASB interaction effects have also been associated with abnormalities in the superior temporal gyrus, with a stronger negative correlation between CD symptoms and volume in girls compared to boys. However, this latter study did not replicate other volumetric abnormalities associated with CD, either in males or females (Michalska et al., 2015). Another study failed to find a sex × psychopathy interaction, although there were negative associations between psychopathy total scores and volumes of the OFC, parahippocampal cortex, temporal poles and hippocampus (Cope et al., 2014). In sum, there is evidence both for and against sex differences in volumetric abnormalities associated with ASB in adolescents. There has been no comparable study in adults, presenting a key knowledge gap.

1.2.2 Task-based fMRI

Although the association between brain structure and function is complex, there is robust evidence from experimental studies showing that repeatedly engaging in a behavior

functionally localized to a specific region of the brain (e.g. motor skill with the motor cortex) leads to increases in the volume of the associated brain region, which coincides with functional changes (Dayan and Cohen, 2011). Vice-versa, pre-existing structural differences are associated with different types of behaviors, and may result from non-behavioral impact (e.g. trauma, toxins, etc.).

With regards to ASB, a recent meta-analysis (Alegria et al., 2016) of 24 functional MRI (fMRI) studies contrasted brain activity across a range of experimental conditions (e.g. task A > no task), comparing n=338 antisocial youths with ASB to n=298 healthy peers (80% males in both groups). Results showed that teenagers with ASB showed reduced activity among in the ACC (more pronounced in the males), medial PFC and caudate. The teenagers with psychopathic traits as compared to healthy peers, showed reduced activity in a cluster covering the thalamus, hypothalamus, striatum and OFC, and increased activity in the dorsolateral PFC and caudate. In emotional processing tasks specifically, antisocial youth showed reduced activity in the fusiform gyrus and middle frontal gyrus.

Surprisingly, in this meta-analysis, results did *not* show that amygdala activity of teenagers with ASB differed from that of the healthy teenagers (Alegria et al., 2016). Differential amygdala activity in response to emotion-evoking stimuli in antisocial youth and adults with and without CU/interpersonal-affective traits is by far the most replicated finding from fMRI studies, and once again emphasizes the need to consider heterogeneity in samples of persons presenting ASB. Studies of specific subgroups (conduct problems and high or low levels of CU traits) (Viding et al., 2012b) and studies using multiple regression techniques (Carré et al., 2013; Dotterer et al., 2017; Harenski et al., 2014; Lozier et al., 2014; Sebastian et al., 2012), have both found that in affective conditions, CU/interpersonal-affective traits are associated with reduced amygdala activity, and that ASB without these traits is associated with increased amygdala activity. Specific correlates of CU/interpersonal-affective traits have also been reported in community samples. One study of young men found that ASB (controlling for CU traits) was related to decreased activity in the striatum during reward anticipation, to decreased activity in the middle frontal gyrus during both reward and loss anticipation, to decreased activity in the inferior parietal lobe activity during loss anticipation, and that CU traits (controlling for ASB) were associated with reduced middle occipital gyrus activity during reward anticipation (Murray et al., 2017). In a mixed-sex sample of young adults, amygdala reactivity to fearful faces was found to be negatively correlated with the interpersonal psychopathy facet, while amygdala reactivity to angry faces was positively associated with the lifestyle facet (only in men). The difference in striatum activity between positive as compared to negative feedback was negatively associated with the lifestyle facet, and that among women only, the affective facet was positively associated with striatum reactivity (Carré et al., 2013).

In addition to heterogeneity related to psychopathic traits, task-based fMRI studies of individuals presenting ASB have not taken account of comorbid mental disorders. In particular, this appears to be the case for comorbid anxiety disorders. Meta-analyses have

revealed robust hyper-activation of the amygdala and insula in response to negative stimuli across different anxiety disorders, with additional hyperactivity in the parahippocampal gyrus, fusiform gyrus, inferior frontal gyrus and more being specific social anxiety disorder (Brühl et al., 2014; Etkin and Wager, 2007). Social anxiety disorder is the anxiety disorder most similar to ASB as both disorders are characterized by symptom provocation by social stimulus (Sareen et al., 2004). Most task-based fMRI studies of CD have excluded participants with comorbid anxiety disorders, making the samples unrepresentative of clinical CD cases (Finger et al., 2008; Finger and Marsh, 2011; Herpertz et al., 2008; Marsh et al., 2008, 2011, 2013, Rubia et al., 2008, 2009a, 2009b, 2010, White et al., 2012a, 2012b, 2014). These studies have not taken subsyndromal anxiety into account. Others have allowed anxiety disorder comorbidity or anxiety symptoms and adjusted analyses group comparisons for these confounders (Lockwood et al., 2013; O'Nions et al., 2014; Sebastian et al., 2012, 2014).

In summary, converging evidence from both structural and functional MRI studies suggest that the amygdala, along with the ACC, PFC and fusiform gyrus, constitute the primary candidates for grey matter abnormalities in antisocial youths and adults. Structural and functional grey matter abnormalities likely vary among those with and without high levels of CU traits, may vary between males and females, and there is ample evidence to suggest that comorbid mental disorders and exposure to maltreatment may confound these associations.

1.2.3 White matter studies

Grey matter, however, constitutes only 55% of the brain's total volume (Lüders et al., 2002). Neuronal cell bodies in cortical and subcortical grey matter are interconnected by myelinated axons forming the white matter layers of the brain. While having the appearance of a homogenous mass on standard MRI images, many axons with similar origin and destination will run alongside each other, constituting the major tracts (fasciculi) of the brain. These white matter pathways, along with smaller tracts, enable processing across spatially distinct grey matter regions. It is possible to quantify and compare white matter volumes in the same way as with grey matter, as done in one study that reported reduced volumes in the superior frontal lobe, ACC, superior temporal gyrus and precuneus, and increased volumes in the middle frontal gyrus, in CD boys with psychopathic tendencies compared to healthy peers (De Brito et al., 2011). However, given the nature of white matter and its organization into tracts, measuring tract properties rather than regional volumes of indistinguishable tracts, is more informative.

Tract properties can be measured using Diffusion Tensor Imaging (DTI), an MRI technique that can estimate tract properties (such as structural integrity and myelination) by measuring the thermal (Brownian) motion of water molecules along different directions, both along and perpendicular to the principle vector. Common DTI metrics include fractional anisotropy (FA), a proxy measure of organizational coherence; axial diffusivity (AD), a proxy measure

of structural organization and integrity; and radial diffusivity (RD), a proxy measure of myelination (see Section 3.1.1 below for details). Such metrics form the basis for structural connectivity: how spatially distinct brain regions are connected structurally to one another by white matter tracts.

The early findings of abnormal grey matter volumes of the OFC and amygdala motivated Craig et al. (2009) to examine the white matter tract connecting these two regions, the uncinate fasciculus (UF) (Von Der Heide et al., 2013). In their sample of adult males with the syndrome of psychopathy they observed reduced FA in the right UF compared to age and IQ matched healthy males. No differences were observed in two control tracts: the inferior longitudinal fasciculus and the inferior front-occipital fasciculus. Moreover, the FA values in both the left and right UF correlated significantly with PCL behavioral factor scores (Craig et al., 2009).

Uncinate abnormalities have since been replicated in a number of studies, in both antisocial adults and adolescents, although there is now robust evidence implicating other major tracts as well (Waller et al., 2017). Of these other tracts, the cingulum is of particular interest due to its role in connecting the ACC to the posterior cingulate cortex (PCC), forming a key circuitry of the Default Mode Network resting-state functional network found to be abnormal among offenders with the syndrome of psychopathy (see Section 1.2.4 below). The fusiform gyrus is connected to the temporal pole and PFC by the inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF), respectively, making these tracts potentially of interest. Finally, the corpus callosum (CC) is also of interest. The CC is the primary enabler of interhemispheric communication and is thus a key structure in all higher-order processing. Abnormalities of all these tracts have been reported in both adults and youth presenting ASB. Findings are summarized in Table 1 below.

Importantly, the findings summarized above include only positive findings. Negative findings are common not only in voxelwise whole-brain studies (where every tract is investigated; starred in table above), but also in tracts-of-interest studies. For example, in both Craig et al. (2009), Sarkar et al. (2013) and Motzkin et al. (2011), the ILF and IFOF were used as comparisons tracts to show that FA abnormalities were specific to the uncinate, thus providing null findings of the former two tracts. Every whole-brain voxelwise study that did not find abnormalities of a specific tract can be considered a null finding. However, in white matter studies, different analysis techniques (such as atlas-derived voxelwise probability maps versus manual dissection with tractography) have different sensitivities to differences in certain tracts (such as the uncinate that is intertwined with the IFOF and ILF; see Section 3.1.1. below). Due to small sample sizes and effect sizes, some tract differences may also not survive the stringent correction for multiple comparisons employed in voxelwise studies.

Table 1. Summary of past white matter findings in a selection of tracts

Tract	**Antisocial adults**	**Antisocial youths**
Uncinate fasciculus 	Reduced FA compared to HC and negative correlation with PCL:R factor 2 [100% ♂] (Craig et al., 2009) Reduced FA compared to HC in overlapping cluster and negative correlation with PCL:R factor 2 [100% ♂] (Sundram et al., 2012)* Reduced FA in psychopathic vs non-psychopathic offenders [100% ♂] (Motzkin et al., 2011) Reduced FA in overlapping cluster in psychopathic offenders vs HC and negative correlation with PCL:R factor 1 [100% ♂] (Hoppenbrouwers et al., 2013)* Negative correlation between FA and interpersonal PCL:R facet scores in offenders [100% ♂] (Wolf et al., 2015) Negative correlation with factor-unspecific psychopathy measure in community sample [100% ♂] (Sobhani et al., 2015)	Negative correlation between CU traits and FA [53% ♂; ages: 10-17] (Breeden et al., 2015) Reduced FA and AD in overlapping cluster in CD compared to HC [61% ♂; ages: 12-18] (Haney-Caron et al., 2014)* Increased FA and positive correlation with both CU and behavioral traits [100% ♂; ages: 12-19] (Sarkar et al., 2013) Positive correlation with FA and negative with RD with grandiose-manipulative traits in overlapping cluster [86% ♂; ages: 12-20] (Pape et al., 2015)* Higher FA compared to HC [100% ♂; mean age: 18] (Passamonti et al., 2012)* Sex × gender interaction between CD symptoms and RD in overlapping cluster [48% ♂; mean age: 10] (Decety et al., 2015)* Increased FA in CD boys compared to HC, yet no differences in UF FA between girls with and without CD [51% ♂; ages: 13-16] (Zhang et al., 2014a). Decreased FA compared to HC [0% ♂; mean age: 16] (Menks et al., 2016)*
Cingulum 	Reduced FA and negative correlation with PCL:R factor 1 scores [100% ♂] (Sethi et al., 2014)	Reduced FA and AD in overlapping cluster in CD compared to HC [61% ♂; ages: 12-18] (Haney-Caron et al., 2014)* Negative correlation between RD and grandiose-manipulative traits in overlapping cluster [86% ♂] (Pape et al., 2015)* Increased FA and decreased MD (cingulate part) and decreased FA (hippocampal part) [0% ♂] (Menks et al., 2016)*
Inferior longitudinal	Reduced FA in overlapping cluster [100% ♂] (Sundram et al., 2012)*	Positive correlation with FA and negative with RD with grandiose-manipulative traits in overlapping cluster [86% ♂; ages: 12-20] (Pape et al., 2015)*

fasciculus 		Reduced FA and AD in overlapping cluster in CD compared to HC [61% ♂; ages: 12-18] (Haney-Caron et al., 2014)*
Inferior fronto-occipital fasciculus 	Decreased FA in overlapping clusters in psychopathic offenders vs HC [100% ♂] (Hoppenbrouwers et al., 2013)* Reduced FA and increased MD in overlapping cluster and negative correlation with PCL:R factor 2 and total scores [100% ♂] (Sundram et al., 2012)*	Positive correlation with FA and negative with RD with grandiose-manipulative traits [86% ♂; ages: 12-20] (Pape et al., 2015)* Reduced FA and AD in overlapping cluster in CD compared to HC [61% ♂; ages: 12-18] (Haney-Caron et al., 2014)*
Corpus callosum 	Reduced FA and increased MD in overlapping cluster and negative correlation with PCL:R factor 2 and total scores [100% ♂] (Sundram et al., 2012)*	Increased FA [100% ♂; mean age 15] (Zhang et al., 2014b)* Reduced AD in overlapping cluster [61% ♂; ages: 12-18] (Haney-Caron et al., 2014)* Positive correlation with FA and negative with RD with grandiose-manipulative traits [86% ♂; ages: 12-20] (Pape et al., 2015)* Increased AD [48% ♂; mean age: 10] (Decety et al., 2015)* Increased FA and decreased MD [0% ♂] (Menks et al., 2016)*

*Whole-brain study. HC: Healthy comparison participants. MD: mean diffusivity = (AD+RD)/2.

The lack of consistency in findings across studies is likely primarily due to sample characteristics. Most white matter tracts (including the UF) continue to develop until age 30 (Lebel et al., 2008), making the wide age range in some adolescent studies problematic. This may also explain the often inverse association between increases or decreases in FA observed in adolescents and adults with ASB, compared to age-matched healthy peers. This is supported by the thus-far only longitudinal VBM study of CD, showing abnormal cortical development associated with different ASB trajectories (Oostermeijer et al., 2016). Further, although pubertal stage has been linked to white matter development independent of age (Asato et al., 2010), and early onset of puberty is related to ASB (Williams and Dunlop, 1999), only one of the CD studies has taken pubertal development into account when matching CD and healthy participants (Menks et al., 2016). Together, these age-related factors may account for some of the variation in findings of white matter abnormalities associated with ASB.

Another factor that may explain contradictory results in studies of ASB is sex. Some samples include only males, a few only females, and others both males and females. The few studies

that have investigated sex differences, or all-female samples, are thus of particular interest. Using a 2 × 2 sampling technique (boys and girls, CD and no CD), one study reported an FA difference between CD and healthy adolescents in boys but not girls (Zhang et al., 2014a). A sex × CD interaction was investigated in one study and revealed stronger associations between CD symptoms and greater AD or RD in the ILF, uncinate, and other tracts in girls (Decety et al., 2015). These two contradictory findings are likely due to sampling techniques, although a lack of detailed information on sample characteristics make it difficult to draw conclusions. Severity of CD symptoms differ in males and females, with females following a more bimodal exponential decreasing distribution than boys (Tiet et al., 2001). Thus, care must be taken in recruiting CD participants that are matched across gender on severity. Interestingly, the only study to include an all-female sample found FA and mean diffusivity abnormalities of the corpus callosum, uncinate, and cingulum associated with CD (Menks et al., 2016), consistent with findings in males. This particular CD sample presented increased levels of CU traits and the expected high comorbid rates of SUDs and ADHD, qualifying it as a more severe sample compared to the study that found no difference between CD and healthy females, which excluded participants with comorbid mental disorders including SUDs (Zhang et al., 2014a). In addition, the healthy group in the latter study presented an average conduct disorder score in the top 15% according to population norms.

The evidence is inconclusive as to whether and how psychopathic traits are related to specific white matter integrity abnormalities. Based on two early findings in male offenders (Craig et al., 2009; Sundram et al., 2012), a Dual-Network hypothesis was formulated stating that the behavioral factor of psychopathy was related to uncinate integrity and the amygdala-OFC circuit, while the interpersonal-affective factor was related to cingulum integrity and the DMN, as was found in one study on male offenders (Sethi et al., 2014). This hypothesis has limited support, since there is equal evidence to suggest that uncinate integrity is associated with the interpersonal-affective factor in both adults (Hoppenbrouwers et al., 2013; Wolf et al., 2015) and adolescents (Breeden et al., 2015; Pape et al., 2015; Sarkar et al., 2013). One additional study on a community adult all-male sample found a negative association between uncinate integrity and a composite psychopathy measure, but did not distinguish between the two factors (Sobhani et al., 2015). Support for cingulum integrity correlating with interpersonal-affective scores is limited (Pape et al., 2015; Sethi et al., 2014), with at least one study of male offenders showing no association (Wolf et al., 2015), despite several studies associating DMN abnormalities with this factor specifically (see below).

Finally, studies differ on whether or not they took account of comorbid mental disorders. While some studies specifically excluded participants with any comorbid disorders (Haney-Caron et al., 2014; Hoppenbrouwers et al., 2013; Sethi et al., 2014; Sobhani et al., 2015; Zhang et al., 2014a, 2014b), others have included participants with one comorbid disorder, e.g. SUDs (Craig et al., 2009; Motzkin et al., 2011; Sarkar et al., 2013; Sundram et al., 2012) or ADHD (Menks et al., 2016; Passamonti et al., 2012; Sarkar et al., 2013), and adjusted group comparisons for this particular comorbid disorder. All the common comorbid disorders characterizing clinical cases of CD have independently been associated with many of the

same white matter abnormalities observed among individuals with ASB, including different SUDs (Bagga et al., 2014; Harris et al., 2008; Liao et al., 2010; Luciana et al., 2013; McQueeny et al., 2009; Moeller et al., 2005; Tobias et al., 2010), anxiety (Ayling et al., 2012), depression (Liao et al., 2013) and ADHD (van Ewijk et al., 2012). Strikingly, none of the reviewed studies in Table 1 even measured childhood maltreatment, despite robust evidence showing that maltreatment is associated with white matter integrity of the corpus callosum, cingulum, uncinate and other tracts that have been associated with ASB (McCrory et al., 2010), even in the absence of comorbid mental disorders (Huang et al., 2012; Lu et al., 2013; Paul et al., 2008) and even in cases of only verbal abuse (Choi et al., 2009). Thus, maltreatment is likely a potential, but unrecognized, source of variability in the extant neuroimaging literature on ASB.

1.2.4 Default Mode Network and resting-state networks

Functional connectivity refers to patterns of correlated activity (as measured by fMRI) over time across different regions (van den Heuvel and Hulshoff Pol, 2010), typically investigated during task-absent resting-state conditions (Song et al., 2011). Synchronized activity patterns across anatomically distinct grey matter regions are considered indicative of common information processing, which occurs also at rest. Several robust resting-state networks have been identified, the most prominent of which is the Default Mode Network (DMN), typically defined to encompass the medial PFC, angular gyrus, inferior parietal lobule, PCC, and less consistently, also the precuneus, and hippocampus, bilaterally (Andrews-Hanna, 2012). The DMN is most active at rest and partially deactivates during explicit task engagement (Anticevic et al., 2012), making it conceptually difficult to infer what mental processes are associated with DMN resting-state activity. The internal mentation hypothesis proposes that the DMN activity is the correlate of common mind wandering, involving mental imagery based on memories and future plans (Andrews-Hanna, 2012). DMN activity has also been associated with related processes such as introspection, social cognition and empathy (Li et al., 2014; Whitfield-Gabrieli and Ford, 2012).

Since these mental processes are disturbed in some constellation and direction in all mental disorders, DMN abnormalities are likely a sensitive, but unspecific neural correlate of mental health problems. Indeed, DMN abnormalities have been associated with mental disorders including schizophrenia, depression, anxiety, autism spectrum disorders, ADHD (Broyd et al., 2009) and alcohol dependence (Chanraud et al., 2011). Disorder-specific, regional hypo- and hyperactivation patterns may distinguish disorders in concordance with their defining symptoms and the regional correlates of these (Whitfield-Gabrieli and Ford, 2012), even among, for example, different anxiety disorders (Peterson et al., 2014). However, connectivity differences between explicitly induced mental states, and the presumed naturally occurring characteristic mental states, make it difficult to draw conclusions, e.g. in the case of rumination and depression (Berman et al., 2014).

Studies of resting-state connectivity have focused on a broader antisocial and psychopathy phenotype in an effort to determine whether DMN abnormalities are associated with CU/interpersonal-affective traits, or ASB. The Dual Network hypothesis (Sethi et al., 2014) states the former, and that uncinate integrity and functional abnormalities of the amygdala-OFC circuit are associated with the ASB factor. However, as with contradictory studies of white matter integrity of the cingulum (connecting the ACC-PCC part of the DMN) (Sethi et al., 2014; Wolf et al., 2015), there is evidence both for and against this hypothesis, as well as inconclusive evidence. Behaviorally, activity in the DMN is associated with introspection, social cognition and empathy, all domains in which persons with ASB *and* high levels of CU or psychopathy interpersonal facet scores show difficulties (Bird and Viding, 2014).

One early study featuring male prison inmates reported that PCL-R factor 1 scores were uniquely associated with DMN activity, while factor 2 scores were uniquely associated with activity of the frontoparietal attention network and visual network (Juárez et al., 2013). Network activity was unrelated to IQ and SUDs, yet networks were extracted during a low-intensity oddball fMRI task, and not resting-state. Additional support for the factor-specificity of DMN abnormalities comes from another study of male prison inmates, reporting that DMN deactivation during a Go/No-Go task was attenuated in the precuneus-PCC region in high-psychopathy versus low-psychopathy offenders, and that the activation in this region was correlated with PCL-R factor 1 but not factor 2 scores (Freeman et al., 2014). High frequency power of the DMN was found to correlate with PCL-R factor 1 but not factor 2 scores in a sample of male juvenile delinquents, although no associations with network spatial maps were found (Thijssen and Kiehl, 2017). One study of juvenile offenders found that resting-state DMN activity in the medial polar PFC correlated positively with CU traits, and that at a less stringent statistical threshold, impulsive-irresponsible traits were positively associated with frontoparietal network activity in the inferior frontal gyrus, and with salience network activity in the amygdala (Cohn et al., 2015). Finally, one study of male prison inmates suggests that the two psychopathy factors may correlate with distinct connectivity abnormalities *within* the DMN: while PCL-R factor 1 scores correlated negatively with connectivity between the inferior parietal lobule and frontal and PCC regions, factor 2 scores correlated positively with connectivity between medial PFC and both frontal and posterior regions (Philippi et al., 2015).

Evidence contradicting a unique association between CU/interpersonal-affective traits and DMN abnormalities comes from a study of male adolescents with CD and healthy peers. The CD group was found to display decreased connectivity between the medial PFC and PCC, which survived correction for SUDs and ADHD, yet connectivity was not associated with any of the psychopathy factors and did not differentiate adolescent-onset from childhood-onset CD subgroups (Broulidakis et al., 2016).

Finally, several studies provide support implicating abnormalities of the DMN in the broader ASB phenotype, yet are inconclusive as to associations with specific psychopathy factors. One study of male adolescents with CD and SUDs reported reduced DMN activity during a

risk-taking decision task in several frontal regions, the lingual gyrus and middle temporal gyrus, which survived adjustment for depression and ADHD, and additionally, increased activity in the cuneus-precuneus when not adjusting for these comorbid disorders (Dalwani et al., 2014). No attempt was made, however, to determine whether there were unique associations with CD and with SUDs. Another study of a CD sample, this time specifically recruited to present no comorbid mental disorders, observed reduced DMN activity in the PCC-precuneus and superior temporal gyrus which was unrelated to impulsivity (Zhou et al., 2015). This later null finding is consistent with DMN abnormalities being associated with CU/interpersonal-affective traits and not behavioral traits (that include impulsivity). However, these results are difficult to interpret given the unrepresentative sample, and since the two psychopathy factors are typically inter-correlated, this a weak correlation in unadjusted analyses would be expected. Another study found reduced medial PFC to PCC resting-state connectivity in male offenders with high psychopathy scores compared to healthy men, but no analyses estimated associations of connectivity with specific factor scores (Pujol et al., 2012).

Finally, two studies investigated functional network topology (see Section 3.1.2. below) in the same sample of young men with ASPD and no comorbid mental disorders, compared to healthy peers. These studies reported increased clustering coefficients, decreased betweenness centrality, and aberrant connectivity between DMN nodes and nodes of other networks (Tang et al., 2016), as well as increased path length, decreased modularity, and decreased efficiency in the ASPD group (Jiang et al., 2016), but no attempts were made to correlate any graph theory measure with specific psychopathy factor scores.

In sum, DMN abnormalities in individuals presenting ASB have been investigated primarily in male offenders, often with overlapping samples, focusing on unique correlations with psychopathy factors, and relying on a wide variety of analysis methods (see Section 3.1.2. for details) that make synthesizing findings difficult. Nonetheless, most studies do suggest that DMN abnormalities are more strongly associated with the CU/interpersonal-affective traits than ASB, consistent with the hypothesized functions of the DMN and the impairments in these traits associated with CU/interpersonal-affective traits specifically.

1.2.5 Summary: Neuroimaging of individuals with antisocial behavior

A number of conclusions can be drawn from the above compilation of neuroimaging findings of adults and adolescents with ASB:

1. Abnormalities of grey and white matter structures and of brain functioning indicate that the amygdala-OFC and ACC-PCC circuits, as well as the fusiform gyrus and insula, are associated with ASB both in adolescence and adulthood.
2. There is considerable evidence to suggest that comorbid mental disorders and experience of maltreatment in childhood, which are more common among adolescents and adults with ASB, confound associations of ASB with neural

abnormalities since each of these disorders, and maltreatment, are independently associated with neural abnormalities.

3. Few previous neuroimagining studies of ASB have assessed and taken account of these commonly comorbid disorders, and maltreatment. Consequently, the neural abnormalities that have been associated with ASB may, in fact, be related to these comorbid disorders and maltreatment. Further, some previous studies have not taken account of CU/interpersonal-affective psychopathic traits, which appear to have unique and specific functional correlates, and perhaps also structural correlates.
4. Most research on ASB has focused on males. There is a scarcity of studies on females presening ASB. Some studies suggest that the neural correlates of ASB are similar in the two sexes, others indicate that there may be differences.

2 THESIS AIMS AND HYPOTHESES

2.1 OVERALL

CD presents a challenge both to clinicians and scientists as it is usually accompanied by comorbid mental disorders, experiences of maltreatment, and elevated levels of psychopathic traits. Few studies have investigated brain connectivity abnormalities among females presenting ASB and none have systematically attempted to disentangle connectivity abnormalities associated with CD from those associated with exposure to maltreatment, current and lifetime mental disorders, and psychopathic traits. Whether connectivity abnormalities associated with CD are present in adulthood, even in the absence of a diagnosis of ASPD, is presently not known. However, evidence of the persistence of ASB and related psychosocial adjustment difficulties lead us to hypothesize that such abnormalities would characterize young adult women who had presented CD as adolescents. The overall aim of the studies included in this thesis was to fill these key knowledge gaps, constituting important contributions to the literature by:

A. Studying neural connectivity abnormalities among young women who had presented CD as adolescents – an important population that has received very little attention in past research.
B. Studying neural connectivity abnormalities in a clinical sample with high external validity.
C. Showing that adolescent ASB is associated with neural correlates that persist into adulthood.

Four studies were designed and executed to answer four research questions not explored in the extant literature:

I. Do young adult women with a history of CD show white matter structural abnormalities compared to healthy peers, and to what degree can any abnormality be attributed to comorbid mental disorders and to maltreatment?
II. Is attenuated amygdala-OFC functional and structural connectivity associated with CD or comorbid anxiety disorders in females?
III. Are specific facets of psychopathy dimensionally associated with white matter integrity of the uncinate, cingulum or across the brain, in females with subsyndromal scores?
IV. Are specific factors of psychopathy dimensionally associated with local or global resting-state functional topology or inter-region connectivity, in females with subsyndromal scores?

Extended background to each study, including specific aims and hypotheses, are presented below.

2.2 STUDY I

Past structural connectivity studies of children/adolescents with CD almost exclusively featured all-male, or mixed-sex CD samples with no or few comorbid mental disorders. No study had taken account of maltreatment. Consequently, the samples in previous research were unrepresentative of clinical cases of CD. The aim of Study I was to explore, for the first time, whether young adult women with a history of CD presented structural connectivity abnormalities and whether abnormalities were associated with CD, comorbid mental disorders, or experience of maltreatment. We hypothesized that the women with CD would show widespread, anatomically non-specific decreased white matter integrity compared to healthy peers, but that adjustment of group comparisons for comorbid mental disorders and maltreatment would render most initial findings insignificant.

2.3 STUDY II

Informed by the results of Study I showing a large confounding effect of anxiety disorders on the whole-brain comparison of white matter integrity between women with prior CD and healthy women, Study II was designed to disentangle the confounding effect of anxiety disorders on structural and functional amygdala-OFC connectivity. Past research has shown this circuit to be important for emotion regulation and threat perception, and impairments of this circuitry have been observed in both individuals with CD and those with anxiety disorders. To our dismay, we were unable to create a group of females with CD and not anxiety disorders. By the average age of 24 years, of the n=17 female ex-clients with CD who did not present anxiety disorders at study entry in mid-adolescence, all but n=6 had developed an anxiety disorder in the subsequent seven years. Consequently, we compared women with CD plus an anxiety disorder to women with only anxiety disorders and women with neither disorder, and explored group-specific correlates. We hypothesized that the CD with anxiety disorders and anxiety-only groups would show similarly reduced structural integrity of the uncinate fasciculus and reduced functional connectivity between the amygdala and OFC, compared to women with neither CD nor an anxiety disorder, with no difference between the two groups. Further, we hypothesized that although connectivity would be reduced in both groups, the trait correlates of this attenuation would differ between groups, consistent with the fact that CD women engage in both approach and avoidance behavior in response to threat, while the anxiety-only women engage only in avoidance.

2.4 STUDY III

The aim of Study III was to test whether the Dual Network model of psychopathic traits applied to females with subsyndromal levels of these traits. Based on findings in male offenders with high trait levels, this model states that cingulum integrity would be uniquely associated with the interpersonal-affective factor of psychopathy, while the behavioral factor

would be uniquely associated with uncinate integrity (Sethi et al., 2014). The model has received partial support in the extant literature (Pape et al., 2015; Sethi et al., 2014; Wolf et al., 2015), and although several studies have found neural correlates of subsyndromal psychopathic traits, these also suggest that there are sex differences (Carré et al., 2013). The fact that women show less physical aggression, resulting in lower behavioral factor scores (Strand and Belfrage, 2005), may render the model inapplicable to females. Whether the model applies to subsyndromal trait levels was also unknown. In Study III, we investigated these questions in a large sample of women with varying levels of psychopathic traits. Unrestricted, whole-brain analyses were also performed to identify additional white matter correlates of psychopathic traits.

2.5 STUDY IV

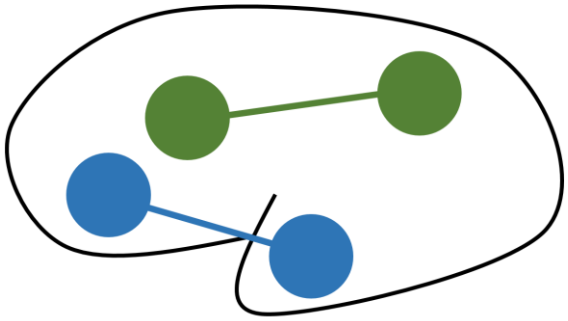
This study tested the predictions made by the Impaired Integration Theory of psychopathy (Hamilton et al., 2015) that psychopathic traits are associated with regionally abnormal, but globally preserved, neural topology with disrupted integration of different neural networks impeding information processing, resulting in impaired learning and the characteristic cognitive, affective and behavioral aspects of psychopathic traits. Like the Dual Network hypothesis, the Impaired Integration Theory is based almost exclusively on findings from adult male offenders. To what degree this theory applies to females with subsyndromal traits was unknown. Using graph theory to estimate network topology in terms of nodes (grey matter structures) and edges (correlations of resting-state activity), we tested the specific predictions from the Impaired Integration Theory. Unlike previous studies of topology and psychopathic traits, the present study adjusted analyses for comorbid mental disorders (anxiety, depression, alcohol and drug dependence), as well as IQ.

3 METHODS

3.1 CONNECTIVITY NEUROIMAGING

The human brain consists of more than 100 billion neurons forming a complex network at both the micro (cellular) and macro level (structurally), referred to as *brain connectivity*. This network can be viewed as a collection of *nodes*, inter-connected by *edges*. In MRI studies, where the imaging resolution is on the scale of mm^3, these nodes are typically defined as anatomically distinct grey matter regions, e.g. the amygdala, OFC, precuneus, ACC, etc.

Figure 1. Simple schematic of connectivity approach.



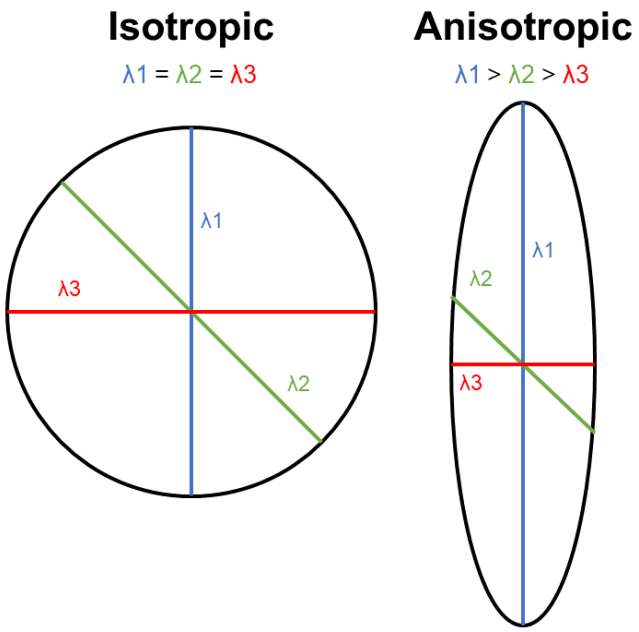
Most neuroimaging research focuses on the activity or structural properties of such nodes. In brain connectivity studies, it is the *edges*, or the *topology* that emerges from the constellation of edges, that is of interest. Connectivity is thus the study of how different regions of the brain are connected. Both *structural* and *functional* aspects of connectivity are of interest, with structural connectivity referring to the white matter pathways that connect distinct grey matter regions, and functional connectivity referring to patterns of correlated activity between distinct grey matter regions. The former can be studied using Diffusion Tensor Imaging, and the latter using functional MRI. These two techniques, and available analysis methods, will now be discussed in turn.

3.1.1 Diffusion Tensor Imaging

Using modern MRI techniques such as Diffusion Weighted Imaging (DWI), white matter tracts can be imaged and reconstructed non-invasively and *in vivo* (Taylor, 2003). As in all MRI techniques, a scanned brain is divided into a three-dimensional grid pattern of voxels. In DWI, individual voxels are typically 2 × 2 × 2 mm large, meaning that an average brain will consist of hundreds of thousands of voxels. Using MRI principles, DWI measures the random thermal (Brownian) motion of water molecules. Diffusion along a myelinated axon is hindered perpendicular to its longitudinal axis by structures such as the axolemma and

neurofilaments, resulting in the parallel diffusion being proportionally greater. In Diffusion Tensor Imaging (DTI), diffusion in at least six non-collinear directions is measured for each voxel and used to fit a tensor, a three-dimensional ellipsoid, with measure of magnitude (eigenvalues) and orientation (eigenvectors) for each dimension. See Figure 2. A voxel is isotropic if the diffusion is similar in all three dimensions, as is the case in the cerebrospinal fluid, for example. In white matter, the principle eigenvalue, referred to as Axial Diffusivity (AD), corresponds to the direction of the tract covered by that voxel, while the average of the second and third eigenvalues is referred to as Radial Diffusivity (RD). Fractional Anisotropy (FA) is another popular metric in DTI and corresponds to the square root of the sum of squares of the diffusivity differences, divided by the square root of the sum of squares of the diffusivities. Hence, an FA value of 0 corresponds to equal diffusion in all directions (isotropy), while an FA value of 1 (the maximum possible value) corresponds to diffusion along only one dimension (anisotropy). Although interpretations should be made with caution (Wheeler-Kingshott and Cercignani, 2009), AD, RD and FA metrics are considered to index different biological substrates: AD is believed to index axonal structure (tortuosity, thinning or loss), RD myelination, and FA being a measure of coherent directionality, interpreted as a proxy measure of structural integrity (Jones et al., 2013).

Figure 2. Tensor model used for DWI data

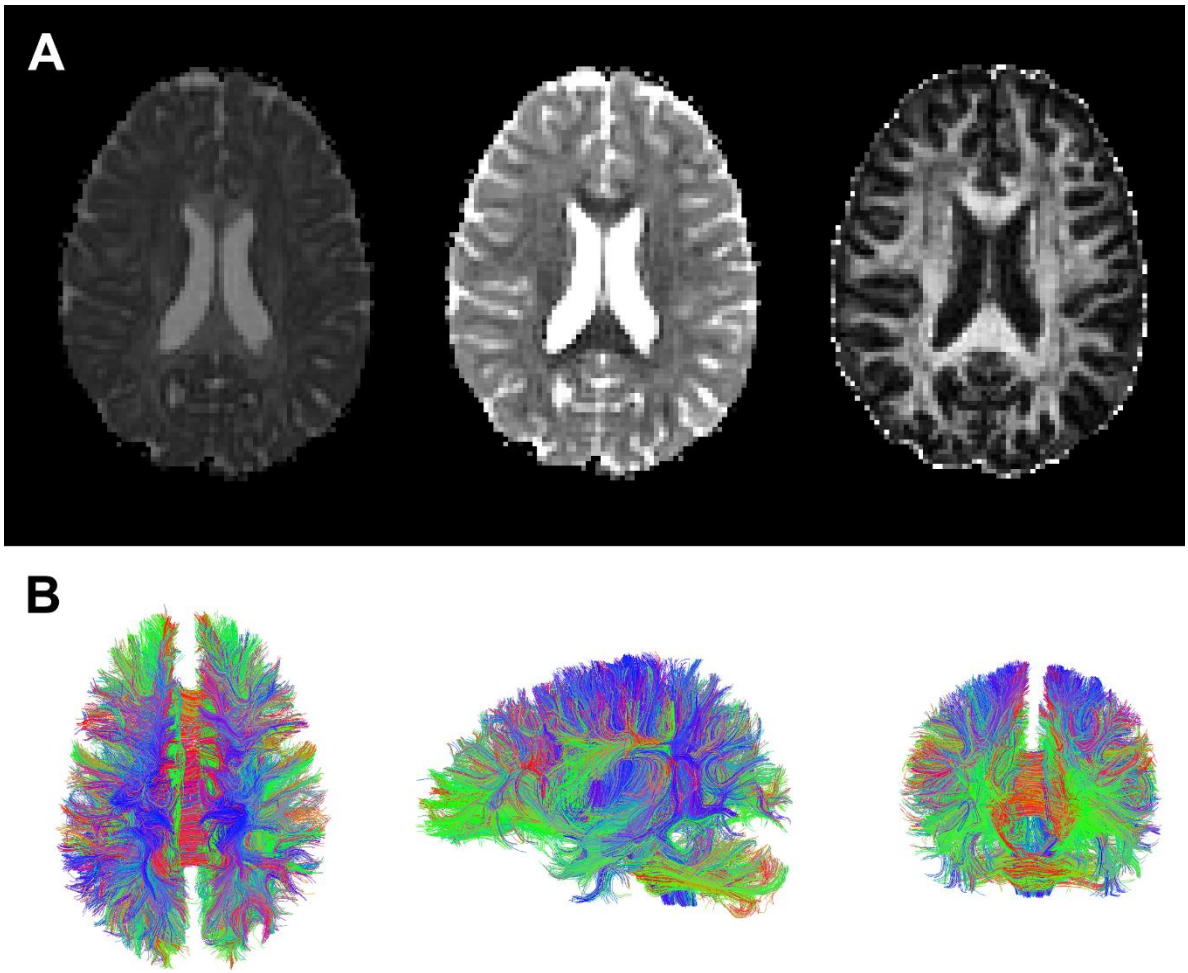


Limitations of the tensor model to accurately capture the complexity of fiber patterns becomes apparent when considering that tensor-fitting is performed on a voxel level, often in the range of 2 mm^3. If a voxel includes crossing, bended, kissing, twisting or fanning fibers, or is adjacent to gray matter or cerebrospinal fluid, the AD, FA and RD values will not

accurately represent the actual fiber constitution. More advanced reconstruction techniques such as spherical deconvolution have been developed to resolve these issues, yet these require more advanced acquisition protocols and produce less interpretable fiber metrics (Dell'acqua et al., 2010).

After pre-processing such as motion-correction and removal of distorted slices, tensor-fitted DWI data is typically analyzed in one of two ways, both relying on voxelwise maps of a DTI metric (e.g. FA) for each subject. DTI maps are either kept on a voxelwise level for inter-subject normalization and comparisons with e.g. Tract-Based Spatial Statistics (Smith et al., 2006), or the spatial information inherent in the voxelwise DTI maps is used to reconstruct the tracts that run along a section of the brain, so called *tractography*. See Figure 3 for examples.

Figure 3. Example DTI voxelwise maps and corresponding tractome

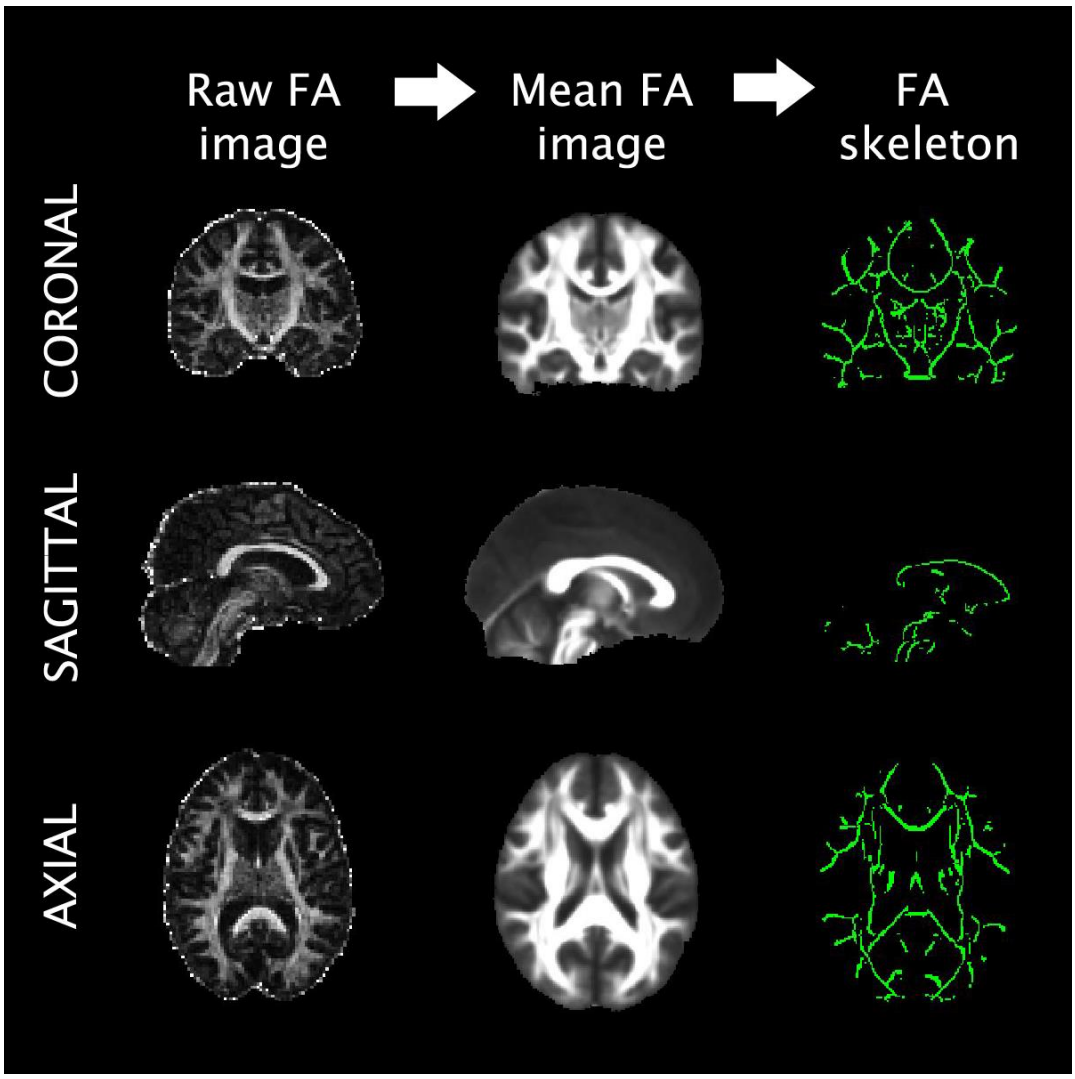


Example from one thesis participants. Top section (A) shows AD, RD and FA maps, respectively from left to right. Image intensity does not compare across images. Bottom section (B) shows same participant's tractome from axial, sagittal and coronal view, respectively from left to right. Green tracts run anterior-posterior, blue tracts run superior-inferior and red tracts run left-right.

3.1.1.1 Tract-Based Spatial Statistics

Statistical analyses of any kind of voxelwise maps require normalization such that any given voxel (and the information contained therein) is anatomically comparable across subjects. In VBM analyses of grey matter, this is achieved by aligning all individual brains to a common, standardized template, and then smoothing the data to improve misalignment issues on the resulting normalized density maps. These can then be used for statistical comparisons, typically mass-univariate in nature where each voxel is treated as a separate variable across *n* subjects, corrected for multiple comparisons by adjusting the p-value cluster extent thresholds (i.e. *k* adjacent voxels required for cluster to be considered significant).

Figure 4. Stages of TBSS analysis



Unpublished images from analysis pipeline of Study I.

Although the same analysis pipeline could in theory be directly applied to DTI-derived brain maps, this has until recently been considered inappropriate due to the complexity of normalizing white matter. The primary reason is that peripheral, smaller tracts display great individual variability in size, trajectories and location, much more so than grey matter gyri and subcortical structures. Smoothing, which in VBM is used to ameliorate registration misalignments issues and render the data more Guassian distributed, is also problematic when using DTI maps since it increases partial volume effects, in addition to generic arbitrary choice of smoothing extent. The Tract-Based Spatial Statistics (TBSS) method resolves these issues by estimating a thinned, thresholded mean FA "skeleton" representing the center of the most prominent white matter tracts, common to all subjects. Individual DTI metrics are then projected onto the skeleton so that skeleton voxels represent the local center of the nearest tract (Smith et al., 2006). The TBSS method thus trades some anatomical coverage and specificity for increased normalization validity (Bach et al., 2014).

Since the data collection for this thesis began, novel registration procedures not requiring skeletonization have been proposed and show initial promise (Schwarz et al., 2014). Nonetheless, more than 10 years since its first release, TBSS remains a popular analysis method for DWI data. At time of writing, the technical paper serving as a reference has over 2,542 citations in Web of Science in total, with 300-400 new citations per year, and a rising trend, in the last five.

3.1.1.2 Tractography

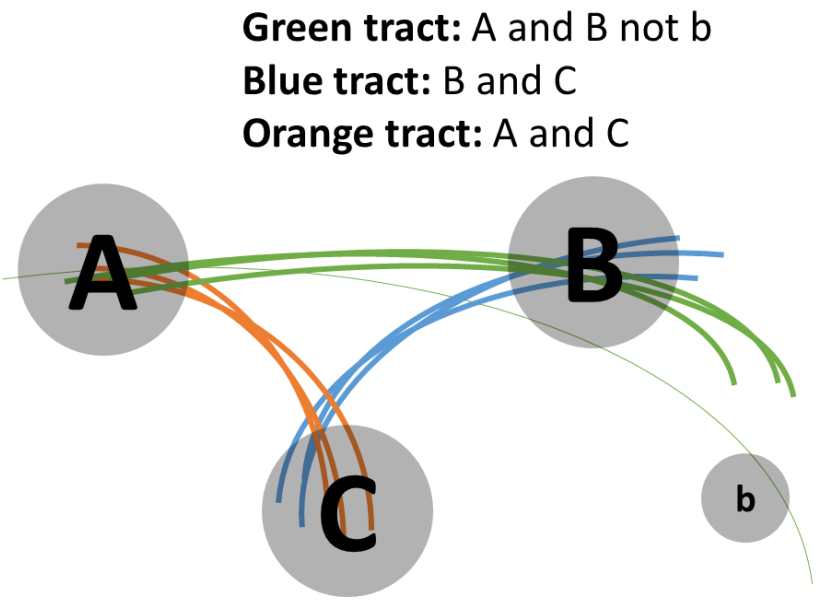
Tractography is a modeling technique used to reconstruct white matter tract pathways in 3D (a *tractome*) from voxelwise data by estimating curvature of streamlines through continuous tracking of the principle eigenvector of adjacent voxels (Catani et al., 2002). This can be done either deterministically or probabilistically. Deterministic tracking involves reconstructing one path from a seed voxel to the next until stopping criteria are met (typically angle and FA thresholds) (Mori et al., 1999), while probabilistic involves reconstructing several paths from a seed voxel to the next through (semi-) random direction selection and iterating this process hundreds or thousands of times to obtain probabilistic maps of streamlines (Parker et al., 2003). Deterministic tractography allows for fast reconstruction of the major white matter tracts of the brain, while probabilistic tractography is superior in reconstructing the full tractome but is computationally very demanding (time-requiring). Both deterministic and probabilistic tractography can be run either on specific seed-to-seed, or whole-brain.

Traditionally, tractomes have been reconstructed and analyzed in native, non-normalized space, requiring manual dissection techniques (Dell'acqua and Catani, 2012). This involves a trained operator manually overlaying regions of interest (ROIs), based on known neuroanatomy and taking individual variability of tract pathways into account, and applying logical operators (NOT, AND, OR and XOR gates) to selected ROIs in order to isolate specific tracts. Using this method, tracts that intersect in certain regions can be isolated based

on their trajectories, and spurious tracts removed. See Figure 5 below for a 2D schematic representation. Structural integrity proxy measures (e.g. FA, AD and RD), averaged across the tract or specific segments of the tract, can then be extracted.

Manual dissection techniques are labor intensive, require operator knowledge of neuroanatomy, and, like all manual techniques, are vulnerable to subjective biases (Dell'acqua and Catani, 2012). The latter can be alleviated through blinded dissections and the application of strict dissection protocols. Although automated dissection techniques have been developed (Yendiki et al., 2011), manual dissection by a trained operator is still considered a gold standard choice (Budisavljevic et al., 2015; D'Anna et al., 2016), especially for tracts with complex, intertwined curvature.

Figure 5. Schematics of manual dissection technique



Lines are individual streamlines (thin line denotes reconstruction artefact), delineated into tracts by common trajectories, as defined by ROIs. Schematic roughly corresponds to the three major limbic tracts of the brain (viewed from side, left is anterior and right is posterior): the uncinate fasciculus (A-C) running from the temporal pole into the PFC, the inferior longitudinal fasciculus (C-B) running from the temporal pole to the occipital cortex, and the inferior fronto-occipital fasciculus running from the PFC to the occipital cortex.

3.1.1.3 Methods used in thesis

See Table 2 for a summary of the advantages and disadvantages of TBSS and tractography. TBSS was used in Study I and III, and tractography in Studies II and III. Analysis methods were chosen based on study objectives and *a priori* hypotheses. In Study I, TBSS was chosen since recent evidence suggested widespread, region-nonspecific abnormalities of white matter integrity among individuals presenting CD (Haney-Caron et al., 2014). In Study II, the focus

was on amygdala-OFC connectivity specifically (both functional and structural). Since the direct fiber pathway between these two regions, the uncinate fasciculus, intersects with the inferior longitudinal fasciculus in the temporal pole and with the inferior fronto-occipital fasciculus in the PFC, tractography was considered necessary to accurately delineate this tract. The uncinate fasciculus was investigated (in a larger sample) also in Study III, along with the dorsal section of the cingulum bundle (Sethi et al., 2014). The dorsal cingulum runs superior to the corpus callosum along an anterior-posterior trajectory, and can be clearly delineated from the TBSS skeleton. Therefore, manual masking of the TBSS skeleton to delineate the combined left and right cingulum was used. Study III also employed whole-brain TBSS.

Table 2. Comparison of the advantages and disadvantages of TBSS and tractography

	TBSS	**Tractography**
Pros	- Allows whole-brain, voxelwise analyses when a specific tracts are not of interest - Easy to perform and few choices of settings that may introduce bias - High sensitivity	- Inter-subject normalization and standardization not required, but possible - Tract and segment metrics are interpretable and meaningful (assuming appropriate within-tract or -segment distributions) - Congenial with functional connectivity and easy to integrate - Allows analyses of tract shape†
Cons	- Specificity reduced by skeletonization and projection procedure - Only skeleton voxels common to *all* participants included - Voxel findings can be hard to interpret and require further analyses	- Manual dissection is labor-intensive and risks subjective bias - Tensor-based reconstruction can result in spurious tracts, broken tracts and other artefacts‡ - Provides tract- or segment-averages that may lack meaning if within-tract or –segment distributions are skewed

† Analysis of tract shape is a novel, thus far rare analysis technique, where the shape itself is of interest, rather than the metrics of the voxels captured by the shape. Shape is analyzed by projecting 3D information into 2D space using an Isomap algorithm, a nonlinear dimensionality reduction technique, metrics from which can be easily analyzed using standard general linear models, e.g. to compare patient and healthy participants (Sun et al., 2017).

‡ This problem can be alleviated to a great extent by using more advances image acquisition methods (e.g. High Angular Resolution Diffusion Imaging, HARDI) and reconstruction techniques (e.g. Spherical Deconvolution).

3.1.2 Resting-state fMRI

Although it has long been known that there is spontaneous, intrinsic resting-state brain activity, as detectable by electroencephalogram and positron emission tomography, the first study to image and analyze resting-state activity using fMRI was not published until 1995 (Biswal et al., 1995). All fMRI techniques rely on detecting the blood oxygen level dependent signal: firing neurons require more energy in the form of sugar and oxygen, and the subsequent release of oxygen from the blood (the hemodynamic response) causes a change in the ratio of oxygenated to deoxygenated blood, which have different magnetic susceptibilities and can thus be differentiated with MRI. The blood oxygen level dependent signal value is thus inherently relative and lacks a meaningful interpretation by itself, hence the reliance in task-based fMRI studies on statistical contrasts, e.g. activity during task as compared to during no-task. When no such task contrasts are available, as in resting-state conditions, different analyses methods are required to make sense of the data. In the year 1995, Biswal et al. (1995) initiated the new field of rs-fMRI research by turning their attention to the spatiotemporal coherence in the data. They found that low-frequency oscillations in cortical motor regions were synchronized across hemispheres, suggesting a network organization. Years later, Greicius et al. (2003), inspired by a wealth of research showing greater ACC and PCC activation when inversing the traditional task > no-task contrast, found that there was indeed a network formed around these two nodes, active at rest and attenuated during tasks (Greicius et al., 2003). This was referred to as the Default Mode Network (DMN).

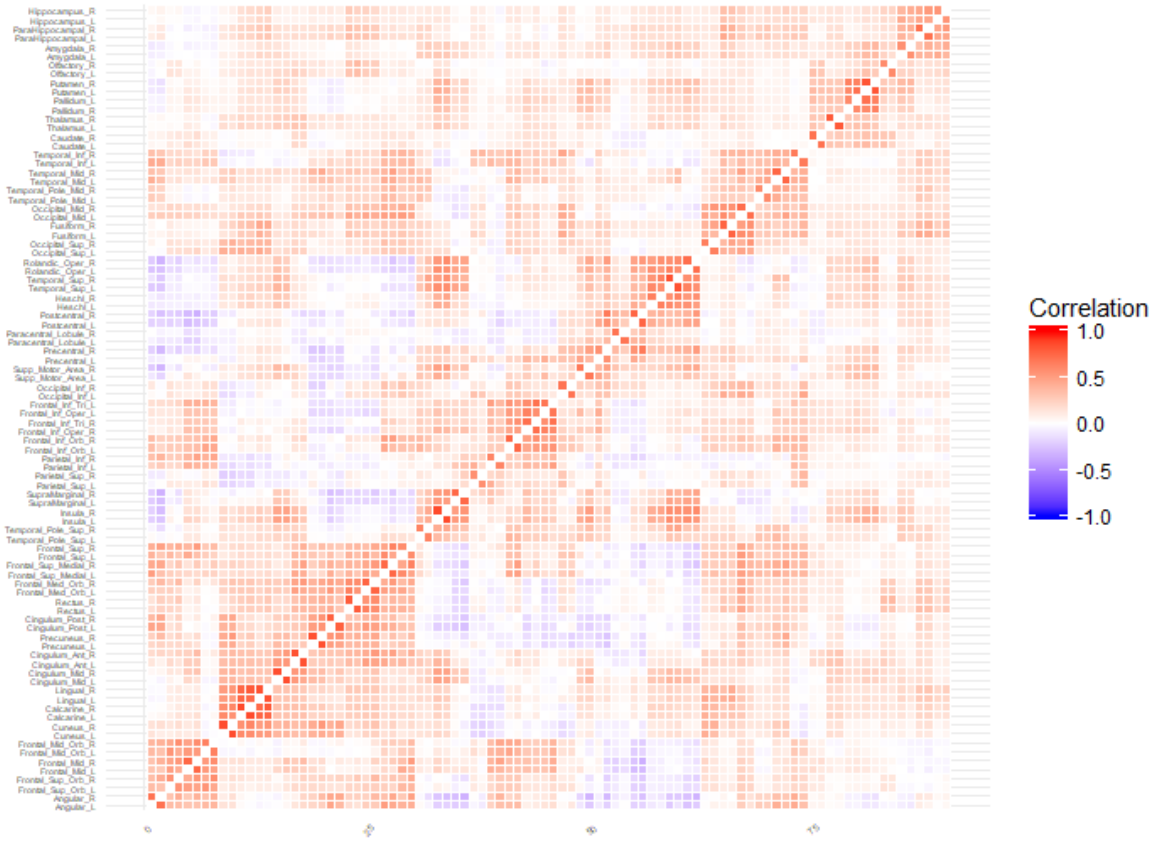
Since these seminal studies, two primary ways of analyzing resting-state data (which can be combined) have emerged: voxelwise analysis with independent component analysis (ICA), and seed region-based analyses (Lee et al., 2013). Briefly, ICA decomposes resting-state data into temporal and spatial components, *functional networks*, the resulting spatial connectivity maps of which can be compared using voxelwise statistics (Beckmann et al., 2009). There are ten or so networks that can be reliably and robustly identified using this method (Franco et al., 2013), including the DMN and the fronto-parietal network (van den Heuvel and Hulshoff Pol, 2010).

These networks can be delineated also using a seed-based approach, as in the pioneering studies, by selecting a ROI prominent in a particular network (e.g. the PCC of the DMN), extracting the average timeseries from this seed and using it as a regressor to find voxels with correlated activity (Franco et al., 2013). An alternative approach is to forgo voxel-level analyses and ICA-derived networks to instead focus on inter-region functional connectivity, which entails dividing the brain into multiple ROIs and extracting timeseries from each. The primary benefits of this approach include more interpretable metrics of connectivity, and both conceptual and statistical compatibility with structural connectivity (Skudlarski et al., 2008). Inter-region functional connectivity was investigated in Studies II and IV of this thesis.

3.1.2.1 Inter-region connectivity

By extracting timeseries from multiple ROIs and computing all possible ROI-to-ROI correlations of activity over the timeseries, a connectivity matrix can be compiled. See Figure 6 for an example. In theory, such a connectivity matrix could be computed containing all the brains voxels, *k*, generating (k^2-k)/2 unique correlations. The number of voxels will vary with imaging resolution, but is typically on the scale of hundreds of thousands. A k=100,000 voxel brain would thus have 4,999,950,000 unique correlations to examine. The obvious risk of false positives due to multiple comparisons notwithstanding, there is no *a priori* reason to believe that a higher temporal resolution in this case would convey more meaningful information: any voxel includes up to millions of neurons, and voxels adjacent to one another are more likely to show correlated activity for the simple reason that brain *is* divided into functionally and anatomically defined subregions, such as specific gyri and subcortical structures.

Figure 6. Example of raw inter-region connectivity matrix



Correlations matrix of raw r values between time series of 90 regions, clustered using the complete linkage technique. Unpublished data from Study IV.

The primary methodological question pertaining to inter-region connectivity analysis is therefore what spatial resolution and division pattern to choose when extracting the timeseries used to compute correlations. There is no single answer to this question (Rubinov and Sporns, 2010). If regions are too large (e.g. dividing the brain into lobes), within-region variance will be large and the region-average will not be interpretable. If regions are too small, boundaries risk being arbitrary and artificial, resulting in superfluous regions, increased risk of false positives and overly conservative multiple comparison correction. Both anatomy-based and data-driven approaches to division exist, each with pros and cons. Anatomy-based approaches divide the brain's grey matter regions based on established anatomical boundaries, resulting in ROIs that correspond to atlas definitions. A popular alternative is the 90 region Automatic Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), covering both cortical and subcortical regions. Advantages of this anatomy-based division is high interpretability and consistency with research that has used this anatomy atlas for localization in voxelwise maps. The major disadvantage is that a perfect overlap between the ROI and the actual center of neural activity cannot be guaranteed. Data-driven approaches to division also exist, wherein spatiotemporal clustering is used to define ROIs based on their activity pattern, performed either on the data itself or on meta-analyses (Power et al., 2011). Having considered the advantages and disadvantages of each approach, both Studies II and IV used anatomically-defined ROIs, since both of these studies tested specific hypothesis on specific structures.

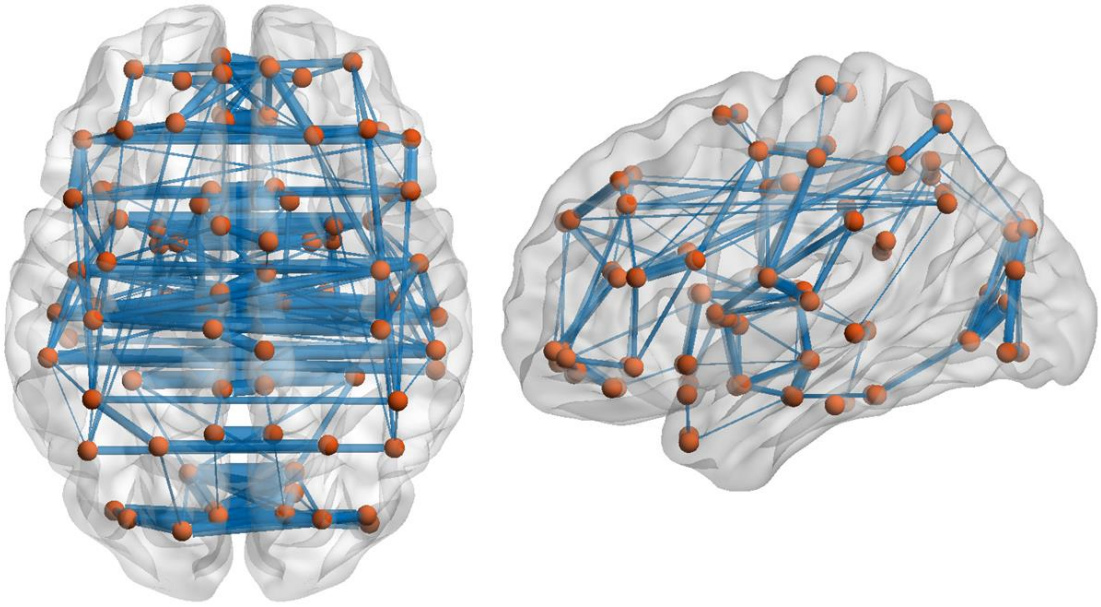
3.1.2.2 Graph theory

Although the bulk of neuroscience is still very much focused on specific structures of the brain and the functions considered localized thereto, there is increasing interest in studying the brain not just as a collection of inter-connected structures, but as an actual network (Bullmore and Sporns, 2009). Graph theory is a network science approach that involves constructing networks based on mathematically defined *nodes* and *edges*. In neuroscience, nodes are typically grey matter structures, while edges are defined as either a structural (white matter) connection, or correlated timeseries, between two nodes. Edges may be either binary or weighted, as per the definition used, and are usually thresholded in some way. If there is meaningful causal information contained in the edges, these are classified as directed, although such applications are still uncommon in neuroscience due to the difficulties in inferring causal relationships from neuroimaging (Rubinov and Sporns, 2010).

The number of edges of a node (as per the threshold used) is referred to as the *degrees* of that node. In naturally occurring networks, be they neural, social acquaintances, internet sites or flightpaths, some nodes will have higher degrees than others and nodes will tend to cluster according to some parameter. In such cases, the resulting network *topology* displays smallworldness: a phenomenon describing a network in which several highly intra-connected clusters are inter-connected by *hubs* that primarily connect to other hubs, which in turn connect to a cluster of inter-connected nodes. This kind of topology is efficient in that it

ensures a short path length between any two nodes, even if they belong to different clusters. Robust evidence shows that the brain has a smallworld structural and functional topology, featuring the insula, ACC, precuneus/PCC, and inferior parietal lobule (van den Heuvel and Sporns, 2013) as hubs. See Figure 7 for an example topology.

Figure 7. Example brain topology



Nodes defined according to the same 90 region AAL atlas used in Studies II and IV. Weighted edges defined according to the example included in the BrainNet Viewer software (Xia et al., 2013), thresholded at >0.5 for visualization purposes.

A large number of graph theoretical measures have been developed to index different aspects of topology, which in turn can be correlated with abilities such as working memory (Stevens et al., 2012), spatial orientation (Arnold et al., 2014), and intelligence (van den Heuvel et al., 2009; Langer et al., 2012; Li et al., 2009). Topology has also been associated with clinical phenomena such as trait anxiety (Markett et al., 2016) and personality (Beaty et al., 2016). Topology measures can be calculated for both specific nodes and across the whole network, with higher-order measures being derived from the degrees of the nodes. The *betweenness centrality* of a node, for example, refers to the fraction of all shortest paths in the network that pass through any given node, while global measures such as the *clustering coefficient*, *characteristic path length*, and *Louvain modularity* refer to the percentage of fully connected triplets divided by the total number of triplets, the average number of steps along the shortest path between all possible pairs of nodes, and the density of edges inside communities compared to edges outside communities, respectively.

Since graph theory measures are built on connectivity matrices, the same methodological caveats apply here (primarily choice of division). Additional analysis considerations apply specifically to graph theory:

1. Whether or not to binarize edges based on an arbitrary threshold.
2. Whether to threshold edges based on an arbitrary threshold.
3. Whether to treat negative correlations between nodes, which have no meaningful biological interpretation, either as they are, as absolute values, or to set to zero.

The decision to analyze edges as either binary or weighted variables should be based on an interpretation of whether the strengths of the edges are reliable and can be meaningfully interpreted. In structural graph theory, where edges are typically defined by the number of streamlines passing from one region to another and/or the average FA value of these streamlines, limitations of reconstruction and tractography methods (see Section 3.1.1) mean that the sensitivity of binary edges are often preferred over the (hypothetical) specificity of weighted edges. In functional graph theory, where edges are defined statistically based on the correlations of timeseries, differences in weighting are typically considered robust and meaningful. For this reason, in Study IV of this thesis, weighted edges were analyzed.

The second methodological decision concerns the choice of thresholding for network formation. Relative thresholding (preserving only the *x* percent strongest connections) is recommended in order not to have the topology obscured by weak associations that likely reflect spurious connections, a particular risk in functional connectomics where ROI boundaries may not perfectly reflect the true anatomical center of activation (Rubinov and Sporns, 2010). The thresholding limit is however arbitrary. For this reason, graph theory software such as GraphVar require the user to apply several different network formation thresholds and any statistical modeling is then applied to all threshold versions (Kruschwitz et al., 2015). This was done in Study IV.

The third methodological decision is how to treat negative correlations between nodes. Such negative correlations have no plausible biological explanation and likely reflect a synchronization phase delay corresponding to the shortest path length between the two anti-correlated nodes (Chen et al., 2011). For Study IV, we used the option that sets these negative correlations to zero, since this postulates the weakest assumptions. Opting instead to treat these values as are would assumed that negative correlations *can* be meaningfully interpreted, while opting instead to treat these values as absolute would require an assumption that negative and positive values can be interpreted similarly despite emerging from different mechanisms (Chen et al., 2011).

3.2 THESIS STUDIES

Four studies were conducted on a same sample of n=99 women, a majority of whom were enrolled in a prospective, longitudinal study, who completed clinical assessments and resting-

state fMRI and DWI. Imaging data were collected between 2012-07-03 and 2014-02-04, and combined (when available) with data from previous assessment waves.

3.3 ETHICS

All waves of data collection, including the current that featured MRI, were approved by the Ethical Review Board in Stockholm (DNR: 2008/1934-31/3, 2012/698-32, 2012/1412-32), and its antecedent, the Karolinska Hospital Research Ethics Committee (DNR: 03-543). When participants were younger than 18 years, parents provided written consent for participation at each wave. Once participants reached 18 years of age, they themselves provided written consented at each wave of data collection. For their participation in the latest follow-up wave that included MRI, participants were compensated with 1600 kronor in gift certificates.

Although the ex-clients were recruited from a clinical setting, all research data were collected independently of clinical practice: there have been no transfers of diagnoses and participation in research was not recorded in official medical record. At each wave of data collection, participants completed clinical interviews. If the participant presented a mental disorder that could benefit from treatment, this was discussed with the participant and self-referral information was provided. At prior follow-up waves, if a participant younger than age 18 or a parent reported on-going maltreatment, this was discussed with parents and a referral made to social services with the parents if possible, if not without them.

Two times prior to undergoing an MRI brain scan, all potential participants were questioned about standard contraindications to MRI and not scanned if any were present. MRI data was collected by operators trained in MRI safety. Participants were told that they could abort the scan at any time. MRI images were reviewed within days by a clinical radiologist to determine whether any condition requiring medical intervention was present. Such a condition was identified in one participant who was excluded from all analyses. Participants were informed prior to scan that they could not undergo the MRI if they were intoxicated or had recently used alcohol or illicit drugs. Objective measures of alcohol and drug use were collected immediately prior to the scan.

3.4 PARTICIPANTS

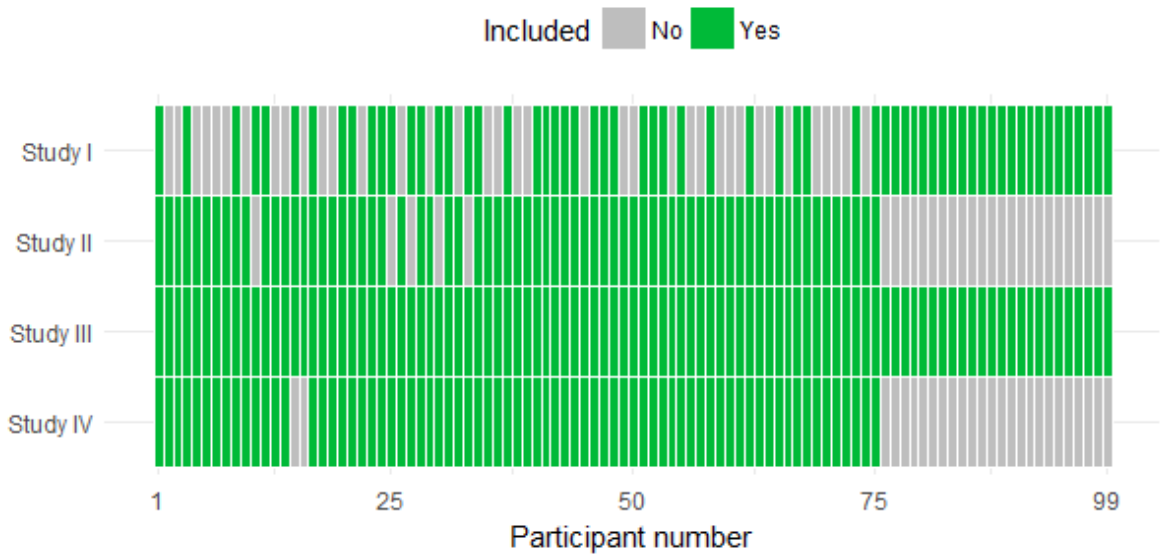
The four studies constituting this thesis recruited participants from a prospective cohort study of males and females who were ex-clients at the only clinic for adolescents misusing substances in a large, Swedish urban center in 2003-2004, along with their siblings and sisters (Hodgins et al., 2007, 2010, 2014). This thesis focused exclusively on the women. At the fourth and latest follow-up assessment, approximately 78-84 months after study entry, the ex-clients and sisters were assessed and scanned. Women with a past history of brief psychotic

disorder, psychosis not otherwise specified, delusional disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, were excluded. One participant meeting lifetime criteria for bipolar II was excluded from Study I that focused on the women meeting CD criteria. Five women in the total sample met lifetime criteria for anorexia nervosa and n=2 for bulimia nervosa. Women who were pregnant or breast-feeding at time of initial invitation were invited to participate at a later date.

For the imaging studies, in addition to the ex-clients and sisters, a group of healthy women of the same age with no history of ASB, mental disorders, or maltreatment was recruited. All participants from the three recruitment groups (ex-clients, sisters of ex-clients, and healthy women) who were assessed and scanned before 2014-02-04 were eligible for inclusion in the final sample. N=9 participants were removed due to low-quality DWI data (see section 3.7.2 below), leaving n=99 participants available for structural connectivity analyses. Of these, n=1 was removed from functional connectivity analyses due to low-quality fMRI data (see section 3.8.2 below).

From this sample of n=99 women, individual participants were selected for each study based on study aims. Study III included all women. Study IV included all but the healthy women and two ex-clients with missing PCL-R data. In Study I, women who met CD criteria as adolescents, women meeting a maximum of one lifetime CD criteria, and healthy women were included. In Study II, women who met CD criteria and who also presented a lifetime anxiety disorder, women who presented a lifetime anxiety disorder but never met CD criteria, and women who never met criteria for either CD or an anxiety disorder (and were not healthy women), were included. See Figure 8 below.

Figure 8. Participant inclusion plot



3.5 PROCEDURE

Ex-clients and sisters were contacted by mail and telephone and invited to participate in a new follow-up assessment that included a brain scan. Healthy women responded to advertisements on company and public bulletin boards, and on the internet. All participants were screened for MRI contradictions on the telephone prior to scheduling. Ex-clients and sisters were scheduled for a single assessment occasion at the Karolinska University Hospital Solna that included both clinical assessment and MRI (almost exclusively in that order). Because healthy women completed additional measurements, and since their inclusion was conditional on their assessment results (e.g. IQ not being too high), assessment and MRI occurred on two separate occasions, roughly one or two weeks apart.

3.6 CLINICAL MEASURES

3.6.1 Diagnoses

Diagnoses were made at each wave using validated clinician-rated, semi-structured instruments, either the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997) if below 18 years at the time, or the Structured Clinical Interview for DSM-IV (First et al., 2002) if older. At the cohort baseline and the one-year follow-up, 15 and 12 cases (respectively) were used to assess inter-rater reliability, which was found to be consistently high (kappa > 0.8 for all diagnoses and both occasions). Comorbid disorders of interest in this thesis were alcohol dependence, drug dependence and major depression disorder, and any anxiety disorder.

Since ADHD is neither included in the diagnostic interview manual that was used in the latest follow-up waves (First et al., 2002), nor was assessed at any time using a validated self-report measure (Kessler et al., 2005), a binary indication proxy measure was constructed by searching for a self-reported diagnosis of ADHD or self-reported use of methylphenidate at any available wave. For the ex-clients and sisters, diagnoses from National Swedish Health Register from the last wave were also available and used as additional indicators.

3.6.2 Medication

Current psychoactive medication (either anxiolytic, antidepressant, sedative, stimulant, or antipsychotic) was extracted from the self-reported Life History Calendar (Freedman et al., 1988), and categories collapsed to form a single binary variable.

3.6.3 Self-rating scales

Current anxiety symptoms were scored using the Beck Anxiety Inventory (Beck et al., 1988), providing a numeric total score for analyses. Participants reported handedness using the

Edinburgh Handedness Inventory (Oldfield, 1971). Because the distribution of the canonical laterality index was severely skewed, percentage left-handedness is reported.

3.6.4 Intelligence

Verbal and performance intelligence (VIQ and PIQ) were estimated using the Vocabulary and Block design subtests of the Wechsler Adult Intelligence Scale III (Wechsler, 1997), administered by a clinical psychologist either prior to scanning (healthy participants) or at the last assessment. Normalized scale scores were used as metrics. One ex-client had missing data on both these measures; in neuroimaging analyses that do not allow for missing data, whole-sample median imputation was used.

3.6.5 Physical abuse and sexual abuse

Physical abuse was defined as severe or extreme physical abuse, self-reported at any wave, as defined by the Conflict Tactics Scale (Straus et al., 1996): hit with a fist or kicked hard, hit on a part of the body other than the bottom with a hard object, thrown or knocked down, grabbed around the neck and choked, beaten up, hit repeatedly very hard, burned, or threatened with a gun or knife. Sexual abuse was defined as at any wave self-reporting being forced to have sex against his/her will by a person in position of authority, by offering alcohol or drugs, or by physical violence, on the Sexual and Physical Abuse Questionnaire (Kooiman et al., 2002), Sexual Experience Survey (Koss and Oros, 1982), or MacArthur Community Violence Instrument (Steadman et al., 1998).

3.6.6 Psychopathic traits

The ex-clients and sisters were assessed using the PCL-R (Hare, 2003) at the last follow-up wave, approximately 18-24 months prior to scan, while the healthy women were assessed prior to scan using the Psychopathy Checklist: Screening Version (PCL:SV), as is recommended for non-clinical samples (Hart et al., 1995). Both are semi-structured interviews, scored by trained interviewers. Although the PCL-R and PCL:SV have the same facet and factor structure, they are not item- and score-equivalent. Hence, for study III that featured all women, PCL-R scores were translated to PCL:SV scores using a validated psychometric procedure (Cooke et al., 1999). For Study IV that featured only the ex-clients and sisters, the original PCL-R scores were used.

3.6.7 Psychosocial functioning

Four aspects of psychosocial functioning were defined and analyzed, all self-reported:

1. Having completed secondary education (*gymnasium*) at time of scan (binary variable).
2. Full-time occupation (work, education, job-training or parental leave) during 11 of the last 12 months, as recorded by the Life History Calendar (Freedman et al., 1988).
3. Having a child (binary variable).
4. Self-reported aggressive behavior in the last 6 months, as per the MacArthur Community Violence Instrument (Steadman et al., 1998). Used both as a continous and binary variable.

3.6.8 Sample characteristics

Sample characteristics are presented in Table 3 below, by recruitment group. Of note, recruitment group was not used as the independent variable in any analysis in any thesis study. Sample characteristics by the independent variable of interest in each respective study are presented in that study.

3.7 STRUCTURAL CONNECTIVITY ANALYSIS

3.7.1 Acquisition

DWI images were collected using a 3-Tesla GE MR750 MRI scanner using a single-shot, echo planar imaging, twice-refocused, spin-echo diffusion pulse sequence, enhanced by slice-selective gradient reversal, and an eight-channel array coil. Images were acquired across 60 noncollinear directions with a gradient strength-duration of b=1000 s/mm^2, and eight initial b=0 directions, with an acquisition matrix of 116 × 116 and a 2 mm^3 isotropic voxel resolution. Echo time was 81.6 ms and repetition time 7600 ms.

3.7.2 Pre-processing

Raw DWI images were quality-controlled and pre-processed using DTIPrep (Oguz et al., 2014). DTIPrep automatically identifies and remove low-quality volumes, and corrects the remaining volumes for motion and eddy-currents. This is done by rigid body and affine (respectively) registration to a mean of the b=0 images. The gradient direction table is then adjusted for these corrections (Soares et al., 2013). The resulting images were visually screened for any remaining artefacts. Remaining preprocessing was done using the FSL software package (Jenkinson et al., 2012; Smith et al., 2004). This included standard-value skull stripping (Smith, 2002) and tensor-fitting using the *dtifit* tool and the weighted least-square method. This generated individual FA, AD and RD maps, the most common DTI metrics in extant literature (Soares et al., 2013).

Table 3. Participant characteristics by recruitment group

Variable	A. Ex-clients (n=44)	B. Sisters (n=31)	C. Healthy women (n=24)	Statistics
Age at scan, M (SD)	24.9 (1.98)	24.28 (4.49)	22.95 (3.43)	F(2,96)=2.73, p=0.071
% Left-handed	4.5%	6.5%	0%	Fisher exact p=0.55
Verbal IQ, M (SD)	8.35 (2.34)	9.55 (2.53)	9.46 (1.56)	F(2,95)=3.24, p=.043, A=B=C
Performance IQ, M (SD)	9.21 (2.70)	11.36 (3.16)	9.92 (1.69)	F(2,95)=5.93, p=.004, A<B
Lifetime maximum CD symptoms met, M (SD)	3.52 (3.41)	1.13 (2.47)	0.0 (0.0)	F(2,96)=15.49, p<0.001, A>(B=C)
% Alcohol dependence, current	0%	0%	0%	Not available
% Alcohol dependence, lifetime	36.4%	19.4%	0%	Fisher exact p=0.001
% Drug dependence, current	4.5%	0%	0%	Fisher exact p=0.501
% Drug dependence, lifetime	34.1%	9.7%	0%	Fisher exact p<0.001
% Major depression, current	6.8%	0%	0%	Fisher exact p=0.329
% Major depression, lifetime	68.2%	25.8%	0%	Fisher exact p<0.001
% Any anxiety disorder†, current	29.5%	6.5%	0%	Fisher exact p=0.001
% Any anxiety disorder†, lifetime	81.8%	54.8%	0%	Fisher exact p=0.001
% Physical abuse	39.5%	13.8%	0%	Fisher exact p<0.001
% Sexual abuse	59.1%	32.3%	0%	Fisher exact p<0.001
PCL:SV Interpersonal facet, M (SD)	0.98 (1.05)	0.32 (0.54)	0.13 (0.34)	F(2,96)=11.47, p<0.001, A>(B=C)
PCL:SV Affective facet, M (SD)	1.11 (1.32)	0.52 (1.09)	0.13 (0.34)	F(2,96)=7.02, p=0.001, A>C
PCL:SV Antisocial facet, M (SD)	1.46 (1.13)	1.10 (1.27)	0.5 (0.89)	F(2,96)=5.59, p=0.005, A>C
PCL:SV Lifestyle facet, M (SD)	1.61 (1.59)	0.68 (1.25)	0.13 (0.34)	F(2,96)=11.56, p<0.001, A>(B=C)
Anxiety symptoms (BAI score), M (SD)	8.28 (8.79)	5.84 (4.70)	5.13 (4.55)	F(2,96)=2.06, p=0.134
% Completed secondary education at time of scan	65.9%	71.0%	79.2%	Fisher exact p=0.516
% Full-time occupation	54.8%	85.7%	100%	Fisher exact p<0.001
% Having a child	45.5%	30.0%	13.0%	Fisher exact p=0.026
% Recent aggressive behavior	25.0%	32.3%	8.3%	Fisher exact p=0.100

† Anxiety disorders include: agoraphobia, generalized anxiety disorder, anxiety disorder not-otherwise-specified, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia, specific phobia and substance-induced anxiety disorder. Post-hoc pair-wise tests are Bonferroni-adjusted.

3.7.3 TBSS

For TBBS analyses, the standard processing pipeline was followed. This included aligning all FA images into FMRIB58 standard space using the FSL-FNIRT nonlinear registration tool, creating a mean FA images and generating an FA skeleton with the standard lower FA threshold of 0.2. All individual FA maps were then projected onto this skeleton. As is recommended, the registration, skeletonization and projection used in the FA procedure were used to calculate corresponding AD and RD skeletons for analyses.

All voxelwise TBSS statistical analyses were performed using the non-parametric *randomize* tool (Winkler et al., 2014) and general linear modeling. In brief, *randomize* performs a pre-defined number of random permutations of shuffled data to build a null-distribution to test against, making only very weak assumptions about the data, unlike parametric approaches. In all studies and all statistical contrasts, we used familywise error (FWE) correction to correct for multiple comparisons (contrast-wise) and threshold-free cluster enhancement. The later avoids arbitrary choices of cluster-extent thresholds by calculating voxelwise cluster-like local spatial support (Smith and Nichols, 2009).

3.7.4 Uncinate tractography

To reconstruct individual tractomes, preprocessed DWI data were independently tensor-fitted using the Diffusion Toolkit software and whole-brain tractography performed in native space using the interpolated streamline algorithm, an angle threshold of 34º and an FA interval of 0.2—1. Manual dissections of the left and right uncinate were then performed on blinded data by the thesis author (trained on the method) according to a strict and validated dissection protocol. This protocol entailed placing a spherical ROI in the temporal pole covering all streamlines originating in this region, and then placing second AND-gated ROI in the OFC extending into the external capsule. This method properly captured the two branches of the uncinate: one terminating in the ventro-lateral OFC, and one terminating in the anterior-medial OFC (Thiebaut de Schotten et al., 2012). Size and positions of all ROIs were manually tuned to ensure all streamlines were captured. Reconstruction artefacts such as spurious tracts were manually removed using NOT-gated ROIs. Voxelwise tract maps were saved and used to extract DTI metrics for statistical analyses.

3.8 FUNCTIONAL CONNECTIVITY ANALYSIS

3.8.1 Acquisition

Resting-state fMRI data were collected using the same GE MR750 scanner, with 90° flip-angle, 2500 ms repetition time, 30 ms echo time, and slice thickness of 3 mm. During acquisition, participants were instructed to stay awake and focus on a white crosshair presented on a black background, viewable via a mirror above their head. This approach was

chosen over eyes-closed and eyes-open (non-fixated) alternatives since it improves reliability of DMN connectivity (Patriat et al., 2013) and reduces the likelihood of participants falling asleep during acquisition (Tagliazucchi and Laufs, 2014). If the scanner software detected substantial movement during acquisition, the acquisition was re-started. For registration purposes, high-resolution (1 mm^3) fast-spoiled T1-weighted anatomical images were also acquired, 176 slices axially, with a 12° flip-angle.

3.8.2 Pre-processing

Pre-processing of resting-state data was performed using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) running on SPM12. The standard preprocessing pipeline was used, including slice timing correction, realignment (motion correction), anatomical co-registration, tissue segmentation, direct normalization into MNI space, 8 mm Gaussian smoothing, and band-pass filtering (0.008—0.09 Hz, after nuisance regression). Nuisance regressors included the six realignments parameters, and five principal components from white matter and cerebrospinal fluid signals (respectively) derived from principal component based noise correction. Volumes exceeding 0.5 mm frame-wise displacement or three standard deviations global signal intensity change were regressed out. For both inter-region connectivity and graph theory analyses, seed regions were defined according to the 90 ROI Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Pre-processed time series from these ROIs were extracted and used for further calculations.

3.8.3 Inter-region connectivity

For Study II, the standardized beta coefficients from the interhemispheric amygdala~OFC connectivity regressions were extracted and compared across groups. For Study IV, all connectivity analyses were performed using the GraphVar (version 1.02) software (Kruschwitz et al., 2015). First, 90 × 90 correlation matrices for each individual and ROI-pair were constructed and r-to-z transformed. Negative correlations were set to zero and no thresholding was applied. Regression analyses were performed covering the entire matrix, using the False Discovery Rate method to correct for multiple comparisons, and confounders treated as nuisance variables (i.e. regressed out prior to primary analyses).

3.8.4 Graph theory

Next, in Study IV, the inter-region connectivity matrices were used to compute weighted network topology. Multiple network formation thresholds of 0.2–0.5 were used and only subsequent findings robust across at least two thresholds were considered significant. As in the inter-region analysis, negative correlations were set to zero. Networks were constructed to include all nodes and was analyzed on two levels: global topology, and local topology in a

subset of k=13 × 2 (bilateral) nodes in the larger network, selected *a priori* to correspond to the nodes of the networks implicated in the IIT of psychopathy. Several measures of topology of these nodes and the global network were calculated, ranging from low-level measures such as degrees and strength, to modularity and clustering coefficient, covering different aspects of network integration and segregation.

4 SUMMARY OF RESULTS

4.1 STUDY I

Study I (Lindner et al., 2016) aimed to determine whether young adult women with a history of CD presented abnormalities of white matter integrity. Additionally, the study aimed to determine whether abnormalities were associated with CD, lifetime comorbid mental disorders, or maltreatment. Study I included three groups of participants: n=28 women with a history of CD, a clinical comparison group composed of n=15 women who had no history of CD but with similar prevalence of comorbid mental disorders (lifetime diagnoses of alcohol dependence, drug dependence, any anxiety disorder and any depression disorder) and maltreatment as the women with prior CD, and n=24 healthy women with no history of maltreatment or mental disorders. Whole-brain TBSS was performed on voxelwise AD, FA and RD maps. The first contrast revealed widespread reductions in AD, covering most major tracts, among the CD women compared to the healthy women. Statistically adjusting for each confounder removed 14-82% of the previous significant voxels, with only a fraction (8.6%) of the previous significant voxels surviving correction for each and every confounder. These surviving voxels were primarily located in the body and genu (including the forceps minor) of the corpus callosum, with additional voxels covering the cingulum, and the intersection of the left corona radiate and inferior fronto-occipital fasciculus. Next, the CD women were compared to the clinical comparison group, restricting the analyses to the conjunction mask of voxels that survived corrections in the previous stage. The CD women showed reduced FA in the body and genu of the corpus callosum (including the forceps minor).

4.2 STUDY II

Study II extended the findings from Study I by focusing specifically on the structural and functional amygdala-OFC circuitry and the impact of comorbid anxiety disorders specifically. Three groups of women were compared on structural and functional connectivity: n=23 with a history of both CD and anxiety disorders, n=30 with a history of anxiety disorders and not CD, and n=17 with neither disorder. Although there was a CD-only group among the ex-clients at the cohort baseline, almost all went on to develop an anxiety disorder during the follow-up period, such that no CD-only group was available. Results showed that the women with CD and anxiety disorders and those with anxiety disorders showed similarly reduced AD of the uncinate fasciculus compared to the women with neither disorder. The group difference survived correction for IQ, lifetime history of depression, alcohol and drug dependence, and exposure to maltreatment. Post-hoc analyses revealed that uncinate integrity was positively associated with harm avoidance traits among the women presenting only anxiety disorders, and with the interaction of poor anger control and anxiety symptoms among those with CD and anxiety disorders. The three groups did not differ on functional connectivity, but regardless of group membership, women with a current anxiety disorder showed reduced connectivity.

4.3 STUDY III

Study III (Lindner et al., 2017) examined linear associations between psychopathic traits and white matter integrity, both across the brain and in the uncinate fasciculus and cingulum specifically, testing the predictions of the Dual Network model. To achieve a wide range of psychopathy scores, n=99 women (ex-clients, sisters and healthy women) were included. We found that right uncinate AD was negatively associated with the interpersonal facet of psychopathy, while cingulum integrity was not associated with any facet. Whole-brain analyses with TBSS revealed that both affective and lifestyle facets were negatively correlated with white matter integrity adjacent to the fusiform gyrus, and the interpersonal facet correlated negatively with the integrity of the fornix. Findings survived correction for the other facet scores, and age, verbal and performance IQ.

4.4 STUDY IV

Extending the findings of Study III, Study IV investigated functional network topology abnormalities associated with psychopathic traits, testing the predictions from the Impaired Integration Theory of psychopathy. Graph theoretical measures of topology on both a local and global level, as well as the raw connectivity matrices, were examined in n=73 women (ex-clients and sisters) presenting a range of psychopathic traits. In partial support of the theory, psychopathy total and factor scores were associated with local, but not global, topology. The implicated nodes were either hubs or belonged to the DMN. Associations with the connectivity matrix were also found, primarily positive associations in limbic and paralimbic regions. These associations were independent of comorbid mental disorders, medication, and IQ.

5 DISCUSSION

The thesis aimed to further the understanding of structural and functional connectivity abnormalities characterizing young adult women who presented ASB as adolescents, and to disentangle the correlates of CD from those of comorbid mental disorders, maltreatment, and psychopathic traits. Four studies were conducted. Below is first a brief summary and discussion of the principal findings, followed by discussions on the clinical implications of the findings. A discussion of the strengths and weaknesses of the studies follows, as does a brief presentation of topics for future research.

5.1 SUMMARY AND DISCUSSION OF KEY FINDINGS

The results of this thesis provide new, valuable insights into connectivity abnormalities associated with CD, the comorbid mental disorders that are commonly present with CD, maltreatment, and psychopathic traits. The studies showed for the first time that:

1. Among young adult women, a history of adolescent CD was associated with abnormalities of white matter integrity, despite very low rates of progression to ASPD.
2. These abnormalities were similar to those previously observed among male and mixed-sex samples with ASB.
3. However, most, but not all, connectivity abnormalities initially found when comparing women with prior CD and healthy peers could be attributed to comorbid mental disorders and maltreatment.
4. Subsyndromal psychopathic traits in females were associated with unique structural and functional regional connectivity and topology abnormalities.

These key findings are discussed in turn below.

5.1.1 Adult correlates of adolescent ASB: Persistence?

Studies I and II showed that white matter structural abnormalities were present among young adult women who had presented CD, very few of whom progressed to meet ASPD criteria. There were however several indications of the persistence of ASB, including failure to complete secondary school, lack of employment, giving birth at a young age, and elevated rates of aggressive behavior. This is an important finding given that typically, only half of adolescents with CD go on to meet criteria for ASPD in adulthood (Loeber et al., 2002; Myers et al., 1998), yet most show poor adult outcomes nonetheless (Breslau et al., 2012; Odgers et al., 2008). Notably, previous neuroimaging research on adults presenting ASB have focused exclusively on the one half who persist with ASB into adulthood. This means that these past studies did not examine individuals with prior CD who failed to meet diagnostic criteria for ASB at age 18 or later.

However, without repeated neuroimaging through childhood and adolescence, it is impossible to ascertain the age at which the neural abnormalities that were observed in young adulthood had initially emerged. While this does constitute a substantial caveat of the interpretation, our findings should be interpreted within the context of the extant literature. The reduced structural integrity of the corpus callosum observed in Study I among the women with prior CD was previously reported in several samples of adolescents with ASB (Decety et al., 2015; Haney-Caron et al., 2014; Menks et al., 2016; Zhang et al., 2014b). Corpus callosum structural abnormalities are, in fact, one of the most robust neural correlates of CD. Further, the corpus callosum abnormality observed among the women with prior CD in Study I was robust to adjustment for comorbid disorders, one of which, anxiety disorders, showed substantial stability over time, as indicated by a greater prevalence at time of scan. In light of previous evidence, it may be that the corpus callosum abnormality that was identified among the women with prior CD was present at least by mid-adolescence. Regardless of when it emerged, this abnormality of the corpus callosum is associated with the ASB presented in adolescence.

Study II showed that the women with prior CD also presented reduced AD of the uncinate fasciculus compared to peers without a history of CD. As indicated by the findings of Study I, this reduced integrity was also observed among the women with a history of anxiety disorders but no CD. Uncinate integrity was inversely related to current anxiety symptoms, although this correlation was weak and primarily driven by those with prior CD and poor anger control, a proxy measure of poor emotion regulation. These findings suggest that the uncinate abnormality observed among adolescents with CD (but not uniquely so) also persists into adulthood, as may the corpus callosum abnormality. The fact that no correlation was observed between structural connectivity and corresponding functional connectivity, and that reduced functional connectivity was observed only in women presenting a current anxiety disorder, supports a hypothesis that the uncinate abnormality is primarily a remnant of disturbed neural development during adolescence that is only weakly associated with current functioning. Adolescence is a crucial period for white matter development, with both the uncinate and corpus callosum not maturing until after adolescence (Asato et al., 2010), and distinct trajectories of development in girls and boys (Schmithorst et al., 2008). Future longitudinal investigations beginning in childhood, featuring repeated neuroimaging, careful clinical characterization, and samples that include both boys and girls are required to draw more definite conclusions.

5.1.2 Female ASB: Do neural abnormalities differ from those presented by males?

It is beyond the scope of this thesis to investigate whether connectivity abnormalities associated with CD, psychopathy and comorbid mental disorders *differ* between males and females. Since there are considerable sex-differences in both structural and functional

connectivity in healthy brains, addressing this question would require investigations of (similar) males and females with ASB, and healthy males and females.

Nonetheless, cautious comparisons with the extant literature can be made given similarities of measurements and analyses, although differences in sample characteristics must be taken into account. The higher prevalence of ASB and the higher levels of psychopathic traits among males as compared to females (Berkout et al., 2011; Strand and Belfrage, 2005), and established sex differences in both the functional (Satterthwaite et al., 2015) and structural connectome (Ingalhalikar et al., 2014), and specifically in fronto-temporal regions of interest in studies of ASB (Gur et al., 2002), support the hypothesis that some, not all, of the neural correlates of ASB differ among males and females. Contrary to our hypothesis, the neural correlates of prior CD and psychopathic traits that we observed among females were similar to those previously reported in male and mixed-sex samples of men presenting ASB. Importantly though, a lack of consistency in the extant literature, differences in sample characteristics other than sex, and failure to account for these in past studies, means that caution is warranted in comparing findings.

Our finding that corpus callosum integrity, particularly the anterior parts constituting the forceps minor, was reduced in women with a history of CD concurs with past findings in male offenders (Sundram et al., 2012), female adolescents with CD (Menks et al., 2016) and a mixed-sex sample of adolescents with CD (Haney-Caron et al., 2014); and concurs with inverse direction (increased integrity) with findings in male adolescents with CD (Zhang et al., 2014b) and mixed-sex adolescents with CD (Decety et al., 2015). Our finding that uncinate integrity correlated negatively with interpersonal psychopathic traits concurs with findings in adult male offenders, both on an exact facet-level (Wolf et al., 2015) and at the less specific factor-level (Hoppenbrouwers et al., 2013). It also concurs on a factor-level with findings in mixed-sex (Breeden et al., 2015) and among male adolescents (Sarkar et al., 2013), and in the opposite direction (positive correlation), on a facet-level with findings in a sample of adolescents 86% of whom were male (Pape et al., 2015). Our finding that uncinate integrity was reduced in women with a history of CD is consistent with one past study featuring an all-female adolescent sample (Menks et al., 2016) and inconsistent with one past study reporting a uncinate abnormality in boys with CD, but not girls with CD, compared to sex-matched peers (Zhang et al., 2014a). Our finding is consistent with findings in mixed-sex CD samples (Haney-Caron et al., 2014), and in the opposite direction, in males (Passamonti et al., 2012). Due to a lack of a CD-only group in Study II however, we cannot exclude the possibility that the uncinate abnormality was driven by comorbid anxiety disorders, despite the post-hoc analyses suggesting otherwise. Likewise, the previous null finding in women (Zhang et al., 2014a) featured an unrepresentative CD sample without any comorbid mental disorders.

The difference in the direction of the structural abnormalities of the uncinate and corpus callosum abnormalities often observed in adolescents (increased FA and AD) and those observed among adults (decreased FA and AD) is consistent with the finding that the

uncinate and corpus callosum are not fully developed until early adulthood (Asato et al., 2010) and that ASB is a disorder of neural development. Consequently, the differences in the mean age and age spans of the adolescents included in the relevant studies (ranging from M=10 to M=18) likely affect the results (Waller et al., 2017). Again, without longitudinal investigations that include repeated neuroimaging featuring also typically developing adolescents, this neurodevelopmental hypothesis is speculative, but indirectly well-supported.

Considering the findings from Studies I, II, and III in light of the extant literature, suggests that white matter abnormalities may be specific to the presentation of ASB, which differs by sex, rather than sex itself. The corpus callosum is a pivotal structure constituting the primary enabler of inter-hemispheric communication, thereby enabling higher-order mental processes that are reliant on the integration of lateralized functions, such as aspects of social cognition (Symington et al., 2010). Congruently, impairments in social cognition characterize children with CD (Oliver et al., 2011). The associated impaired inter-hemispheric connectivity may drive a different presentation of ASB than that which is driven by threat-hyperreactivity and anger, promoting physical aggression and associated with amygdala hyperactivity and reduced PFC down-regulation (Dotterer et al., 2017; Hyde et al., 2014; Lozier et al., 2014; Viding et al., 2012b). According to this hypothesis, almost all adolescents and adults presenting ASB will present corpus callosum abnormalities, since all subtypes of CD based on onset and trajectory pattern show reduced social cognition (Oliver et al., 2011). Yet only those who additionally show severe anger-driven aggression would present uncinate abnormalities. If this reasoning is correct, it would explain why uncinate abnormalities are more prominent in samples with a higher proportion of males, since women in general present less physical aggression then men (Card et al., 2008). If however, the females in any given sample present severe CD symptoms, or multiple comorbid disorders, the same uncinate abnormality may be present in these females as observed in males.

It should be noted however that uncinate integrity appears to be unrelated to trait anger and aggressive behavior in healthy males (Beyer et al., 2014). Further, abnormalities of this tract do not appear to characterize individuals with intermittent explosive disorder (Lee et al., 2016), a disorder characterized by explosive, brief outbursts of anger and impulsive aggression but not broader and persistent ASB. Thus, uncinate abnormalities may only characterize those with more general emotion regulation difficulties, manifesting for example as comorbid anxiety. This interpretation is in line with the post-hoc findings of Study II showing that there was a negative correlation between state anxiety and uncinate integrity only in the women who also presented poor anger control. Additional seemingly contradictory evidence comes from Study III and the finding that uncinate integrity was associated with PCL-R facet 1 indexing interpersonal psychopathic traits, and not with facet 4 indexing ASB. The most parsimonious interpretation is that the uncinate serves several functions based on common lower-level attributes (such as integration of affective and cognitive processing). Emotion regulation is typically seen as a top-down mechanism (the OFC down-regulating amygdala activity), while affective reinforcement learning, that also relies on the amygdala-OFC circuit (Blair, 2008), is a bottom-up mechanism (the amygdala

relaying affective information to update contingencies and outcome expectancies in the OFC, and the ventromedial PFC in particular). Impairments in either top-down or bottom-up communication may result, at least in part, from reduced uncinate integrity. Until future research featuring careful neuropsychological characterization is conducted, this account remains speculative.

The scarcity of previous research investigating functional network topological properties associated with psychopathic traits, and differences in analysis techniques, makes it hard to draw conclusions as to whether these associations differ between males and females. The Impaired Integration Theory was based on findings from adult male offenders with very high levels of psychopathic traits. Our findings were however broadly consistent with this theory (Hamilton et al., 2015), that suggests that psychopathy is associated with preserved global topology, but abnormal topology characteristics in specific nodes, particularly in hubs. See section 5.1.4 below for further discussion on the applicability of the IIT in our sample.

5.1.3 The importance of assessing and taking account of comorbid mental disorders

As every clinician knows, in mental health settings, comorbidity is the norm and not the exception. This is especially the case with CD and ASPD. This thesis studied a clinical sample of females with high rates of comorbid SUDs, affective and anxiety disorders, and childhood maltreatment were similar to those reported in other clinical samples (Armstrong and Costello, 2002; Spatz Widom et al., 2006). Psychopathic trait scores were elevated compared to general population estimates, but lower than in forensic samples (Hart et al., 1995). Considering that psychopathic traits, maltreatment and the comorbid mental disorders have all been independently associated with matter integrity abnormalities, and resting-state connectivity, there is an obvious need to take these factors into account.

A confounder is defined as parameter that is associated both with the predictor (e.g. CD) and outcome (e.g. white matter integrity) that unadjusted for, may lead to erroneous conclusions about the associations between the predictor and outcome, when the association is actually driven partially or fully by the confounder. In this thesis, three approaches were taken to handle confounders. These approaches are borrowed from epidemiological research, an area, like our own, where randomization can seldom be used to truly control for confounders. These three approaches are:

1. *Restriction*: In this thesis, only women were studied, in order to exclude any confounding effect of sex, as suggested by several studies showing main effects of sex, and sex × ASB interaction effects in antisocial samples (Decety et al., 2015; Fairchild et al., 2013; Zhang et al., 2014a)
2. *Statistical adjustment:* Using multiple regression techniques, the independent impact of any predictor on the outcome can be modeled while holding the other predictors constant.

3. *Matching:* By creating groups that are matched on all parameters except those of interest, the confounding effect is weakened.

These methods have distinct advantages and disadvantages (Rothman, 2012). In Study I, which like all studies was restricted to female participants, a stepwise procedure was used to control for the confounding effects of lifetime comorbid mental disorders and maltreatment: first, unadjusted analyses were run. Second, the group contrast was re-run confined to the brain regions showing significant group differences between CD and healthy women in the first stage, yet this time statistically adjusting for the confounders. Third, confining the analysis to the surviving brain regions, CD women were compared to a clinical comparison group matched on the confounders. This stepwise procedure revealed that of the widespread reductions in AD observed in comparisons of the women with prior CD and healthy women (covering 13 469 voxels), only a small fraction (68 voxels) survived both the statistical adjustment and matching procedures. A volumetric study performed on an overlapping sample showed similar results: none of the increases and decreases of gray matter volume initially shown to characterize young adult women with a history of CD compared to healthy peers, survived correction for internalizing and externalizing disorders and maltreatment (Budhiraja et al., 2017). Study II also featured a clinical comparison group, matched on all but the variable of interest (CD). Statistical adjustment was also used. Using this procedure, we showed that the uncinate abnormality previously believed to be specific to CD, was also associated with anxiety disorders, or even with subclinical anxiety symptoms. Together, these findings emphasize the importance of measuring possible confounders and taking them into account when studying neural correlates in clinical samples.

Our findings also pose the question of whether past findings on neural correlates of ASB are really related to ASB, or some confounder. Importantly, even studies that have explicitly excluded participants with comorbid mental disorders may have included participants with subclinical depression and anxiety symptoms that have been associated with uncinate integrity (Baur et al., 2012; Hayakawa et al., 2012; Modi et al., 2013), for example. Importantly, almost no imaging study of CD or ASB has even measured childhood maltreatment, despite knowledge that maltreatment is more common in youth and adults with ASB, and despite reports of robust structural and functional abnormalities associated with maltreatment (Lim et al., 2014; McCrory et al., 2011), even in samples presenting no adult mental disorders (Paul et al., 2008), and samples presenting only verbal but no physical parental abuse (Choi et al., 2009). Interestingly, structural abnormalities of the corpus callosum is one of the most well-replicated neural correlates of childhood maltreatment, with some evidence of sex differences (McCrory et al., 2010). These abnormalities are primarily located in the midline and posterior sections, unlike the anterior sections found to be independently associated with CD in Study I.

Special considerations likely apply to the confounding effects of alcohol use. Adolescents with CD begin consuming alcohol at an earlier age and drink more and more frequently into adulthood (Kim-Cohen et al., 2003; Kuperman et al., 2001; Roberts et al., 2007; Sartor et al.,

2007). There is now strong evidence from longitudinal studies that alcohol and other substance use affects white matter integrity (Bava et al., 2013; Jacobus et al., 2013; Luciana et al., 2013). Hence, cross-sectional measures of heavy alcohol use, e.g. a DSM-IV diagnosis of alcohol dependence (used in this thesis) or standardized self-reports of recent consumption (Bush et al., 1998), may not adequately capture the full impact of the accumulated hazardous alcohol consumption over time. Instead, longitudinal consumption data from onset, preferably prospective but rather suboptimal retrospective reports than none, along with latent growth modeling techniques that can estimate individual trajectories of consumption and corresponding area under the curve (i.e. accumulated consumption), would arguably provide a better measure of the confounding effect of substance use, assuming linear neurotoxic effect of a hazardous alcohol consumption.

5.1.4 Neural correlates of subsyndromal psychopathic traits

Psychopathic traits in adolescence predict adverse adult outcome over and above CD symptoms (Hemphälä and Hodgins, 2014) and are associated with worst treatment outcomes (Hawes and Dadds, 2005), emphasizing the need to assesses these traits in children and adolescents presenting ASB. Although historically designed as a categorical construct, psychopathic traits are increasingly recognized as dimensional in nature (Edens et al., 2006; Guay et al., 2007; Murrie et al., 2007). Earlier studies often categorized offenders into subgroups according to whether they scored below or above the PCL-R total score cutoff (Harenski et al., 2010; Kiehl et al., 2001; Ly et al., 2012; Motzkin et al., 2011), yet with increasing recognition that it is scores on the interpersonal-affective factor that distinguishes a subgroup with a different clinical (Viding et al., 2012a) and neural presentation (Dotterer et al., 2017; Hyde et al., 2014; Lozier et al., 2014; Viding et al., 2012b), attention has shifted towards instead distinguishing subgroups based on this factor, as done in recent intervention (Baskin-Sommers et al., 2015) and neuroimaging studies.

To what degree past neuroimaging findings in male offenders with high total scores would agree with findings in community females with subsyndromal trait levels, was uncertain. Few neuroimaging studies have investigated neural correlates of subsyndromal traits in non-forensic samples. Overall, these studies have shown that the correlates of specific traits (facets) are indeed similar across severity levels. This includes the distinct amygdala hyper-hypo association with interpersonal-affective versus behavior traits (Carré et al., 2013; Hyde et al., 2014), insula functional abnormalities during anticipated guilt (Seara-Cardoso et al., 2016), structural abnormalities of the amygdala, OFC and striatum (Vieira et al., 2014) and uncinate fasciculus integrity (Sobhani et al., 2015), congruent with findings in offenders (Craig et al., 2009; Glenn et al., 2010; Glenn and Yang, 2012; Kiehl et al., 2001; Yang and Raine, 2009).

Our findings too, are similar to those reported in youths and adults with ASB and high psychopathy scores. In Study III, we found psychopathic traits to be associated the fornix, the

uncinate fasciculus and fusiform gyrus white matter. The fornix primarily serves to connect the hippocampus with the rest of the brain. Structural hippocampal abnormalities have been found in offenders with high psychopathy scores (Boccardi et al., 2010; Laakso et al., 2001; Raine et al., 2004) and may reflect either the reinforcement learning deficit observed among youths and adults with ASB and interpersonal-affective traits (Budhani et al., 2006; Budhani and Blair, 2005), and/or possibly DMN abnormalities frequently reported in samples with ASB, albeit never specifically located to the hippocampus (Broulidakis et al., 2016; Cohn et al., 2015; Dalwani et al., 2014; Juárez et al., 2013; Philippi et al., 2015; Pujol et al., 2012; Thijssen and Kiehl, 2017; Zhou et al., 2015).

As discussed above, the association between uncinate integrity and interpersonal psychopathic traits found in Study III was the same as the association found in adult male offenders (Wolf et al., 2015) and other studies implicating the uncinate specifically in the presentation of interpersonal-affective, rather than behavioral psychopathic traits. Our finding that fusiform white matter integrity correlated with both affective and lifestyle traits is consistent with robust structural (Aoki et al., 2014) and functional (Alegria et al., 2016) meta-analytic findings in youths and adults with ASB, although the association with specific psychopathy factors was not investigated in those meta-analyses.

Strikingly, the whole-brain analysis conducted in Study III did not reveal any association between the behavioral facet scores of the PCL and corpus callosum integrity. Since CD symptoms overlap with the items covered by these two facets (particularly facet four, Antisocial), finding both CD and behavioral facet scores to be associated with the same neural abnormality would be harmonious. The fact that distinct correlates of CD and behavioral psychopathic traits were found, likely stems from clinical heterogeneity allowed by the CD construct. At the extreme end, CD criteria can be met by an adolescent (<13 years old) that is frequently truant from school and often stays out at night and runs away from home without parental approval, assuming such behaviors causes a clinically significant impairment. This adolescent would, despite meeting CD criteria, score low on the Lifestyle and Antisocial PCL facets, that index more severe ASB. Since the women in our sample presented low facet scores and low rates progression from CD to ASPD, unique correlates of a CD diagnosis and PCL facet scores respectively are not unexpected.

The explicit goal of Study IV was to test the applicability of the Impaired Integration Theory (IIT) of psychopathy, built mostly on findings in male offenders (Hamilton et al., 2015). This theory unifies cognitive and affective perspectives of psychopathy and relates neuropsychological impairments and behaviors to specific topology abnormalities. The IIT predicts that psychopathic individuals (i.e. scoring high on both factors) will present low between-network integration and stronger within-network connections, resulting in increased modularity and decreased efficiency. In its current form, the IIT assumes a categorical psychopathy construct. To what degree the predicted topology abnormalities are linearly associated with subsyndromal psychopathic traits, or even to what degree the IIT is

applicable to females given the sex difference in presentation (Strand and Belfrage, 2005), was unknown.

The results of Study IV are complex, yet are largely congruent with the predictions of the IIT. Importantly, neither psychopathy total or factor scores were associated with global topology abnormalities. The IIT is ambiguous in whether global topology abnormalities are to be expected, stating both that the topology is likely to be different but preserved, and that the topology is characterized by increased modularity and decreased efficiency. Whether the latter is at network (global) or subnetwork level remains unspecified. Study IV did find regional topology abnormalities, particular in DMN and hub structures, as predicted by the IIT. These were both in the direction predicted by the IIT – such as decrease edge strength of the left inferior parietal lobule – and in the opposite direction – such as the increased betweenness centrality of the right inferior parietal lobule. The latter may reflect a compensatory mechanism to accommodate other topology abnormalities, yet without longitudinal neuroimaging, this interpretation remains speculative. To our knowledge, Study IV is the first study to explore functional topology abnormalities within an IIT framework. Regardless of how well our findings in females with subsyndromal psychopathic traits concur with the predictions of the IIT, we demonstrate that subsyndromal traits do have regional, but not global topology correlates.

In sum, this thesis shows for the first time that even subsyndromal psychopathic traits are associated with brain connectivity abnormalities in females – abnormalities that largely mirror those found in samples with more severe ASB. These findings add to the growing body of evidence showing that these traits need to be considered in both research and clinical settings.

5.2 CLINICAL IMPLICATIONS

The results of this thesis have several clinical implications. First, neural abnormalities were observed among women who had presented CD as adolescents, the great majority of whom did not present ASPD, but who did present several indices of ASB (educational attrition, unemployment, aggression), emphasizing the importance of providing effective, evidence-based treatment during adolescence. A previous study on the cohort from which the sample for the imaging studies was drawn showed that treatment-as-usual failed to prevent the persistence of SUDs into adulthood (Hodgins et al., 2014). This study, however, did not investigate the persistence of ASB. CD is however a strong predictor of adult SUDs (Kim-Cohen et al., 2003), suggesting that treatment-as-usual was equally unsuccessful in preventing the persistence of ASB and related impairments in adult psychosocial adjustment, although may have been successful in preventing the progression to ASPD. This remains unexplored, however. Recently, there have been several trials of behavioral parent training programs in a Swedish context, revealing good efficacy in reducing conduct problems in both self-referred community samples (Kling et al., 2010) and in clinical samples (Axberg and

Broberg, 2012), as well as when delivered over the internet (Enebrink et al., 2012). Whether Swedish implementations of these programs are effective in reducing persisting ASB and associated comorbid mental disorders over longer periods of time, remains unexplored. The wide range of serious, adverse, adult outcomes reported in this thesis and in past studies on adolescents from the same clinic (Hodgins et al., 2009b) emphasize the need to provide effective treatment as early as possible. Given the high rates of mental health comorbidity and exposure to maltreatment typically presented by adolescents with CD, treatment efforts should ideally address the full clinical picture.

Another clinical implication of this thesis pertains to psychopathic traits. Until recently, it was widely considered controversial to claim that children presented CU traits from an early age (Dadds et al., 2005). Since then, accumulating evidence has shown that these traits are highly heritable, onset early and are life-course persistent, and associated with ASB even at less severe levels. (Viding et al., 2012a). This resulted in the novel DSM-5 specifier of limited prosocial emotions (opposite-worded as to avoid stigmatizing). This thesis adds to the growing body of evidence emphasizing the need to carefully assess youth with ASB for psychopathic traits, by showing that in females, even at a subsyndromal level, these traits have specific neural correlates that are different from those uniquely associated with CD, and that correlates differ between different facets and different factors of psychopathy. Importantly though, in both Study III and IV, we investigated and found linear associations, not categorical. This is consistent with taxometric analyses showing that both psychopathic traits (Guay et al., 2007; Murrie et al., 2007) and the associated neural abnormalities (Walters et al., 2015) are dimensional, rather than categorical, in nature. Whether there is clinical utility in having categorical diagnostic constructs, and whether pros outweighs cons over having purely dimensional ones, are long-standing, controversial and unresolved topics in psychiatry (Widiger and Samuel, 2005), not addressed in this thesis.

This thesis also provides some indirect evidence for novel therapeutic strategies to reduce CD and psychopathic traits. The results of Study II support the hypothesis that anxiety disorders and CD share a common substrate of threat hyperreactivity, manifesting as the same uncinate abnormality, and that this is distinct from the responses that distinguish the two disorders (avoidance in anxiety; avoidance and approach in CD). Cognitive behavior therapy for anxiety disorders, which is highly effective in both adults and children (Hofmann and Smits, 2008; James et al., 2015), targets both the behavioral avoidance and the threat perception (Craske et al., 2014). Parent training programs, however, typically only involve contingency management aimed at reinforcing desired behaviors and ceasing to reinforce undesired behaviors (Forehand et al., 2013), with little attention paid to the underlying cognitive biases and conditioned responses that likely promote frustration and anger. Whether treatment efficacy for CD can be improved by incorporating such aspects remains to be evaluated. Indirect support for the common substrate hypothesis of CD and anxiety disorders comes from studies showing that children with both anxiety and conduct problems show the same improvement from anxiety treatment as children with only anxiety (Kendall et al., 2001; Rapee, 2003), and from one innovative study showing that an anxiety treatment program was

as effective in treating both anxiety and aggressive behavior as a treatment program covering both (Levy et al., 2007).

Study IV tested the applicability of the Impaired Integration Theory (IIT) (Hamilton et al., 2015) of psychopathy to females with subsyndromal traits. Results were largely in line with the specific predictions of the IIT concerning global versus regional abnormalities and hubs showing abnormalities consistent with reduced integration between networks. The IIT raises the possibility that psychopathic traits, which in the past have been considered treatment-resistant in adulthood (Salekin et al., 2010), may be modifiable by therapies specifically designed to promote information integration, e.g. cognitive training. As would be expected, such treatments have been shown to promote changes in brain connectivity (Román et al., 2017). One recent proof-of-concept supports the hypothesis that cognitive remediation therapy tailored to the presumed underlying cognitive-affective impairment, leads to improvements (Baskin-Sommers et al., 2015). Using the two factors of the PCL-R, offenders scoring high on factor 2 of the PCL-R were categorized as either psychopathic or externalizing based on a median-split of factor 1 scores. Psychopathic offenders were hypothesized to benefit from only cognitive training aimed at improving attention to context, while externalizing offenders were hypothesized to benefit from only cognitive training aimed at affective cognitive control. Each group was then split and randomized to one treatment, either the appropriate or inappropriate based on their grouping. Results revealed that as hypothesized, the psychopathic group benefitted only from attention-to-context training and the externalizing group benefitted only from affective cognitive control training, with improvements in performance on cognitive tasks (Baskin-Sommers et al., 2015). However, this first proof-of-concept study did not assess changes in interpersonal-affective traits and real-life ASB, nor was neuroimaging used to assess changes in amygdala hypo- versus hyper-reactivity. Nonetheless, the results reveal the value of carefully considering subtypes of ASB and designing novel tailored interventions aimed at remedying the deficits found to characterize that respective subtype in neuropsychological and neuroimaging research.

5.3 FUTURE RESEARCH

Longitudinal studies of well-characterized cohorts have been key in furthering our understanding of the cognitive, affective and behavioral aspects of ASB and associated conditions (Fergusson and Horwood, 2001). So too have cross-sectional neuroimaging studies furthered our understanding of the neural underpinnings of ASB and psychopathic traits. However, there is a striking scarcity of longitudinal neuroimaging research in this field, despite the robust evidence of the early onset and persistence of ASB, and the consensus present in the literature that ASB is a disorder of abnormal neural developmental (Raine, 2011). At time of writing this thesis, there is only one published longitudinal neuroimaging study of individuals with CD, showing that three subgroups, defined by trajectories of conduct problems over time, differed as to the development of cortical thickness in the

dorsolateral PFC, ACC and hippocampus (Oostermeijer et al., 2016). The studies included in this thesis featured longitudinal clinical data but cross-sectional neuroimaging data, thereby complementing past cross-sectional research and allowing novel conclusions as to the developmental nature of CD and neural outcomes in young adulthood. Such studies, however, are a poor substitute for longitudinal, prospective investigations that include neuroimaging at different ages. The primary advantage of such a design would be to document the onset and development of neural abnormalities and their association with the onset and development of clinical symptoms. This will be important in order to design novel therapies that target disorder mechanisms.

Longitudinal neuroimaging data will also be required to show whether successful treatment of CD normalizes neural abnormalities present before treatment. In social anxiety disorder, emerging evidence suggests that cognitive behavioral therapy normalizes amygdala volume and reactivity (Månsson et al., 2016) and increases uncinate structural integrity (Steiger et al., 2016). Whether something similar would be observed after successful treatment of CD with behavioral parent training (Fagan and Benedini, 2016; Michelson et al., 2013; Serketich and Dumas, 1996), remains unknown.

Future cohort studies should ideally recruit participants of a much younger age than has been done in the past. Although the mean age of CD onset is 12 years (Afifi et al., 2011), there is now robust evidence that childhood aggression can be predicted as early as in 6 months old infants (Hay et al., 2014; Wagner et al., 2016), and that when reaching toddlerhood, trajectories into adolescence can be accurately distinguished (Fanti and Kimonis, 2017). For research purposes, when the aim is to disentangle the causal impact of one factor (e.g. maltreatment) on subsequent ASB, longitudinal assessments should ideally start prior to onset of serious ASB, given that parental practices and conduct problems in children show a bidirectional impact (Lansford et al., 2011; Pardini et al., 2008; Serbin et al., 2015; Shaffer et al., 2013), as do engagement in social deviant contexts, e.g. socializing with delinquent peers (Miller et al., 2009). Recent research has also shown that the neurocognitive impairments observed in children after exposure to maltreatment can largely be explained by pre-exposure impairments (Danese et al., 2016). By not longitudinally assessing the important characteristics before and from actual onset, cohort studies risk confusing causality. From a clinical perspective, engaging children in treatment at an earlier age may also increase the efficacy and be preventive (Petitclerc and Tremblay, 2009), even in the case of heritable CU traits (Hyde et al., 2016).

Finally, there is a need for more research on antisocial females (Berkout et al., 2011). The increased prevalence of CD and ASB in males, at least in the moderate severity range (Tiet et al., 2001), along with the preference in the field of neuroimaging for non-complex cases with little comorbidity, has resulted in an underrepresentation of females in neuroimaging samples, even when considering the prevalence gender ratio of 4:1 (see e.g. Table 1 in the Background section). The established sex differences in symptom presentation (Card et al., 2008) and onset- and trajectory-patterns (Fontaine et al., 2009), the female-specific outcomes of early

pregnancy and intergenerational transfer of ASB through non-optimal parenting practices (Jaffee, 2002; Jaffee et al., 2006), as well as the initial evidence for sex differences in the neural correlates (Decety et al., 2015; Fairchild et al., 2013; Rogers and Brito, 2015; Zhang et al., 2014a), all emphasize the need for more studies on females with ASB to further our understanding of psychological and neural mechanisms driving ASB in females, in order to create better diagnostic instruments that capture the characteristics with high clinical utility, and to create a new generation of more effective therapies that prevent the onset and persistence of ASB.

5.4 THESIS STRENGTHS AND LIMITATIONS

The limitations and strengths of each thesis study are discussed in the respective study. Overall strengths of this thesis include a large, all-female sample, well-characterized in terms of clinical presentation over time. Diagnoses and psychopathic traits were assessed using gold standard, clinician-rated instruments – the former at multiple occasions. As discussed above, the lack of longitudinal neuroimaging means that *persistence* of neural abnormalities can only be inferred, not investigated. The same with abnormalities of neural development trajectories.

Although longitudinal clinical data was available, data collection began in mid-adolescence, when the ex-clients came in contact with the clinic, *after* the onset of multiple clinical symptoms (ASB, SUDs and more) and exposure to maltreatment. This means that the data is ill-suited by design for studying the causal effect of one problem domain on another, or even the sequence of disorder onsets. Nonetheless, the advantage of having longitudinal clinical data was made apparent in Study II, where we could show that although there were n=17 females with CD but no anxiety disorder at cohort baseline (Hodgins et al., 2011), n=11 went on to develop an anxiety disorder by the latest follow-up.

Another limitation pertains to the lack of neuropsychological data on the thesis sample. The neuroimaging findings presented in this thesis suggest that our sample show impaired social cognition, emotion regulation, threat perception, and/or reversal learning, and that these impairments are associated with the connectivity abnormalities found. Since no measures of these domains were collected, the assumed mediating role of these impairments in explaining the association between ASB and connectivity abnormalities remains speculative.

Finally, there is no ideal strategy to disentangle neural associations of inter-related conditions (De Brito et al., 2009). Regression models featuring inter-related, non-randomly assigned independent variables risk multicollinearity. Group matching may introduce new, unobserved confounding. For these reasons, in this thesis, we used a combination of statistical adjustment and group matching to disentangle connectivity abnormalities associated with adolescent CD, comorbid mental disorders, maltreatment and psychopathic traits.

6 CONCLUSIONS

The results of this thesis show that adolescent conduct disorder is associated with both structural and functional brain connectivity abnormalities in young adulthood in women, despite low rates of ASB persistence severe enough to warrant a diagnosis of antisocial personality disorder. Most of the brain-wide abnormalities of white matter integrity (structural connectivity) in women with a history of CD compared to healthy women could be explained by lifetime histories of comorbid mental disorders and exposure to maltreatment, common to clinical cases of CD. Abnormalities of the anterior corpus callosum (including the forceps minor) were found to be specific to a history of CD. Women with a history of CD, all of whom also had a history of anxiety disorders, also presented lower white matter integrity of the uncinate fasciculus tract connecting the amygdala and orbitofrontal cortex. The same uncinate integrity reductions was however also found in women with a history of only anxiety disorders. Trait correlates of the same uncinate integrity reduction did however differ between the two groups.

Subsyndromal psychopathic traits in young adult women were found to have unique associations with structural and functional connectivity. Interpersonal traits were negatively associated with uncinate fasciculus and fornix integrity, and both affective and lifestyle traits were negatively associated with white matter integrity adjacent to the fusiform gyrus. Psychopathic traits were not associated with global resting-state functional topology, but trait scores were found to correlate with topology indices in hub structures and nodes belonging to the Default Mode Network.

These findings were largely consistent with previously reported findings in all-male or mixed-sex samples of antisocial adolescents and adults. Our findings emphasize the need to measure and take into account comorbid mental disorders, exposure to maltreatment, and psychopathic traits when studying clinical samples characterized by antisocial behavior. Finally, our findings show the importance of providing effective, evidence-based treatment of antisocial behavior and comorbid mental disorders in adolescence, in order to prevent the persistence of antisocial behavior, mental disorder, psychosocial maladjustment, and associated neural abnormalities.

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