Investigating Structural and Functional Neural Correlates in Children and Adolescents with Antisocial Behavior.

Inauguraldissertation
zur
Erlangung der Würde
eines Doktors der Philosophie
vorgelegt der
Fakultät für Psychologie
der Universität Basel

von

Willeke Martine Menks

aus Bellingwolde, the Netherlands

Basel, 2017

Genehmigt von der Fakultät für Psychologie

auf Antrag von

Prof. Dr. Dr. Christina Stadler
Prof. Dr. Dominique de Quervain

Basel, den 07-06-2017

_____

Prof. Dr. Roselind Lieb

UNI
BASEL

Voor Barbera Winkelman

"It is easier to build strong children than to repair broken men."

attributed to Frederick Douglass (1855)

Contents

Abstract

Antisocial behavior is highly prevalent in young and adult populations worldwide and constitutes a major public health problem due to the huge burden on the individual as well as the significant economic burden on society. A better understanding of the underlying neurobiological mechanisms of antisocial behavior is warranted to improve current diagnostics (e.g. early detection of children at risk) and effective prevention/treatment programs. So far, neuroimaging studies have indicated neural atypicalities in youths with antisocial behavior; however, the direction and location of these brain alterations vary across studies. These ambiguities are most likely caused by the heterogeneity of the young samples with antisocial behavior studied, especially regarding sex, clinical diagnoses, and the presence of callous-unemotional traits.

The central aim of this dissertation was to further the neuroscientific knowledge of antisocial behavior in children and adolescents by investigating the underlying structural and functional neurobiological characteristics, with an extra focus on possible sex differences and callous-unemotional traits. First, we examined the current neuroimaging literature, through meta-analyses, with the purpose of overcoming the heterogeneity of antisocial behavior and generating a common "overlapping" pattern of structural and functional atypicalities in youths with antisocial behavior. Secondly, the relation between callous-unemotional traits and brain structure was investigated separately for sex and independently of psychiatric comorbidities. Thirdly, this work investigated the white matter integrity within a homogenous group of girls with conduct disorder –the severe variant of antisocial behavior– in comparison to typically developing peers.

This work expands our current knowledge on the structural and functional neural correlates in children and adolescents with antisocial behavior in several ways. For one, our meta-analytic results indicate a consistent pattern of gray matter reductions and hypoactivations in brain areas within the prefrontal and limbic cortex. These findings fit a recently proposed neurobiological model that connects alterations within similar brain regions with the behavioral dispositions of antisocial behavior (e.g. dysfunctions in empathy, emotional learning, and decision making). Secondly, we observed a positive relation between callous-unemotional traits and bilateral insula volume in a large international population of typically developing boys, but not in girls, independent of psychiatric disorders. This demonstrates that callous-unemotional traits have a sex-specific neurobiological basis beyond psychiatric samples. Thirdly, this work presents novel findings of white-matter integrity alterations in the body of the corpus callosum of girls with antisocial behavior, indicating possible reduced interhemispheric processing and consequent emotion processing abilities. In short, the present thesis provides original findings regarding the neurobiology of antisocial behavior in youths and emphasizes the importance of callous-unemotional traits and sex differences. Our results encourage future studies to further investigate the developmental trajectories and potential neural markers of antisocial behavior in order to enhance early detection and improve intervention programs, which could ultimately reduce antisocial behavior and delinquency in our society.

Chapter 1. General Introduction

1.1. Antisocial behavior in children and adolescents

Antisocial behavior is one of the most common psychiatric problems in young and adult populations worldwide and causes a huge burden for the individual and the society as a whole. Examples of antisocial behaviors are theft, bullying, truancy, physical cruelty to animals and people, sexual aggression, and destruction of property. Antisocial behavior can commence at an early age in childhood. Young children are especially prone to develop poor social functioning skills and this in turn often leads to social exclusion affecting social relationships and family life, which continues throughout adulthood. Besides social difficulties, antisocial behavior also negatively impacts other aspects of the individual's life, such as an academic and occupational career. Not only does antisocial behavior cause personal distress for the child, it also affects the families, the communities, and the society as a whole. For example, children with antisocial behavior increase the societal expenses with a tenfold by using the resources of child mental health and juvenile justice organizations (Bardone et al., 1998; Pedersen & Mastekaasa, 2011; Scott et al., 2001). Also, children with antisocial behavior have a higher risk to develop an antisocial personality disorder during adulthood which extensively increases their burden throughout life (Storm-Mathisen & Vaglum, 1994). So far, a few studies have shown that family and parenting interventions have beneficial effects for the juvenile delinquents such as reducing institutionalization and criminal activity (Woolfenden, Williams, & Peat, 2002). Nevertheless, the general treatment success rates are limited and remain modest. Comprehensive treatment could potentially reduce the antisocial behavior by 12-25% but appears unable to normalize the behavior completely. A better understanding of the underlying neurobiological mechanism of antisocial behavior could explain this modest treatment's efficacy and assist the development of innovative interventions. Improving the existing treatments or developing new methods is necessary to prevent and reduce antisocial behavior and delinquency in our society.

Antisocial behavior in children and adolescents can be subdivided into several clinical diagnoses depending on the behavioral symptoms and severity as is described in the diagnostic and statistical manual of mental disorders (DSM-5; (APA, 2013)). Till the age of 18, youths with antisocial behavior symptoms generally receive a disruptive behavior disorder (DBD) diagnosis, an umbrella term for two sub-diagnoses: oppositional defiant disorder and conduct disorder. Oppositional defiant disorder (ODD) is the less severe form of DBD and usually identified in early childhood. Typical symptoms that belong to ODD are angry and irritable mood, defiant and noncompliant behavior, or vindictiveness. Children and adolescents with ODD easily lose their temper, deliberately annoy others, or refuse to comply with rules or authority; this behavior can cause substantial impairment in the child's educational and social functioning. Twenty-five percent of children with an ODD diagnosis will ultimately also develop conduct disorder (Tolan & Leventhal, 2013). In contrast to ODD, children

with conduct disorder (CD) display severer features such as aggression and violence in their behavior; for example, physical aggression to people and animals, property destruction, deceitfulness, theft, and serious violation of societal norms and rules (DSM-5 312.8;(APA, 2013)). These children frequently bully and fight with others, engage in shoplifting or mugging, or vandalize property. The estimated life time prevalence of conduct disorder corresponds to 7% in girls and 12% in boys (Nock et al., 2006). Not only is conduct disorder a more severe variant of antisocial behavior in youths, it is also the most stable variant functioning as a key precursor for an antisocial personality disorder (ASPD) in adulthood (Lahey et al., 2005). Another indicator for the severity of the antisocial behavior is the presence of psychopathic traits such as lack of remorse, pathological lying, and callousness (Frick & White, 2008).

1.2. Behavioral dispositions and risk factors in antisocial behavior

In the last few decades, researchers intensively investigated the behavioral dispositions and etiology of antisocial behavior. Impulsivity, fearlessness and lack of empathy are the most commonly observed behavioral dispositions underlying antisocial behavior (Cloninger & Svrakic, 1997; Eysenck, Milton, & Simonsen, 1998; Lahey, Waldman, & McBurnett, 1999; Quay, 1993). Based on these behavioral abnormalities several theoretical neuropsychological explanations emerged. An oversensitive (i.e. hyperactive) behavioral activation system may explain impulsivity (Gray & McNaughton, 1982), and an abnormal cognitive control and emotion regulation system could lead to dysfunctional inhibition of behavior. Insensitivity to punishment, poor decision making, and hyperresponsiveness to reward are all mechanism linked with fearlessness (Blair et al., 2006; Byrd, Loeber, & Pardini, 2014; Fairchild et al., 2009b; Pujara et al., 2014). Difficulties in emotion recognition or altered moral reasoning are proposed as underlying mechanisms for the lack of empathy in antisocial behavior (Blair et al., 2001; Blair & Lee, 2013). Various risk factors for developing antisocial behavior exist and are classified as biological predispositions and environmental factors. Biological predispositions are present at birth and comprise genetic, neural, endocrine, and psychophysiological factors. Early genetic studies investigating twins and adopted children estimated an important magnitude (~56%) of genetic influences on the development of antisocial behavior (Eley, Lichtenstein, & Stevenson, 1999; Ferguson, 2010; Rhee & Waldman, 2002). Several candidate genes (e.g. COMT, MAOA, and 5-HTTT genes) function as potential risk factors to develop antisocial behavior (Caspi et al., 2002; Ficks & Waldman, 2014; Retz et al., 2004; Thapar et al., 2005). These discovered genes likely interact with each other through complex regulation pathways that most probably involve numerous genes that yet have to be identified. Even though a genetic base is evident, still maltreatment exposure is equally important in the development of antisocial behavior. For example, a reduced activity of the X-chromosomal MAOA gene enhances the risk for developing antisocial behavior, however, only in combination with familial maltreatment and till a certain extend of trauma exposure (Caspi et al., 2002; Kim-Cohen et al., 2006; Nilsson et al., 2007). These findings indicate a complex interplay of

genetic and environmental factors in regards to the developmental trajectory of antisocial behavior. Due to the close interaction between genes and hormones, it is not surprising that hormonal –testosterone and cortisol– levels may function as such biological risk factors (Alink et al., 2008; van Honk et al., 2010) for review: (Hawes, Brennan, & Dadds, 2009; van Goozen et al., 2007)). Also on a psychophysiology, level robust indicators such as low heartrate and atypical heartrate variability exist for antisocial behavior in children and adolescents (Ortiz & Raine, 2004; Raine, Venables, & Mednick, 1997). In addition to these multitude of biological factors also the individual's temperament should be mentioned as an significant factor, since children with increased novelty-seeking behavior and less harm-avoidance are at risk to develop conduct disorder (Schmeck & Poustka, 2001). Besides these biological aspects the trajectory of antisocial behavior is also influenced by environmental factors such as familial and societal life experiences. Family dysfunction, harsh parenting, and emotional neglect are a few examples that could obstruct the normal development of prosocial behavioral skills in young children, such as recognition of social cues, empathy, and self-control (Lansford et al., 2003; Pardini, Lochman, & Powell, 2007; Schaffer, Clark, & Jeglic, 2009; Schwartz et al., 2000). Negative life experiences (e.g. neighborhood violence, poverty, and social peer conflicts (Vitaro, Brendgen, & Tremblay, 2000)) strongly correlate with parental socio-economic status and induce aggression-oriented behavioral schemes, e.g. strong emotional reactions and wrong cognitive interpretations (Lahey et al., 1999). In sum, a multitude of factors from womb to adulthood may initiate and/or affect the developmental trajectories of antisocial behavior in youths.

1.3. Neurobiological basis of antisocial behavior

The improvement of neuroimaging techniques, i.e. magnetic resonance imaging (MRI), in the last three decades provided neuroscientists the ability to non-invasively investigate the neural phenotype of youths with antisocial behavior. Consequently, a rapid increase in neuroimaging studies on the psychopathology of antisocial behavior laid the foundation for its possible neural correlates (Dolan & Fullam, 2009; Finger et al., 2008; Kiehl et al., 2001; Sterzer et al., 2007; Yang et al., 2009a). The amygdala is, for example, one of main brain areas that is numerously linked to antisocial behavior, this is not surprising since normal amygdala functioning is crucial for behaviors (such as emotional processing, empathy, and fear response) that are disrupted in individuals with antisocial behavior (Blair, 2003; Ledoux & Schiller, 2009). Therefore, amygdala dysfunction is recognized as one of the key characteristics in the symptomatology of antisocial disorders (Albein-Urios et al., 2013; Blair, 2003, 2008b; Jones et al., 2009; Marsh et al., 2008).

Other important brain areas that are often linked with antisocial behavior in youths are the insula, the cingulate cortex, and the prefrontal cortex. The involvement of the insula is not unexpected, since this brain structure plays an important role in emotional behavior (i.e. emotion processing, emotion recognition, and empathy) often disrupted in youths with antisocial behavior (Decety et al., 2009;

Decety, Skelly, & Kiehl, 2013; Fairchild et al., 2014; Lockwood et al., 2013; Passamonti et al., 2010; Rubia et al., 2009). The insula not only plays a role in the evaluation, experiencing, or expression of internally generated emotions, but is especially associated with disgust and anger (Lindquist et al., 2012; Phan et al., 2004; Phillips et al., 1997). Similarly, the anterior part of the cingulate cortex (ACC) is also an essential brain structure involved in emotional processing and empathy, and additionally for response inhibition (Dalwani et al., 2011; Lockwood et al., 2013; Stadler et al., 2007; Sterzer et al., 2005). Not only is the ACC part of the emotion processing network (Botvinick, 2007; Etkin et al., 2006), but the ACC is also involved in executive functioning e.g. regulating cognitive and emotional processes (Botvinick, 2007; Ridderinkhof et al., 2004). The amygdala, insula, and ACC all belong to the limbic system located beneath the cerebrum on both sides of the thalamus. This system supports a variety of functions essential for human behavior such as memory, social cognition, motivation, emotional responses, and regulation of the autonomic nervous that needs interconnections between numerous brain structures system (Rajmohan & Mohandas, 2007); the ACC for example connects with various brain areas located within as well outside the limbic system, e.g. the insula and the prefrontal cortex (Derbyshire, 2000; Vogt, 2005). The prefrontal cortex, a neocortical structure that is most developed in primates and humans, is responsible for cognitive control, by means of attention, decision-making, and behavior regulation, over the simple and more automatic behaviors (Miller & Cohen, 2001). Previous neuroimaging studies have indicated strong correlations between the altered regions within the prefrontal cortex and antisocial behavior (Beyer et al., 2014; Blair, 2004; Decety et al., 2013; Ermer et al., 2012; Liu et al., 2014; Loeber et al., 2000; Potegal, 2012; Raine et al., 2000). It is evident that the increased, though still limited, amount of neuroimaging studies provided significant insight into the neuronal dispositions of antisocial behavior in children and adolescents.

Recently a cognitive neurobiological model of antisocial behavior in youths, with a particular focus on psychiatric traits, has been proposed (Blair, 2013). This model includes two core cognitive impairments, i.e. reduced emotional empathy and dysfunctional decision making, and connects these with several brain regions that are frequently implicated in antisocial behavior: the amygdala, the ventromedial prefrontal cortex (vmPFC), the dorsomedial prefrontal cortex (dmPFC), the striatum, and the anterior insula (see Figure 1.). According to the model, the underlying cause of reduced empathy is the dysfunctional processing of social distress cues (e.g. fearful facial expressions); these cognitive characteristics are linked with reduced amygdala responses –and possible lack of attention– to such cues. Impaired processing of social distress cues is also proposed to negatively affect social (reinforcement) learning, which is associated with anterior insula and vmPFC dysfunction. For example, observing distress cues from others (e.g. pain or other emotional reactions) diminishes an aggressive response in typical individuals. According to the model inadequate processing and/or associating of these distress cues reduces such empathic responding, as is commonly observed in youths with antisocial behavior. Dysfunctional decision making, the second core impairment in this

model is likely caused by a disrupted association between reinforcements (either reward or punishment) and an individual's action. Blair's model (2013) suggests that the abnormalities in reinforcement learning are twofold. First, youth with antisocial behavior are more insensitive to reinforcements due to a lower prediction error (difference between expected and received outcome), a process that involves the amygdala, vmPFC, and striatum. Secondly, these youths have a poorer representation of the expected reward of an action, which is linked to abnormal activity within the anterior insula and dmPFC. Overall, this neurobiological model has described a detailed theoretical relationship between the behavioral and neuronal characteristics of youths with antisocial behavior.

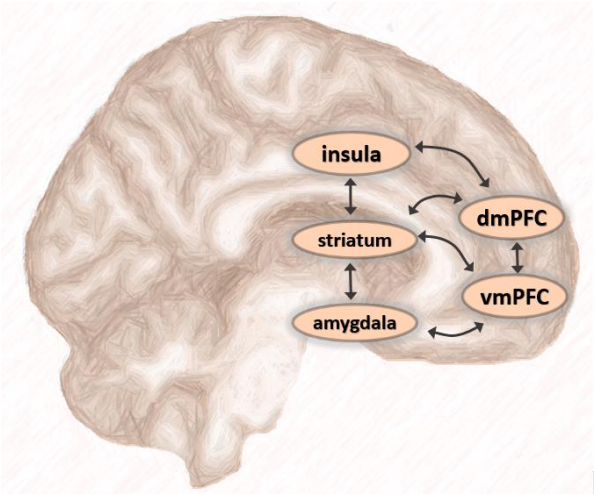


Figure 1. A schematic neurobiological model of brain regions implicated in youths with antisocial behavior.
Dysfunctions within the amygdala, the striatum, the ventromedial prefrontal cortex (vmPFC), the dorsomedial prefrontal cortex (dmPFC), the anterior insula, and the striatum are linked with impairments in emotional empathy and/or decision-making.

Picture is an adapted version from Blair (2013) Nature Reviews Neuroscience.

Despite the accumulated evidence of atypical brain structure and function in youths with antisocial behavior, the brain regions that are commonly affected are still not objectively determined. This is mainly due to the ambiguity of current neuroimaging findings: For example, studies not only differ regarding the set of altered brain regions observed, but also in the direction of these alterations –increases or decreases– even within the same brain regions. The main reason for these inconsistencies are likely the different inclusion criteria applied, especially considering the clinical definitions of antisocial behavior, age, and sex of the participants included. In the following sections, we will review the evidence of the neuroimaging studies investigating antisocial behavior in youths in more depth.

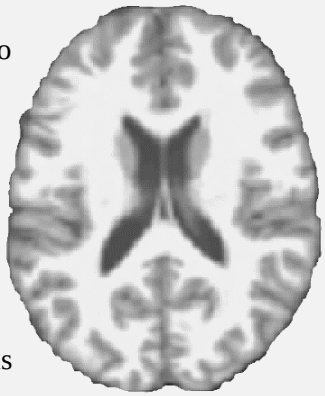
1.4. Structural brain correlates

To date, magnetic resonance imaging (MRI) is the most frequently used technique in psychopathology research to investigate anatomical features of the human brain in relation to psychological disorders or abnormal behaviors. Depending on the specific disorder and study aim, researchers investigate either gray matter, white matter, cerebrospinal fluid, or a combination of these (see Box 1. for an overview of brain anatomy). Structural MRI images allow researchers to compute the morphometry of the brain in terms of gray matter density, gyrification, cortical thickness, white matter tracts, total brain volume, or

the amount of cerebrospinal fluid. The subsequent sections provide an overview of the techniques and outcome of previous neuroimaging studies investigating the gray and white matter structural correlates of antisocial behavior in youths.

Box 1. Anatomy of the human brain.

In the neuroimaging work field, the human brain is roughly subdivided into three distinct types of tissues: gray matter, white matter and cerebrospinal fluid/meninges (*see image: a typical structural MRI scan*). Gray matter consists of abundant neuron cell bodies, dendrites, and small blood capillaries for oxygen and glucose transportation; this tissue covers the brain (cortex) as a thin layer with sulci and gyri. White matter primarily consists of the long-range neuronal axons that connect with other neuronal cell bodies located throughout the brain. Myelin is a fatty white substance that protects and nurtures the axons by surrounding them; it is also the source for the white color and thus the name of this type of brain tissue. Cerebrospinal fluid and the meninges surround all brain tissues and ventricles to protect against injuries, pathogens, and waste accumulation.



1.4.1 Gray matter alterations

Voxel-based morphometry (VBM) has become the most popular computational imaging technique, due to its simplified approach and automated algorithm, for investigating gray matter morphometry in antisocial behavior (Alegria, Radua, & Rubia, 2016; Ashburner & Friston, 2000; Baker et al., 2015; Lagopoulos, 2007; Wright et al., 1995). This sensitive technique distinguishes the different types of brain tissue on a voxel-level from T1-weighted anatomical 3D MRI images and can compute two output quantities for gray matter: its volume and its density. The VBM application consists of three general processing steps, the first step starts with spatial normalization; each individual brain is transformed to a standardized template, this can be either a customized group template or a more generic template available online (for a more detailed overview about VBM see Ashburner & Friston, 2000). During normalization, a non-linear-registration algorithm morphs each voxel within the brain to the standardized template by stretching and compressing the global brain regions embodying that voxel. The second step consists of segmenting the earlier normalized brain data into three tissue types (e.g. gray matter, white matter, and cerebrospinal fluid). This segmentation step classifies each voxel based on their gray-scale color intensity and their location, i.e. the likelihood of a tissue type at a given location, and outputs segmented images containing values that indicate the probability of belonging to the specific tissue type the so-called tissue density. The third step is spatially data smoothing, this advances the normalization and enhances the normal distribution of the data, thus increasing the power of the forthcoming parametric statistical analyses. During smoothing the intensity of every voxel is replaced by the weighted average of its neighboring voxels. After these crucial VBM processing steps the statistical analysis starts using the general linear model (GLM) followed by voxel-wise standard

parametric (e.g. *t*-test, F-tests) or nonparametric (e.g. permutation test) statistical testing, hereby a correction for multiple comparisons is necessary to correct for the numerous voxel-by-voxel analyses (Friston et al., 1995). In sum, VBM is a useful technique that can infer about disorder-specific gray matter atypicalities.

A less frequently used method to measure gray matter in youth with antisocial behavior is surface-based morphometry (SBM); this technique measures the thickness and folding of the gray matter using specialized geometric models. First, SBM extracts the cortical surface of the brain (i.e. segmentation and skull-stripping) by stripping the outer cortex's layer away and creating a cortex volume with two surfaces: the gray/white surface (adjoins white matter structures) and pial surface (adjoins the pia mater) (Dale, Fischl, & Sereno, 1999; Fischl, 2012; Fischl & Dale, 2000; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999). The subsequent step is the deformation of the extracted surfaces using triangular tessellation to inflate or flatten the cortex's surface in order to compute the morphometrical features of the brain. In this manner the surface area, the thickness, and the curvature of the cortex can be calculated (Fischl et al., 1999). The following step is spatial normalization; just as with VBM this is also a crucial step in SBM for the acquirement of accurate results when performing group comparison analyses. Similar to VBM, SBM uses a high-dimensional non-linear registration algorithm, but instead of using the image's intensities SBM uses the surface curvature. In this way the major sulcal and gyral patterns are used as homologous anatomical regions for the alignment to a specialized surface-based atlas (Dale et al., 1999). After normalization a smoothing step is applied to the flattened 2D surface of cortex allowing a more precisely smoothing and thus improving the biologically meaningfulness, subsequently similar statistical analyses as mentioned for VBM can be applied here for group comparison.

The increased usage of VBM and SBM techniques has broadened our knowledge of cortical alterations in children and adolescents with antisocial behavior. The majority of neuroimaging studies have utilized VBM to investigate antisocial behavior, these studies have frequently reported reduced gray matter density, especially in frontal and temporal brain regions (Cope et al., 2014; Dalwani et al., 2011; Dalwani et al., 2015; De Brito et al., 2011; De Brito et al., 2009; Ermer et al., 2013; Fahim et al., 2011; Fairchild et al., 2013a; Fairchild et al., 2011; Huebner et al., 2008; Kruesi et al., 2004; Michalska et al., 2015; Sarkar et al., 2013; Sterzer et al., 2007; Stevens & Haney-Caron, 2012). Likewise, studies using SBM have provided additional evidence of reduced thickness and atypical curvature of the cortex within similar brain regions involved in emotion processing, reward and empathy, i.e. the orbitofrontal cortex, insula, and amygdala (Fahim et al., 2011; Hyatt, Haney-Caron, & Stevens, 2012; Wallace et al., 2014). However, some VBM studies had opposing results observing gray matter increases in the anterior cingulate and prefrontal cortices (Dalwani et al., 2011; De Brito et al., 2011; De Brito et al., 2009), or were unable to identify any gray matter deviations from typically

developing youths (Hummer et al., 2015; Michalska et al., 2015). Although many studies indicated gray matter atypicalities in youths with antisocial behavior, still the direction and location of these alterations vary across studies and are likely caused by the differences in inclusion criteria applied to compose young samples with antisocial behavior.

1.4.2. White matter alterations

Several neuroimaging techniques exists nowadays to investigate the volume, density, or the microstructural properties of white-matter structures (i.e. white matter fiber tracts), thus far two techniques have been used to investigate antisocial behavior in youth (Baker et al., 2015; Waller et al., 2017). One method is the previously mentioned voxel-based-morphology (VBM) technique which computes the volume and density of white brain matter with identical processing steps for gray matter as described within the previous section. The other more frequently applied technique is diffusion tensor imaging (DTI). This technique is based on the three-dimensional displacement of water molecules throughout the brain, which is assessed through specially designed multiple-directional diffusion-weighting gradient pulses. The basic concept behind DTI is that water molecules diffuse differently depending on the microstructural barriers within each brain tissue; for example, white matter forces the water molecules to flow along the direction of their fiber tracts (Beaulieu, 2002; Chenevert, Brunberg, & Pipe, 1990; Douek et al., 1991; Moseley et al., 1990). DTI translates the diffusion within each voxel into tensors, i.e. a matrix describing the diffusion's features, and these tensors help to characterize the microstructure of white matter fiber tracts. This translation is not only technically and competitively demanding but requires many steps for data processing (Basser, Mattiello, & LeBihan, 1994a, 1994b; Soares et al., 2013). Diffusion weighted imaging is highly susceptible to artifacts, therefore the first general preprocessing step is to remove or at least reduce commonly encountered artifacts such as magnetic susceptibility distortions or eddy currents, i.e. electrical currents resulting from the rapid switching of the diffusion weighting gradients. Several different computational programs, for example DTIprep and FMRIB, exist to automatically recognize and correct aforementioned artifacts in the diffusion weighted images (Jenkinson et al., 2012; Oguz et al., 2014). After data preprocessing, the DTI tensors need to be estimated: mathematical equations describe and calculate the tensor for each voxel based on the voxel's eigenvectors (diffusion direction) and eigenvalues (diffusion magnitude). Several types of tensors exist, each indicating a distinct features of the measured diffusivity: mean diffusivity (diffusion magnitude), fractional anisotropy (anisotropic fraction of diffusivity), axial diffusivity (diffusion magnitude of fastest diffusion direction), and radial diffusivity (diffusion magnitude of transverse direction) (Basser and Pierpaoli, 1996; Vilanova et al., 2006; Jones, 2008; Abe et al., 2010; Chanraud et al., 2010). Subsequently, specialized algorithms transform and combine the tensor of every single voxel into a global diffusion map, this allows within- and between-group comparison (Abe et al., 2010; Chanraud et al., 2010; Jones, 2008; Pierpaoli & Basser, 1996; Vilanova et al., 2006). During the final step these diffusion

maps are normalized for statistical analysis. The type of normalization depends on the predetermined statistical method. Two statistical methods that are typically applied in DTI are voxel-based analysis (VBA) and tract-based spatial statistics (TBSS). VBA runs statistical analysis on a voxel-by-voxel basis where registration algorithms normalize the diffusion maps to a standard space followed by a standardized smoothing step. Whereas TBSS estimates a mean skeleton-tensor structure that represents the centers of all common fiber tracts of the investigated participant group (Andersson, Jenkinson, & Smith, 2007; Smith et al., 2006). This TBSS skeleton is then used for the normalization of each individual brain, smoothing is not necessary in this method.

Another DTI method that should be shortly mentioned is fiber tractography, here the diffusion maps of fractional anisotropy are used to build up individual 3D fiber tracts (Basser & Pajevic, 2000; Jones, Horsfield, & Simmons, 1999; Mori et al., 1999; Mori et al., 2002; Wedeen et al., 2012). In this method, mathematical algorithms follow the tensor directions within specific diffusion maps to reconstruct probable fiber tracts between two a-priori chosen brain regions, or so-called seeding points (Le Bihan et al., 2001). Researchers have hypothesized that the uncinate fasciculus is most likely disrupted in antisocial behavior, since this fiber tract interconnects the amygdala and prefrontal areas commonly affected in antisocial behavior (Blair, 2013; Marsh et al., 2011a). Therefore, DTI-based studies in youths and adults with antisocial behavior have mainly focused on the fiber consistency and microstructural integrity of the uncinate fasciculus and found atypicalities within this tract (Breeden et al., 2015; Motzkin et al., 2011; Sarkar et al., 2013; Sobhani et al., 2015; Sundram et al., 2012; Zhang et al., 2014a). The ability to non-invasively estimate brain structural connectivity by investigating individual tracts have led fiber tractography to become a more popular method nowadays.

To date, a handful of VBM studies and numerous DTI studies investigating white matter structure have led to ambiguous results in children and adolescents with antisocial behavior (for review see (Baker et al., 2015; Waller et al., 2017). For instance, one VBM study reported decreased white matter volume within the frontal, temporal and limbic regions of boys with antisocial behavior compared to their typically developing peers (De Brito et al., 2011), while another was unable to observe white matter differences at all (Stevens & Haney-Caron, 2012). This trend of ambiguity continues in DTI studies investigating the integrity, mostly through fractional anisotropy, of white matter tracts in youths with antisocial behavior. A majority of DTI studies observed increased or decreased white matter integrity in numerous fiber tracts comprising the corpus callosum, corona radiata, superior longitudinal fasciculus, fronto-occipital fasciculus, uncinate fasciculus, stria terminalis, and cerebellar peduncle (Breeden et al., 2015; Haney-Caron, Caprihan, & Stevens, 2014; Passamonti et al., 2012; Zhang et al., 2014b), while some found no white matter alterations (Beyer et al., 2014; Finger et al., 2012; Hummer et al., 2015). Furthermore, different aspects of antisocial behavior, for instance psychopathic traits, callous unemotional traits, and conduct disorder symptoms, assumingly correlate

with two DTI measures namely fractional anisotropy (FA) and axial diffusivity (AD), (Breeden et al., 2015; Decety, Yoder, & Lahey, 2015; Haney-Caron et al., 2014; Pape et al., 2015). However, also here the correlational direction varies between these studies. These inconsistencies in white matter alterations and correlations may result from differences in DTI methods or analysis approaches applied, small sample sizes, group heterogeneity, or differences in the age of the participants tested. Zhang and colleagues (2014a) observed sex differences within the uncinate fasciculus of youth with antisocial behavior; indicating sex as another important factor that could explain the ambiguous findings within the DTI literature, since past studies included only male or mixed-gender groups to investigate antisocial behavior. To date it is unclear, whether the previously identified white matter alterations in boys with antisocial behavior are also present in girls with antisocial behavior. Two studies, one using a region of interest approach, the second based on post-hoc examinations of adult females with a prior diagnosis of antisocial behavior provide first evidence about potentially unique white-matter characteristics in girls with antisocial behavior (Lindner et al., 2016; Zhang et al., 2014a). However, no study to date has investigated whole-brain white matter alterations in young girls with antisocial behavior using DTI.

1.5. Functional brain correlates

Functional magnetic resonance imaging (fMRI) has become the leading research technique for mapping brain activity, and therefore this subchapter will solely focus on this technique by describing its underlying theory and examining the neural correlates observed in youths with antisocial behavior to date. The principle of fMRI is based on the hemodynamic responses –changing oxygen levels in the blood– throughout the brain as an indirect measure of neural activity. This principle is called the blood oxygenation level-dependent (BOLD; also called $T2^*$ parameters) contrast and is measured with radiofrequency pulses and rapidly changing magnetic fields in the MRI scanner (Lee et al., 2010; Logothetis & Pfeuffer, 2004). The BOLD contrast is based on the concentration of deoxygenated and oxygenated hemoglobin, the protein in red blood cells that transports oxygen, in the blood. High concentrations of deoxyhemoglobin molecules have paramagnetic features that induces magnetic field inhomogeneities which in turn decreasing the BOLD contrast (Ogawa et al., 1990; see Logothetis & Wandell, 2004 for a more entailed description of this technique). Active neurons get an overshoot of oxygenated hemoglobin supply that, in contrast to deoxygenated hemoglobin, increases the BOLD contrast. In this way fMRI can record brain activity with a temporal resolution of a few seconds covering the whole brain, producing images with a spatial resolution of a few millimeters.

Analyzing fMRI images comprises the following three general phases: preprocessing, model specification, and statistical analysis. Additionally, each phase consists of numerous standardized steps that can be implemented using brain-imaging-analysis software (e.g. FSL, SPM, BrainVoyager). The goal of the preprocessing phase is to correct for artifacts caused by head movements or magnetic

inhomogeneities (i.e. realignment, unwarping, and/or slice time correction), and normalize each individual brain to a standardized brain template to improve statistical analysis (i.e. coregistration, segmentation, normalization, and smoothing). The following phase consists of designing a general linear model that predicts the brain activity during the employed fMRI paradigm. For an accurate model, the implementation of essential parameters extracted from the paradigm is a necessity, such parameters are the MRI sequence settings, the hemodynamic response model, timing parameters, regressors, and covariates. The last phase consists of setting up the statistical design consisting of the general linear model followed by voxel-wise standard parametric or nonparametric statistical testing. As it true for all neuroimaging techniques, also here correcting for multiple comparisons is essential for an accurate interpretation of the final results (Friston et al., 1995; Holmes et al., 1996). It is important to note that the outcome of fMRI studies is highly dependent on the quality of the designed fMRI paradigm, model specification, and statistical analysis involved. Therefore, a full and detailed methodological description in fMRI publications is a necessity for the reproducibility of the results (Poldrack et al., 2008).

The behavioral aspects of antisocial behavior in youths encompasses merely higher-order processes, as a result functional MRI studies have mainly focused on unconscious/conscious processes that involve emotion processing, empathy, decision making, moral judgement, or avoidance learning. A multitude of neuroimaging studies have indicated altered brain activity in youths with antisocial behavior compared to their typically developing peers (Baker et al., 2015). Brain regions involved in emotion processing (e.g. amygdala, anterior cingulate cortex, and insula) and executive control (e.g. several regions within the prefrontal cortex) are frequently found to have altered activation patterns during paradigms using emotional stimuli (Dotterer et al., 2017; Fairchild et al., 2014; Hwang et al., 2016; Jones et al., 2009; Klapwijk et al., 2015; Lozier et al., 2014; Marsh et al., 2008; Passamonti et al., 2010; Sebastian et al., 2014; White et al., 2012) or empathy aspects (Decety et al., 2009; Lockwood et al., 2013; Marsh et al., 2013b; Sebastian et al., 2012). Neuroimaging studies investigating the poor decision-making and avoidance-learning characteristics in antisocial behavior have found atypical neural activation during reward and punishment paradigms (Bubenzer-Busch et al., 2015; Cohn et al., 2013; Finger et al., 2011; Finger et al., 2008; Gatzke-Kopp et al., 2009; Rubia et al., 2009), and decision making tasks (Crowley et al., 2010; Klapwijk et al., 2016; Sakai et al., 2017; Sharp, Burton, & Ha, 2011; van den Bos et al., 2014; White et al., 2016). Impaired moral judgement may result from impairments in emotional empathy and decision-making, and is repeatedly linked with dysfunctional amygdala, frontal cortex areas (Blair, 2007a; Glenn & Raine, 2014; McColgan, Rest, & Pruitt, 1983; Moll et al., 2005; Van der Velden et al., 2010), and temporal regions in youth with antisocial behavior (Harenski, Harenski, & Kiehl, 2014; Harenski et al., 2010; Marsh et al., 2011a). In sum, the accumulation of fMRI studies provides strong evidence for atypical brain functioning within a wide variety of brain areas in youths with antisocial behavior, however, the direction and location of these

atypicalities vary between studies. This indicates once more the importance of investigating the consistency and stability of these fMRI findings of past studies.

A correct processing and interpretation of distress-related cues, for example facial expressions, are a necessity in social human behavior for eliciting affective behavior and empathy, and inhibiting aggression towards others; behaviors that are often impaired in antisocial behavior (Blair et al., 2005; Blair, 2013; Marsh et al., 2011b). Dysfunctional recognition and processing of facial expressions (e.g. fearful and sad) have been observed in adolescents with antisocial behavior (Fairchild et al., 2010; Fairchild et al., 2009a); these deficiencies are associated with altered neural activation patterns, especially within the amygdala, the prefrontal cortex, and the insula (Fairchild et al., 2014; Herpertz et al., 2008; Passamonti et al., 2010; Sterzer et al., 2005). Additionally, psychopathic characteristics such as callous unemotional traits could mediate the effect on the neural activation pattern in antisocial behavior. For example, studies observed reduced amygdala activation in adolescents with both conduct disorder and callous unemotional traits (Jones et al., 2009; Lozier et al., 2014; Marsh & Blair, 2008a). In contrast, adolescents with conduct disorder and low on callous unemotional traits exhibit increased neuronal activation within the amygdala as a response to negative emotional stimuli (Sebastian et al., 2014; Viding et al., 2012b) (Han et al., 2011). Research has suggested that a dysfunctional amygdala in healthy individuals cause recognition impairments of facial expressions (Adolphs et al., 1994; Adolphs et al., 1995). Moreover, these recognition impairments are linked to a lack of attention to the eye region: instructing to focus on the eyes abolished earlier observed recognition impairments, unfortunately, its effect on amygdala activity was not measured (Adolphs et al., 2005). The eye region is proven to be crucial for the recognition and thus processing of facial expressions (Baron-Cohen 1997; Eisenbach 2011); Consequently, Dadds and colleagues (2006) have hypothesized that the facial-expression-recognition deficits observed in individuals with antisocial behavior could be a result of reduced attention to the eyes. Indeed, young children (4- to 8-year old) and adolescents (till 15 years) with antisocial behavior and elevated callous-unemotional traits had reduced attention to the eyes of static pictures or during real life (parental play) interaction (Dadds et al., 2014; Dadds et al., 2008; Dadds et al., 2011; Dadds et al., 2006). Redirecting the attention to the eye abolished the impaired facial-expression recognition within these young samples (Dadds et al., 2008; Dadds et al., 2006). So far, the neural underpinnings of these attentional deficits within antisocial behavior populations have not been thoroughly investigated. Only two functional neuroimaging studies have found a relation between neural correlates, callous-unemotional traits, and attention to the eye region (Han et al., 2011; Sebastian et al., 2014). However, both studies manipulated the patient's eye gaze indirectly, by means of a fixation point or a mask, to the eye region of pictures with different facial expressions. To date, no study has investigated the direct correlation between the patient's natural eye gaze (e.g. voluntary attention to the eye region) and neural activation patterns in antisocial behavior.

1.6 Neural correlates of callous-unemotional traits

Children and adolescents with antisocial behavior form a highly heterogeneous population behaviorally, thus researchers proposed meaningful subtypes of antisocial behavior (Fairchild et al., 2011; Frick, 2009; Frick & Marsee, 2006; Kruesi et al., 2004; Moffitt et al., 2008). In particular, callous-unemotional traits are a potential quantitative indicator for the severity (e.g. more delinquency and aggression) and persistence of antisocial behavior (Frick & White, 2008). Callous-unemotional traits reflect a lack of empathy, reduced guilt combined with a shallow affect, or limited prosocial emotions. Nowadays, callous-unemotional traits are also implemented as an additional specifier to the diagnosis of conduct disorder within the DSM-5 labeled as 'Limited Prosocial Emotions' (APA, 2013; Fairchild et al., 2013b; Pardini, Frick, & Moffitt, 2010). Behaviorally, callous-unemotional traits have been associated with reduced empathy and increased reward sensitivity, punishment insensitivity, and thrill seeking behavior in young populations with and without a diagnosis of antisocial behavior (Centifanti & Modecki, 2013; Chabrol et al., 2012; Frick et al., 2003; Frick et al., 1994; Jones et al., 2010; Kimonis et al., 2008; Pardini & Byrd, 2012; Pardini, Lochman, & Frick, 2003). Recent studies investigating the neurobiology of callous-unemotional traits have most commonly linked areas of the limbic and threat system to the variability in callous-unemotional traits. Elevated levels of callous-unemotional traits have frequently been linked with gray matter alterations in the paralimbic and limbic brain areas, studies found either a negative (Cohn et al., 2016; Cope et al., 2014; Rogers & De Brito, 2016; Sauder et al., 2012; Sebastian et al., 2016; Wallace et al., 2014) or positive correlation (De Brito et al., 2009; Fairchild et al., 2013a). Functional neuroimaging studies suggest that callous unemotional traits are also negatively correlated with amygdala activity (Viding, Fontaine, & McCrory, 2012a) and connectivity between the anterior cingulate and the insula (Yoder, Lahey, & Decety, 2016). Additionally, one meta-regression study found a negative correlation between callous-unemotional traits and putamen gray matter volume (Rogers & De Brito, 2016). Evidently, these studies indicate an important connection between callous-unemotional traits and neurobiological correlates in youths with antisocial behavior. However, it remains open whether this correlation is driven by the presence of antisocial behavior, or whether callous-unemotional traits only modulate the brain structure within antisocial behavioral populations.

1.7. Gaps in knowledge

To date, most evidence for neural correlates in antisocial behavior is based on individual neuroimaging studies that suffer from small sample sizes and low reliability, e.g. low statistical power. Furthermore, the findings of these studies are to some extent ambiguous: studies identified both hypo- and hyperactivations within the same brain regions (e.g. the amygdala) or observed a completely different set of altered brain regions. These inconsistencies are likely caused by different inclusion criteria applied, especially considering the clinical definitions of antisocial behavior, age, and sex of the participants included. The consistency and robustness of previous neuroimaging findings are of

importance to evaluate which brain areas are repeatedly affected throughout the literature; such brain regions can be identified with an activation likelihood estimation (ALE) meta-analysis –a statistical technique– specialized for analyzing neuroimaging data (Eickhoff et al., 2009; Turkeltaub et al., 2002; Turkeltaub et al., 2012). Therefore, the **first aim** of this thesis is to aggregate and investigate the robustness of all structural and functional neuroimaging studies conducted in youths with antisocial behavior using an ALE meta-analysis (see chapter 2).

Neuroimaging studies have suggested a significant correlation between callous-unemotional traits and neurobiological –functional and structural– correlates in youths with antisocial behavior. However, it remains open whether this correlation is driven by the presence of antisocial behavior, or whether solely callous-unemotional traits modulate the brain structure within antisocial behavioral populations. In order to bridge this gap, the **second aim** of this thesis is to investigate callous-unemotional traits in typically developing youths free from –and thus independent of– any psychiatric disorder. Furthermore, since most studies have focused solely on males, the variations in callous-unemotional traits and brain structure will be investigated for boys and girls separately (see chapter 3).

Besides gray matter alterations also the white matter appears to differ between the brains of youths with and without antisocial behavior. DTI studies have observed white matter alterations within several white matter tracts. However, these studies have mostly focused on boys or mixed-gender samples, and thus it is unclear whether the previously identified white matter alterations are also present in girls with antisocial behavior. No study to date has investigated whole-brain white matter alterations in girls with antisocial behavior using DTI. Therefore, the **third aim** of the present work aims at bridging this gap in knowledge by comparing white matter tracts in girls with antisocial behavior compared to typically developing controls (see chapter 4).

In the last decennia studies investigating young samples with antisocial behavior have associated dysfunctional recognition and processing of facial expressions with altered neural activation patterns. Studies have proposed that reduced attention to the eye region could be the cause of such impairments. Interestingly, when the attention is redirecting to the eye region these recognition impairments are abolished. So far two fMRI studies have found alterations in amygdala activity when manipulating attention to the eye via fixation point or mask in youth with antisocial behavior. Nevertheless, no study has investigated the direct correlation between the natural eye gaze and neural activation in antisocial behavior. Therefore, the **fourth aim** of this thesis is to investigate the neural underpinnings of facial-expression processing and its relationship with eye gaze, using a modified facial-expression paradigm in combination with real-time eye-tracking. Real-time eye tracking allows researchers not only to measure eye-gaze patterns, such as fixations and saccades, but also the possibility to control the task compliance/performance of the participants (see chapter 5).

Nowadays scientists are becoming more aware of their responsibility and the importance of good communication of science to the general public. A poor understanding of the basics of science may force the public to make uninformed decisions, ultimately leading to negative consequences, such as mistrust or misunderstanding of scientists and their research. Therefore, our **fifth** aim was to raise awareness about antisocial behavior and the importance of neuroscientific research in youths by translating the results from our meta-analysis project to the general public using accessible language, attractive illustrations, and popular examples (see chapter 6).

1.8. Thesis Aims

(1) Aggregate all structural and functional neuroimaging studies conducted in adolescents with aggressive or antisocial behavior to date.

(a) Conduct a systematic literature review of neuroimaging findings in adolescents with antisocial behavior.

(b) Perform meta-analyses to examine gray matter volume reductions as well as functional alterations during emotion processing tasks in adolescents with antisocial behavior.

(c) Identify potential overlaps in brain structural and functional alterations in adolescents with antisocial behavior.

(2) Investigate callous-unemotional traits in typically-developing boys and girls without antisocial behavior.

(a) Investigate variations in callous-unemotional traits and brain structure for typically developing males and females.

(3) Investigate the white matter in female adolescents with antisocial behavior.

(a) Investigate white matter alterations in females on a whole brain level and within a priori defined regions of interest to allow comparability to past studies and data in males.

(4) Investigate the neural underpinnings of facial-expression processing in youths with antisocial behavior, and its relationship with eye gaze to the eye region.

(5) Translate neuroscience and neuroimaging results to the general public.

(a) Translate the findings of our meta-analysis to children and adolescents.

(b) Explain the neuroimaging technique and importance of neuroscience research.

Chapter 2. Structural and functional alterations in right dorsomedial prefrontal and left insular cortex co-localize in adolescents with aggressive behavior: an ALE meta-analysis.

Nora M. Raschle, **Willeke M. Menks**, Lynn V. Fehlbaum, Ebongo Tshomba, & Christina Stadler
4 September 2015.
PloS one 10.9 (2015): e0136553.

Abstract

Recent neuroimaging work has suggested that aggressive behavior (AB) is associated with structural and functional brain abnormalities in processes subserving emotion processing and regulation. However, most neuroimaging studies on AB to date only contain relatively small sample sizes. To objectively investigate the consistency of previous structural and functional research in adolescent AB, we performed a systematic literature review and two coordinate-based activation likelihood estimation meta-analyses on eight VBM and nine functional neuroimaging studies in a total of 783 participants (408 [224AB/184 controls] and 375 [215 AB/160 controls] for structural and functional analysis respectively). We found 19 structural and eight functional foci of significant alterations in adolescents with AB, mainly located within the emotion processing and regulation network (including orbitofrontal, dorsomedial prefrontal and limbic cortex). A subsequent conjunction analysis revealed that functional and structural alterations co-localize in right dorsomedial prefrontal cortex and left insula. Our results are in line with meta-analytic work as well as structural, functional and connectivity findings to date, all of which make a strong point for the involvement of a network of brain areas responsible for emotion processing and regulation, which is disrupted in AB. Increased knowledge about the behavioral and neuronal underpinnings of AB is crucial for the development of novel and implementation of existing treatment strategies. Longitudinal research studies will have to show whether the observed alterations are a result or primary cause of the phenotypic characteristics in AB.

Introduction

Aggressive behavior (AB), as observed in social disorders such as DBD (including conduct (CD) and oppositional defiant disorder (ODD)), is characterized by a repeated pattern of antisocial behavior and severe aggression, where the basic rights of others, major age-appropriate norms or societal rules are violated (R. J. Blair, Leibenluft, & Pine, 2014). Such problems can cause significant impairment in social, academic, or occupational functioning (Association, 2013; Scott, Knapp, Henderson, & Maughan, 2001). Clinical and subclinical forms of AB are observed in up to 14% of all girls and 16% of all boys (Ravens-Sieberer et al., 2008). The negative impact of aggression-related problems reaches beyond a patient's family, ultimately affecting society as a whole (e.g. school-dropouts, delinquency, teen-pregnancies, substance abuse or difficulties integrating into work life (Bardone et al., 1998; Pedersen & Mastekaasa, 2011; Scott et al., 2001)). Early conduct problems are key precursors of persistent AB and thus also predictive for ODD, CD and antisocial personality disorder in adulthood (Lahey, Loeber, Burke, & Applegate, 2005). Neurodevelopmental theories (Frick & Viding, 2009; Gao, Glenn, Schug, Yang, & Raine, 2009; Glenn & Raine, 2008) and longitudinal studies (Vloet, Konrad, Huebner, Herpertz, & Herpertz-Dahlmann, 2008) are in line with these behavioral observations, suggesting that the presence of early brain alterations in individuals with aggressive behavior may heighten the risk for long-lasting social impairments (McEwen, 2003; Raine & Yang, 2006). In the current paper we particularly focus on adolescents with *aggressive behavior* (AB), hereby summarizing neuroimaging research in youths with either conduct problems, CD or ODD.

In recent years structural (e.g. voxel-based/surface-based) and functional (e.g. fMRI/PET) neuroimaging techniques have grown into powerful tools to investigate the neuronal basis of the human brain in typically developing individuals as well as patients. It has been demonstrated that both, brain structure and function, may be modified by experience (Maguire et al., 2000; Schmidt-Wilcke, Rosengarth, Luerding, Bogdahn, & Greenlee, 2010). Activation-dependent structural plasticity can even occur after as little as seven days of training (Draganski et al., 2004; Driemeyer, Boyke, Gaser, Buchel, & May, 2008) and it is suggested to play a key role in human adaptation to environmental changes and disease. Even though neuroimaging evidence points toward a neuronal basis of AB (R. J. Blair, 2003; Raine & Yang, 2006), the overall number of research studies within this population remains relatively scarce. Furthermore, it has to be noted that AB characteristics as seen in CD and/or ODD are considered heterogeneous in respect to their pathologies. CD and ODD are frequently associated with comorbidities such as attention-deficit hyperactivity disorder (ADHD) or anxiety (Loeber, Burke, Lahey, Winters, & Zera, 2000)). These comorbid disorders can differ in their pathophysiological mechanisms, some of them seem exclusive on a biological level making it possible that different developmental trajectories with varying neurobiological bases lead to the clinical

manifestations of AB (Crowe & Blair, 2008). The vagueness of the group definition within many of the current studies on AB is thus bound to impact general conclusions drawn from it.

Even though the total number of studies is still limited, neuroanatomical and functional variations in youths with AB have been reported with increased frequency since the advent of modern neuroimaging. In particular, brain structure in AB has been investigated using voxel-based morphometry (VBM), diffusion tensor imaging (DTI) or surfaced-based morphometry. VBM studies for example have revealed differences in gray and white matter volume in brain regions including the amygdala, insula, orbitofrontal and dorsomedial prefrontal cortex (e.g. (De Brito et al., 2009; Fairchild, Hagan, et al., 2013; Fairchild et al., 2011; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007)) when comparing adolescents with AB and typically developing controls. Similarly, studies using surface-based morphometry (Hyatt, Haney-Caron, & Stevens, 2012; Wallace et al., 2014) or DTI (Finger et al., 2012; Haney-Caron, Caprihan, & Stevens, 2014; Li, Mathews, Wang, Dunn, & Kronenberger, 2005; Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014a; Zhang, Zhu, et al., 2014) provide evidence for structural alterations and/or impaired connectivity within brain regions involved in emotion processing, reward and empathy. Functional neuroimaging studies corroborate the structural neuroimaging literature. Cognitive paradigms employed in the investigation of AB have focused on disturbances in the emotion processing and regulation network of the brain. These tasks particularly target emotion processing/regulation (Herpertz et al., 2008; Jones, Laurens, Herba, Barker, & Viding, 2009; Lockwood et al., 2013; Marsh et al., 2008; Mathews et al., 2005; Passamonti et al., 2010; Sebastian et al., 2014; Stadler et al., 2007; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005; White et al., 2012), empathy (Decety, Michalska, Akitsuki, & Lahey, 2009; Lockwood et al., 2013; Marsh et al., 2013), theory of mind (Sebastian et al., 2012), passive avoidance (Finger et al., 2011), decision making (Dalwani et al., 2014; White et al., 2013) or executive functioning (Mathews et al., 2005; Rubia et al., 2008; White et al., 2012). Overall, studies point towards aberrant brain function in AB in key areas of social cognition and emotion, including prefrontal (orbitofrontal, dorsolateral and medial prefrontal cortex), limbic (e.g. amygdala, anterior insula, cingulate cortex) and temporal cortices.

Despite increasing evidence about the uniformity of atypical brain structure and function in AB, it has yet to be objectively determined which brain regions are commonly affected. Functional and structural neuroimaging studies are crucial for the understanding of the phenotype and etiology of AB. However, most results and interpretations are based on individual neuroimaging studies and present various limitations (e.g. small sample sizes, low reliability, dependency on task chosen (Eickhoff et al., 2009; Raemaekers, du Plessis, Ramsey, Weusten, & Vink, 2012; Stark & Squire, 2001)). Furthermore, very

few imaging studies have yet investigated brain structure and function in the same population. Activation likelihood estimation (ALE) meta-analyses allow the identification of consistent findings of brain activation and structure across multiple data sets. Hereby, ALE quantitatively investigates communalities between reported foci based on modelling them as probability distributions centered around the corresponding coordinates. The resulting probability maps mirror the likelihood of morphological change and/or activation on a voxel-wise level across an entire set of studies (Eickhoff et al., 2009). ALE has been successfully applied in meta-analyses of various neuropsychiatric disorders to date (Fusar-Poli et al., 2011; Glahn et al., 2008; Kollndorfer et al., 2013; Linkersdorfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Schwindt & Black, 2009) and provides a promising tool for a more unified investigation of pathophysiologic changes in disease.

Therefore, the present paper intends to close this gap in research and aims to aggregate all structural and functional neuroimaging studies conducted in adolescent AB to date. In a first step, we planned to conduct a systematic literature review of neuroimaging findings in adolescents with AB. Secondly two separate meta-analyses looking at gray matter volume reductions as well as hypoactivations during emotion processing tasks in AB were carried out. Finally, we decided to run a conjunction analysis to identify potential overlaps in deviant brain structure and function in adolescents with AB.

Method

Participants

We decided to focus our analysis on adolescents with *aggressive behavior* (AB) in general as opposed to a specific clinical diagnosis. By including both community samples and clinical samples in the present meta-analyses we adhere to the heterogeneity in juvenile aggression. This heterogeneity is further reflected by different behavioral symptoms of aggression and antisocial tendencies, such as oppositional behavior, impulsive hot-tempered quarrels or premeditated violent acts, the presence of callous unemotional/psychopathic traits or co-morbid conditions in CD and ODD patients. All studies were conducted during childhood and/or adolescence and share the communality of aggression and antisocial tendencies within the populations studied. Thus, AB as defined here may be considered an umbrella term for children and adolescents with a range of subclinical and clinically relevant symptoms of pathological aggression.

Study Selection

For the structural and functional neuroimaging meta-analyses we used PubMed and Google Scholar to systematically search for neuroimaging literature in AB. Literature searches were conducted and reviewed by several research team members (NMR, WMM, LVF, ET) and adhered to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality Of Reporting Of Meta-analyses (QUOROM) statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). Our main search (see **Figure 1**) conducted through PubMed included the following key words: *"conduct disorder", "conduct problems", "disruptive behavior disorder", "oppositional defiant disorder"* and *"aggression"*, each in combination with methodologically relevant terms including *"VBM"*, *"fMRI"* and/or *"neuroimaging"*. Moreover, a number of review articles published on conduct disorder, antisocial behavior and aggression in adolescents were considered (e.g. (Anderson & Kiehl, 2014; R. J. Blair, 2010; Cappadocia, Desrocher, Pepler, & Schroeder, 2009; Dolan, 2010; Fairchild, van Goozen, Calder, & Goodyer, 2013; Viding & McCrory, 2012; Vloet et al., 2008)). Finally, additional publications were explored by searching the reference list of the articles obtained to assure integration of all data available. Studies were included in our meta-analyses if the following criteria were given: (**I**) included at least one clinical group with described aggressive behavior, (**II**) in combination with a healthy control sample, (**III**) conducted during adolescence, (**IV**) reported whole brain gray matter volume alterations or whole brain functional neuroimaging data, (**V**) results are described using a standard reference space (Talairach or MNI) and (**VI**) the same threshold was used throughout the whole brain analysis. All structural studies included employed a standard VBM analysis protocol. In both meta-analysis of structural and functional brain alterations in adolescents with AB versus controls, no studies providing results based on a priori region-of-interest analysis only were included (since they violate the assumption, under the null hypothesis, that the likelihood of locating activated foci is equal at every voxel). Similarly, no animal studies or case reports were included in any meta-analysis and only studies from peer-reviewed journals that are written in English were considered. Data is current up to July 2015.

Of the 1021 studies identified through our systematic review (see **Figure 1**), we screened 930 (after removal of duplicates) and consequently assessed the full texts of 173 articles. 156 studies had to be excluded from the functional or structural meta-analysis in adolescents with AB, because they did not meet the criteria listed above (for detailed exclusion reasons, see **Figure 1**). Looking more closely at our review on *structural research studies* in AB revealed that only five studies reported on gray matter volume increases in AB (four reported de- and increases, one study only reported increases). Therefore we did not conduct a separate meta-analysis for gray matter volume increases in AB. Consequently,

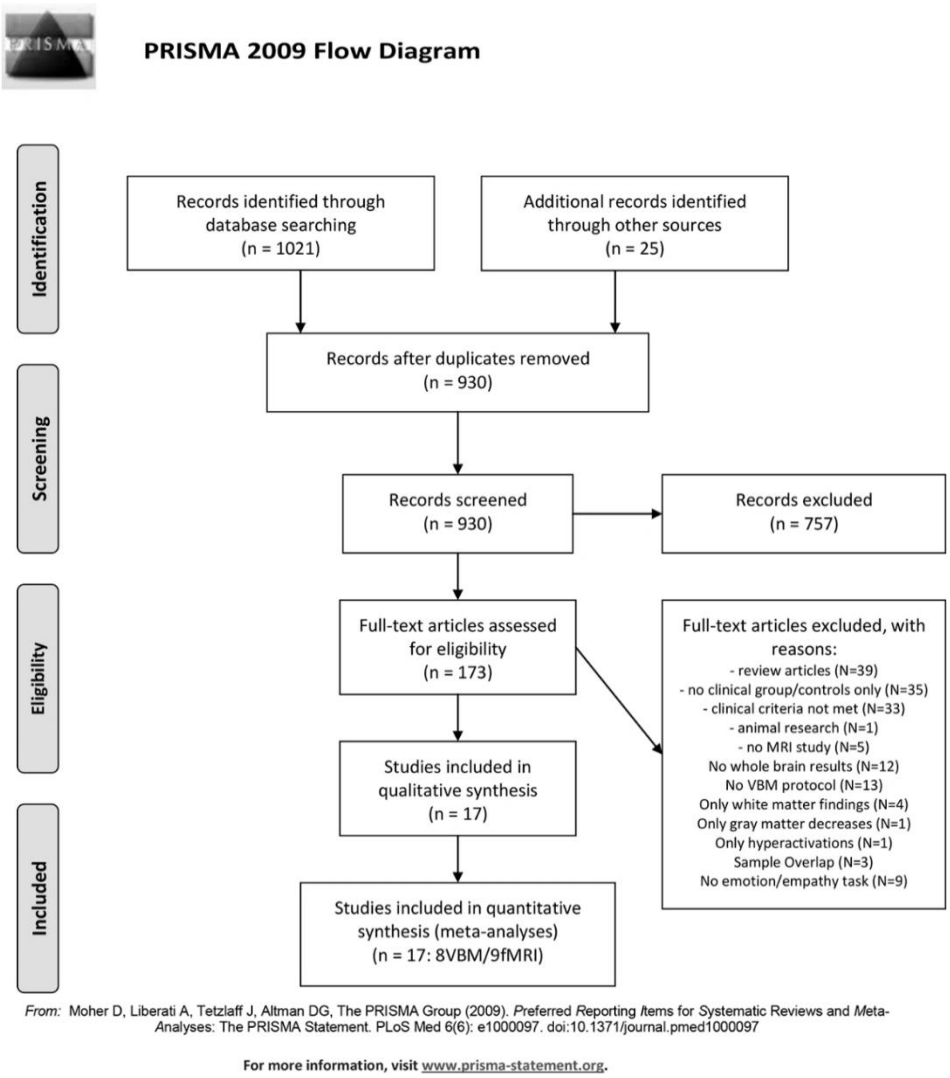


Figure 1. *Systematic literature research. Literature research according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality Of Reporting Of Meta-analyses (QUOROM) statement (59) resulting in 17 neuroimaging studies included in the current meta-analyses.*

eight studies were included in our meta-analysis about gray matter volume reductions, together reporting data from 408 research participants (224 AB, 184 typically developing controls=TD), and 50 foci of gray matter volume decreases in youths with AB (**Table 1,** (Dalwani et al., 2011, 2015; De Brito et al., 2009; Fahim et al., 2011; Fairchild, Hagan, et al., 2013; Fairchild et al., 2011; Huebner et al., 2008; Stevens & Haney-Caron, 2012)).

Table 1. *Characteristics of the studies in adolescents with AB included in the current structural meta-analysis.*

#	*First author*	*Year*	*Method*	*Diagnosis [N]*	*Sex [m/f]*	*Average age and [range] in years*
1	**Huebner**	2008	VBM	CD, early-onset [23] TD [23]	[23/0] [23/0]	CD, early-onset: 14.5 TD: 14.2 [12-17]
2	**De Brito**	2009	VBM	CP/CU+ [23] TD [25]	[23/0] [25/0]	CP/CU+: 11.5 TD: 11.8 [10-13]
3	**Dalwani**	2011	VBM	CP+SUD [25] TD [19]	[25/0] [19/0]	CP+SUD: 16.6 TD: 16.6 [14-18]
4	**Fahim**	2011	VBM	DBD [22; 11CD/11ODD] TD [25]	[22/0] [25/0]	DBD: 8.4 TD: 8.4
5	**Fairchild**	2011	VBM	CD, early-onset [36] CD, late-onset [27] TD [27]	[36/0] [27/0] [27/0]	CD, early-onset: 17.7 CD, late-onset: 17.9 TD: 18.5 [16-21]
6	**Stevens**	2012	VBM	CD [24] TD [24]	[19/5] [16/8] [16/8]	CD: 15.7 TD: 16.0 [12-18]
7	**Fairchild**	2013	VBM	CD [22] TD [20]	[0/22] [0/20]	CD: 17.6 TD: 17.2 [14-20]
8	**Dalwani**	2015	VBM	CP [22]TD[21]	[0/22][0/21]	CP: 16.7 TD: 16.1 [14-18]

CD = Conduct disorder. DBD = Disruptive behavior disorder. CU+ = with high callous-unemotional traits .
SUD = Substance use disorder. TD = Typically developing subjects. VBM = Voxel-based morphometry

Our systematic literature review of ***functional neuroimaging studies*** in youths with AB identified experiments targeting emotion processing (Herpertz et al., 2008; Jones et al., 2009; Lockwood et al., 2013; Marsh et al., 2008; Mathews et al., 2005; Passamonti et al., 2010; Sebastian et al., 2014; Stadler et al., 2007; Sterzer et al., 2005; White et al., 2012), empathy (Decety et al., 2009; Lockwood et al., 2013; Marsh et al., 2013), theory of mind (Sebastian et al., 2012), passive avoidance (Finger et al., 2011), decision making (Dalwani et al., 2014; White et al., 2013) or executive functioning (Mathews et al., 2005; Rubia et al., 2008; White et al., 2012). We decided to restrict our functional meta-analysis to tasks only including emotionally loaded and visually presented stimuli (e.g. tasks of emotion processing and empathy). In case of sample overlap, the study with the highest subject number

meeting all other criteria listed above was selected. In case of comparisons between AB and TD in more than one contrast, only foci from the contrast putting the highest demand on emotion processing, were included. The majority of studies indicated hypoactivations in AB. Only six studies

Table 2. *Characteristics of the studies in adolescents with AB included in current functional meta-analysis.*

#	First author	Year	Stimuli	Diagnosis [N]	Sex [m/f]	Average age and [range] in years
1	Sterzer	2005	Pictures with neutral or strong negative affective valence (IAPS).	CD [13] TD [14]	[13/0] [14/0]	CD: 12.9 TD: 12.7 [9-15]
2	Passamonti	2010	Pictures of angry, sad and neutral faces.	CD, early-onset [27] CD , .late-onset [25] TD [23]	[27/0] [25/0] [23/0]	CD, early-onset: 17.7 CD, late-onset: 17.1 TD: 17.8 [16-21]
3	Marsh	2011	Emotional words (categorization task).	CD/ODD+PT [14] TD [14]	[8/6] [11/3]	CD/ODD+PT: 14.4 TD: 13.5
4	White	2012	Pictures of fearful and neutral faces.	CD/ODD+PT [15] TD [17]	[12/3] [9/8]	CD/ODD+PT: 15.7 TD: 14.5 [10-17]
5	Lockwood	2013	Pictures of others in pain or no pain.	CD [37] TD [18]	[37/0] [18/0]	CD: 14.1 TD: 13.7 [10-16]
6	Marsh	2013	Pictures of others in pain or no pain.	CD/ODD+PT [14] TD [21]	[8/6] [15/6]	CD/ODD+PT: 15.4 TD: 14.3 [10-17]
7	Fairchild	2014	Pictures of emotional or neutral faces.	CD [20] TD [20]	[0/20] [0/20]	CD: 17.0 TD: 17.6
8	O'Nions	2014	Cartoons (affective picture series)	CP/CU+ [16] TD [16]	[16/0] [16/0] [16/0]	CP/CU+: 14.2 TD: 13.5 [10-16]
9	Sebastian	2014	Pictures of fearful and calm facial expressions.	CP/CU+ [17] CP/CU- [17] TD [17]	[17/0] [17/0] [17/0]	CP/CU+: 14.0 CP/CU-: 14.5 TD: 13.5 [10-16]

CD = Conduct disorder. CP = Conduct problems. ODD = Oppositional defiant disorder. PT = with psychopathic traits. CU+ = with high callous-unemotional traits. CU- = with low callous-unemotional traits . TD = Typically developing subjects.

that fulfilled all other criteria listed above reported hyperactivations in AB compared to TD. Therefore, we did not conduct a separate meta-analysis on functional overactivations in AB. Consequently nine studies suggesting hypoactivations in adolescents with AB compared to TD were selected (**Table 2**; (Fairchild et al., 2014; Lockwood et al., 2013; Marsh et al., 2013; Marsh et al., 2011; O'Nions et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014; Sterzer et al., 2005; White et al., 2012)). Together the selected studies report data from 375 research participants (215 AB, 160 TD) and describe 58 foci of hypoactivation in AB compared to TD.

ALE meta-analysis procedure

We conducted two separate meta-analyses on gray matter volume alterations and functional hypoactivations in adolescents with AB. Data analysis was carried out using the revised version of the ALE approach for coordinate-based meta-analysis of neuroimaging data (Ginger ALE software, version 2.3; available from http://brainmap.org/ale/ (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2012)). In short, this new approach implements a random-effects model, a quantitative uncertainty model to determine the FWHM and an exclusive gray matter mask (for further details, see also (Eickhoff et al., 2012; Eickhoff et al., 2009; Laird et al., 2005; Stark & Squire, 2001; Turkeltaub et al., 2012)). Most importantly, instead of testing for an above-chance clustering between foci, the revised ALE algorithm assesses above-chance clustering between experiments. The spatial relationship between foci in a given experiment is now assumed to be fixed and ALE results are assessed against a null distribution of random spatial association between experiments. Prior to running any analyses, coordinates reported in Talairach space were transformed to MNI space using the tal2icbm algorithm (Laird et al., 2010; Lancaster et al., 2007). The here employed revised ALE approach identifies areas of convergence of activation across various experiments, minimizing the within-groups effects (approach by Turkeltaub and colleagues (Turkeltaub et al., 2012)). Each focus is represented as a center for 3D Gaussian probability distributions, where the standard deviation depends on group size (capturing spatial uncertainty) rather than single time points. First, the probabilities of all activation foci in a given experiment are combined for each voxel, which is represented in modelled activation maps (fMRI) or modelled anatomical maps (VBM). Secondly, the ALE method combines all modelled maps (fMRI and VBM separately) on a voxel-by-voxel basis to form an ALE image containing all unthresholded voxel ALE values. In the last step, this ALE image is tested against the null hypothesis under the assumption that all activated voxels are homogeneously distributed in the brain, independent of the experiments. This null-hypothesis model (a distribution map made by multiple permutations of random voxel activation) was created using a random-effects statistical method and tested against the original ALE image according to the selected significance threshold. Therefore, the null distribution is constructed

reflecting a random spatial association between different studies. Comparing the "true" ALE score to this distribution allows a focused inference on convergence between studies while preserving the relationship between individual foci within each study. Critically, this change from fixed- (foci-based) to random-effects (testing between study effects) inference in ALE analysis allows generalization of the results to the entire population of studies from which the analyzed ones were drawn. This more conservative approach with an increased specificity (Eickhoff et al., 2012; Eickhoff et al., 2009) does also accommodate the idea of convergence across heterogeneous studies. We used a statistical threshold of $p<0.05$ False Discovery Rate (FDR) corrected for multiple comparisons and a minimum cluster size of $500mm^3$. ALE maps are overlaid onto a standard brain in MNI space (Colin27 available at http://www.brainmap.org/ale/) using the Multi-image Analysis GUI (Mango available at http://ric.uthscsa.edu/mango/mango.html) and clusters were anatomically labelled by cross-referencing the Talairach Daemon (Lancaster et al., 1997; Lancaster et al., 2000) and aal (Tzourio-Mazoyer et al., 2002). In order to further investigate possible overlaps between the structural (VBM) and functional (fMRI) meta-analysis in adolescent AB, a formal conjunction analysis was performed by multiplying binarized versions of the individually thresholded ALE maps.

Results

Our meta-analysis of *structural neuroimaging studies* in adolescents with AB revealed 19 clusters of significant convergence between the studies (see **Table 3**; **Figure 2**). The largest clusters were found in the right inferior frontal lobe (inferior frontal/precentral gyrus), right precuneus and left-hemispheric insula. Further smaller clusters were found bilaterally in the frontal (e.g. dorsolateral and medial frontal gyrus), parietal (e.g. precuneus) and temporal lobe (e.g. middle/superior temporal gyrus) as well as the cerebellum (e.g. culmen). Our meta-analysis of *functional hypoactivation* in adolescents with AB revealed 8 clusters of significant convergence between the studies with the largest clusters in the right middle/superior frontal gyrus, left thalamus and basal ganglia, as well as left-hemispheric insula (see **Table 3, Figure 2**). Beyond others, further clusters included the right anterior cingulate, left middle temporal gyrus and right amygdala.

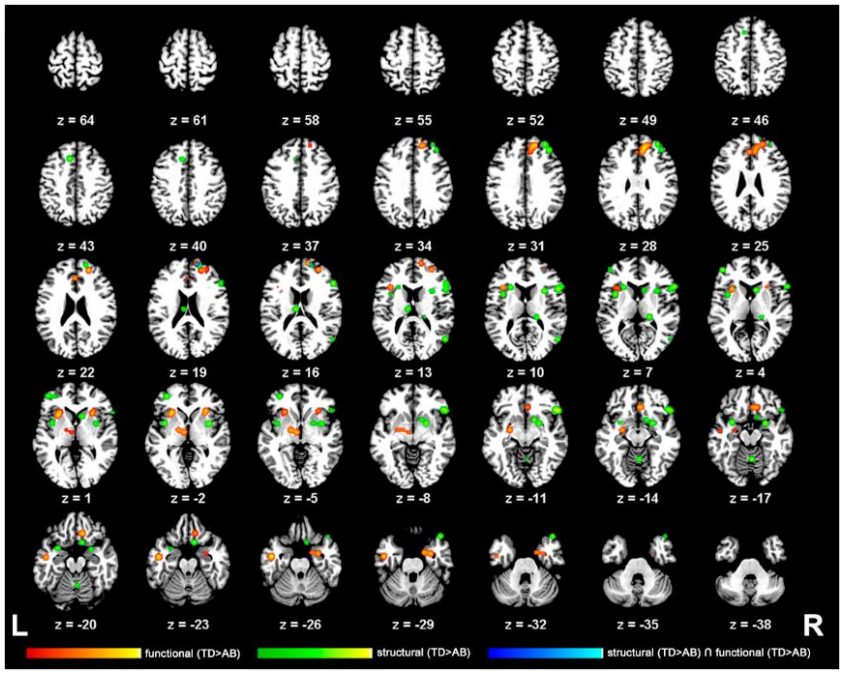


Figure 2. Neuronal alterations in adolescents with aggressive behavior (TD>AB): Results from an ALE meta-analysis. *2-D axial slices displaying the thresholded and binarized ALE maps of significant overlap (P<0.05, FDR-corrected) in studies of structural (green) and functional (red) alterations in adolescent AB (TD>AB) as well as a conjunction analysis (blue) overlaid on the Colin T1-template in MNI space. Z-slices depicting the results range from z=21 to 120 and are displayed in neurological view using the Multi-image Analysis GUI (Mango available at http://ric.uthscsa.edu/mango/mango.html).*

Table 3. *Results of the structural and functional ALE-meta analyses and conjunction analysis of structure and functional alterations in adolescents with AB*

#	Region	BA	H	Volume	Local Maxima		
					x	y	z
Structural Meta-Analysis (TD>AB)							
1	inferior frontal/precentral gyrus, insula	13, 44 , 45	R	1952	54	16	10
					62	20	6
					56	26	16
2	subcallosal gyrus, putamen, lateral globus pallidus, amygdala	34	R	1672	26	4	-16
					22	4	-8
					14	10	-12
3	inferior frontal gyrus	45, 47	R	1304	52	26	-10
4	insula	13	L	1144	-38	8	8
					-38	4	-2
5	middle/superior frontal gyrus	9,8	R	1112	34	48	30
					40	38	30
6	middle/inferior frontal gyrus	10,46	L	1040	-36	48	-2
					-46	48	2
7	putamen, claustrum		R	688	34	2	-2
8	thalamus		R	560	20	-30	8
9	subcallosal/middle frontal gyrus, cingulate	25	R	528	10	14	-22
10	cingulate/middle frontal gyrus	32	L	528	-10	24	42
11	claustrum		L	520	-24	20	8
12	claustrum, insula		R	520	32	14	10
13	subcallosal/parahippocampal gyrus, amygdala	34	L	512	-30	4	-18
14	culmen, declive		R	512	4	-58	-16

15	caudate		R	512	10	14	2
16	thalamus		L	512	-8	-16	15
17	inferior frontal gyrus	47	R	504	46	26	-30
18	middle temporal gyrus	37	R	504	54	-68	12
19	superior frontal gyrus	9	R	504	18	56	20
#	**Region**	**BA**	**H**	**Volume**	**Local Maxima**		
					x	**y**	**z**
Functional Meta-Analysis (TD>AB)							
1	middle/superior frontal gyrus, anterior cingulate gyrus	8, 9, 10, 32	R/L	3728	14	44	30
					8	36	28
					22	48	22
					32	50	14
					0	36	24
2	thalamus, lentiform nucleus, putamen, medial globus pallidus		L	1944	-6	-12	-4
					-26	-8	-12
	amygdala				-16	-8	-4
3	claustrum, insula	13	L	1896	-28	20	0
					-38	20	12
4	middle frontal gyrus, anterior cingulate	11, 24	R	1328	12	30	-20
					4	30	-14
5	inferior/middle temporal gyrus	21	L	1288	-48	-8	-26
6	amygdala, parahippocampal gyrus	28	R	1224	30	-4	-28
					20	-2	-30
7	claustrum, putamen, insula	13	R	776	28	20	0
					30	24	-2
8	superior, middle frontal gyrus	9	R	552	14	60	16
Conjunction: Structural (TD>AB) ∩ Functional (TD>AB)							
1	superior frontal gyrus (dmPFC)	9	R	128	16	58	18
2	claustrum, insula		L	8	-26	20	4
3	claustrum, insula		L	8	-28	18	6

All x, y, z-coordinates represent local maxima in MNI space. AB=Aggressive Behavior. Volume=Volume (mm3). TD=Typically developing controls. H=Hemisphere. BA= Brodmann areas. R=Right. L=Left.

A formal conjunction analysis using the thresholded ALE maps from the structural and functional meta-analysis discovered three areas of regional overlap (**Table 3, Figure 3)**. The biggest area of functional and structural overlap (128mm^3) in adolescents with AB was identified within the right dmPFC. Additionally, the analysis exposed two smaller, close-lying clusters of convergence with a peak in the left claustrum, extending into the insular cortex.

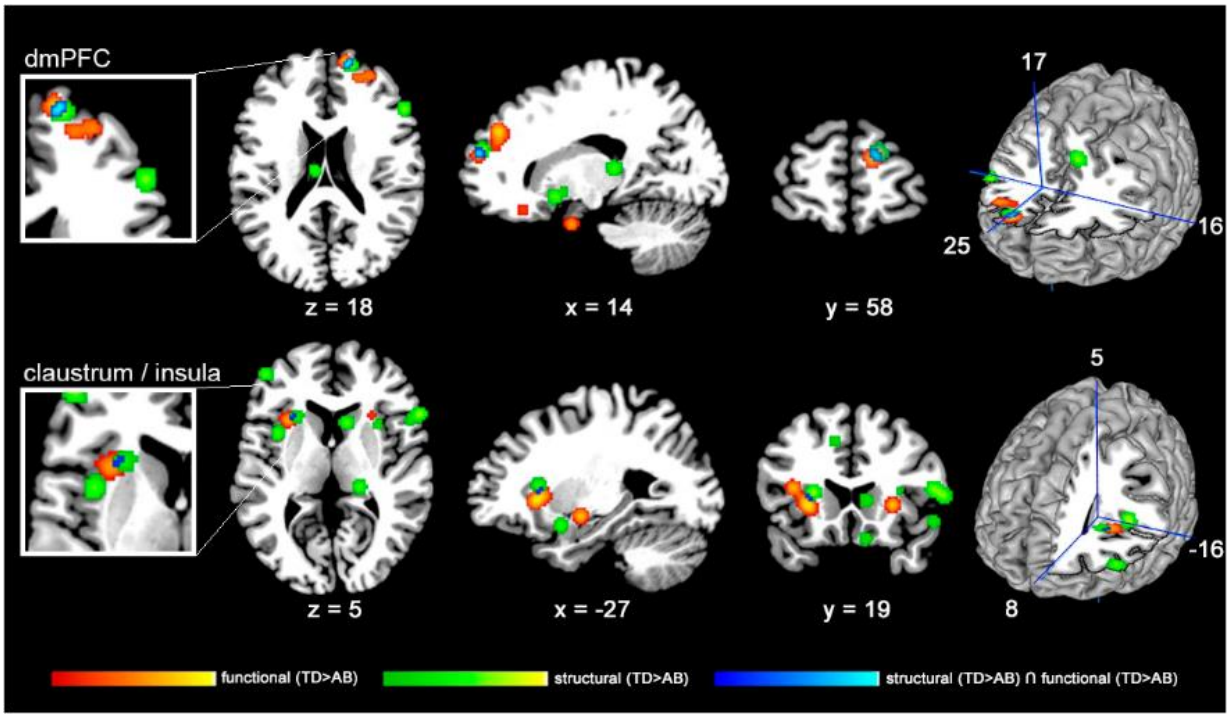


Figure 3. Structural and functional neuroimaging findings in youths with AB co-localize in right dorsomedial prefrontal cortex (dmPFC) and left insular cortex. *2-D slices displaying the thresholded and binarized ALE maps of significant overlap (P<0.05, FDR-corrected) in studies of structural (green) and functional (red) alterations in adolescents with AB (TD>AB) as well as a conjunction analysis (blue) overlaid on the Colin T1-template in MNI space. The upper-row including left cut-out as well as right surface-model highlight the right dmPFC where structural and functional alterations co-localize. The lower-row including left cut-out as well as right surface-model illustrate left insular cortex/claustrum where structural and functional alterations overlap.*

Discussion

To our knowledge, the current work provides the first quantitative summary of functional hypoactivations and gray matter volume reductions in adolescents with AB by summarizing findings of eight structural and nine functional neuroimaging studies in a total of 783 participants (408 [224 AB/184 TD] and 375 [215 AB/160 TD] for structural and functional analysis respectively). Our findings indicate 19 structural and eight functional foci of significant alterations in AB, mainly located within the emotion processing and regulation network of the human brain (including orbitofrontal, dorsolateral/medial prefrontal cortex and limbic brain regions; for reviews on emotion processing and regulation see also (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Ochsner, Silvers, & Buhle, 2012; Rubia, 2011)). Conjunction analysis reveal that functional and structural alterations in AB overlap in three areas, with the largest cluster centered in the right dmPFC and two smaller clusters that encompass the left insula.

In the following sections we will review structural and functional neuroanatomical evidence derived from healthy participants as well as those with aggressive behavior (e.g. conduct problems, CD, ODD) for the key areas implicated here (orbitofrontal and dorsomedial prefrontal cortex, insula, cingulate cortex, amygdala).

Orbitofrontal and Dorsomedial Prefrontal Cortex

Our findings identify prefrontal brain regions including orbitofrontal and dorsomedial prefrontal cortex as main locations of aberrant brain function and structure in youths with AB. Furthermore, an overlap in the foci representing structural and functional changes that co-localize in AB is centered in the right dmPFC. While the orbitofrontal as well as the dorsomedial prefrontal cortex can be differentiated based on quantitative as well as qualitative markers (Zald, 2007), both have equally been suggested in emotion processing and working memory/inhibitory control (Golkar et al., 2012). The medial prefrontal cortex in particular has been implicated in emotional self-regulation (Davidson, Jackson, & Kalin, 2000), general self-referential activities (D'Argembeau et al., 2007) and emotion-related decision making (Euston, Gruber, & McNaughton, 2012). Meta-analytic evidence suggests a more generic role of the dmPFC in emotion processing (e.g. appraisal, evaluation, experience, response), non-specific to a particular emotion (Phan, Wager, Taylor, & Liberzon, 2002). In addition, lesion, neurophysiological and neuroimaging evidence have linked the orbitofrontal and dorsomedial prefrontal cortex to stimulus-reinforcement association learning (Bechara, Damasio, & Damasio, 2000). The ability to rapidly decode and readjust values of different input signals is likely to be crucial to emotional behavior and may ultimately influence emotional learning. It has been suggested that the observed deficits in decision making may directly result from aberrant emotion processing as for example observed after frontal brain damage (Bechara et al., 2000). Research has for instance demonstrated that aberrant self-monitoring abilities may be responsible to preclude the generation of social emotions typically associated with the resolution of social mistakes (Beer, John, Scabini, & Knight, 2006). Finally, a whole line of evidence (e.g. (Beyer, Munte, Gottlich, & Kramer, 2014; R. J. Blair, 2003; Potegal, 2012)) has linked the prefrontal cortex to aggression. In its extreme, antisocial personality disorder and psychopathy are exemplary for individuals displaying increased aggressive behavior and studies of both have linked structural (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012; Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000) and functional (Decety, Skelly, & Kiehl, 2013; Liu, Liao, Jiang, & Wang, 2014) changes to the prefrontal cortex.

Insula

Both our functional and structural AB meta-analysis have found significant clusters of hypoactivations or altered brain structure within the insula. In addition to that, two smaller clusters reached

significance in the left insular cortex during our conjunction analysis, mapping structural and functional alterations in youths with AB. The insula or insular cortex is part of the cerebral cortex forming the base of the lateral sulcus (or sylvian fissure (Gasquoine, 2014)). From a neurodevelopmental perspective it is the first region of the cortex to develop and differentiate around 6 weeks of fetal life (Afif, Bouvier, Buenerd, Trouillas, & Mertens, 2007). The insula is bi-directionally connected to various brain regions, including the orbitofrontal cortex, anterior cingulate, supplementary motor areas, parietal and temporal cortices, but also to subcortical structures such as the amygdala, basal ganglia and thalamus (Dupont, Bouilleret, Hasboun, Semah, & Baulac, 2003; Gasquoine, 2014). Connectivity to and from the insula is divided, in that the anterior part of the insula has greater connectivity with the frontal lobe, while posterior parts are more strongly connected to the parietal lobe. Neuroimaging evidence has suggested that the insula may play a key role in the awareness of bodily sensations and affective feelings (A. D. Craig, 2009; Lindquist et al., 2012). Meta-analytic data supports this idea, and suggests that the insula is a key player in the evaluation, experience or expression of internally generated emotions (Phan et al., 2002). Particularly the left insula, along with frontal and temporal brain regions, is associated with anger (Lindquist et al., 2012). Furthermore, an emotion-specific role of the insula for disgust (Phillips et al., 1997) has been discussed. However, the majority of neuroimaging findings and meta-analytic reviews to date support a generic role of the insula in emotional behavior (e.g. (Lindquist et al., 2012; Phan, Wager, Taylor, & Liberzon, 2004)).

Atypical neuronal functioning of the insula (e.g. during tasks of emotion processing and empathy) are linked to AB (e.g. (Decety et al., 2013; Lockwood et al., 2013)). However, so far, both hyper- (Decety et al., 2009; Fairchild et al., 2014) and hypoactivations (Lockwood et al., 2013; Passamonti et al., 2010; Rubia et al., 2009) are observed during tasks of empathy, face or pain processing. In psychopathy particularly fear conditioning has been linked to aberrant insula activation (Birbaumer et al., 2005). Functional atypicalities within the insula are further observed in borderline personality disorder (Koenigsberg et al., 2009), schizophrenia (Manoliu et al., 2013), depression (Manoliu et al., 2014) or anorexia nervosa (Bar, Berger, Schwier, Wutzler, & Beissner, 2013). Gray matter volume alterations within the insula are associated with various psychiatric conditions beyond antisocial populations (e.g. (Ermer et al., 2012; Sterzer et al., 2007)), including bipolar disorder (Selvaraj et al., 2012), schizophrenia (Glahn et al., 2008), drug dependence (Garavan, 2010), major depression (Bora, Fornito, Pantelis, & Yucel, 2012) or anorexia nervosa (Nunn, Frampton, Fuglset, Torzsok-Sonnevend, & Lask, 2011).Therefore, the neuronal and structural alterations within the insula may reflect a characteristic of psychiatric conditions per se (Gasquoine, 2014).

Cingulate Cortex

The cingulate cortex showed functional as well as structural foci of significance in each of our two meta-analyses individually. Cytoarchitectonically, the cingulate gyrus may be divided into four functionally independent but interconnected subregions, including the anterior cingulate cortex (emotion), the midcingulate cortex (response selection), the posterior cingulate cortex (personal orientation), and the retrosplenial cortex (memory formation and access) (Vogt, 2005). Overall the cingulate cortex has been implicated in the regulation of cognitive as well as emotional processes (Phan et al., 2002; Vogt, 2005) (e.g. processing of acute pain (Shackman et al., 2011) or affective stimulus material (Vogt, 2005)), most likely through an interaction with the prefrontal cortex, anterior insula, premotor area, the striatum and cerebellum (Derbyshire, 2000; Vogt, 2005). We here particularly identified regions within the bilateral anterior cingulate as foci of interest through both our functional and structural meta-analysis. While dorsal aspects of the anterior cingulate have been linked to tasks of executive functioning (Botvinick, 2007; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), the anterior part of the cingulate is part of the emotion processing network (Botvinick, 2007; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). It is further suggested that the cingulate gyrus may serve as a transition and/or interaction zone between affective and cognitive processing (Phan et al., 2002).

Studies in AB and antisocial personality disorder have found both gray and white matter increases as well as decreases within the cingulate (e.g. (De Brito et al., 2009; Fahim et al., 2011; Wu, Zhao, Liao, Yin, & Wang, 2011; Yeh et al., 2009)); the developmental pathway within this region thus still needs further assessment. Hypoactivation in AB within the cingulate has been reported during tasks of emotion processing (Stadler et al., 2007; Sterzer et al., 2005), empathy (Dalwani et al., 2011; Lockwood et al., 2013), response inhibition (Zald, 2007) and sustained attention (Rubia et al., 2009). Similarly, individuals with antisocial personality disorder or psychopathic tendencies show reduced activation within the cingulate during tasks of emotion processing and conflict resolution, as for example observed in moral decision making (Glenn, Raine, & Schug, 2009; Prehn et al., 2013), deception (Jiang et al., 2013), frustration (Pawliczek et al., 2013) and emotion processing (Kiehl et al., 2001).

Amygdala

Both our functional and structural meta-analyses have identified the right and left-hemispheric amygdala as significant foci of interest, even though this area has not reached significance in our conjunction analysis. The amygdala is crucial for the perception and encoding of emotionally loaded stimulus material and has been suggested as the brain locus of fear (e.g. detection, generation,

maintenance of fear and coordination of response in the danger of such) (LeDoux, 2000; Lindquist et al., 2012). To summarize the existing fMRI evidence, neuronal activation within the amygdala has been observed in healthy individuals in tasks that include arousing stimulus material (e.g. emotionally loaded images (Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; Irwin et al., 1996), facial expressions (Morris et al., 1998; Vuilleumier, Armony, Driver, & Dolan, 2001; Whalen et al., 1998) or words (Hamann, Ely, Hoffman, & Kilts, 2002; Kensinger & Schacter, 2006)), during tasks of empathy (Baron-Cohen et al., 1999; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003), moral reasoning (Luo et al., 2006) or when processing potential threats (Phelps et al., 2001)). A range of tasks investigating amygdala responses to different evocative stimulus material led to the suggestion that increased activation within the amygdala may particularly mirror affective processing under acute danger or threat, rather than fear per se (Phan et al., 2002). Furthermore, neuronal activation is thought to mirror dispositional affective style (Davidson & Irwin, 1999; Phan et al., 2002), whereby increased amygdala activity correlates with affective reactivity to negative stimuli. Interestingly, amygdala activation in response to emotionally loaded stimuli may be attenuated by task demand (K. S. Blair et al., 2007; Etkin et al., 2006; Mitchell et al., 2007) or comorbid anxiety and depression symptoms (Sterzer et al., 2005). For example, concurrent goal-directed processing can disrupt amygdala activation that is evoked by emotional images (K. S. Blair et al., 2007). This is in line with meta-analytic evidence indicating that studies employing a cognitive task during affect processing are less likely to demonstrate amygdala activation (Phan et al., 2002).

Because of its role in aversive conditioning, instrumental learning and fear processing, the amygdala is often chosen as a region of interest in investigations targeting AB, antisocial personality disorder or psychopathy (R. J. Blair, 2003). Amygdala dysfunction is suggested to be one of the core features in the symptomatology of antisocial disorders (e.g. (R. J. Blair, 2003; Dolan & Fullam, 2009; Sebastian et al., 2014; Sterzer et al., 2005)). Structurally, the amygdala is altered in AB similarly as in antisocial personality disorders and psychopathy (e.g. (Boccardi et al., 2011; M. C. Craig et al., 2009; Sterzer et al., 2007)). Finally, it is to note that the amygdala is strongly interconnected with the orbitofrontal brain regions and alterations in the connectivity between these two centers have been reported in AB and psychopathy (e.g. connectivity between key regions of the emotion processing and regulation network (e.g. (R. J. Blair, 2007; van Honk & Schutter, 2006), for a further discussion see following section).

Structure-Function Relationship and Connectivity Findings

While neuroplasticity is known to potentially range from synaptic plasticity to more complex changes (e.g. shrinkage in cell size, neural or glial cell genesis, spine density or even changes in blood flow or

interstitial fluid (May et al., 2007)), the neurophysiological basis of experience-induced neuroplasticity is still a matter of extensive research (Schmidt-Wilcke et al., 2010). Some studies indicate that functional and structural measures of plasticity may be related. For example it could be hypothesized that experience-related gray matter volume changes correspond to task-specific processing, or, more precisely, synaptic remodeling within specific processing areas (Ilg et al., 2008). Another possibility may be that impaired connectivity between key regions leads to the functional alterations observed. For example researchers have argued that the social and emotional deficits seen in AB may be mediated by impaired connectivity between the emotion processing and regulation network (R. J. Blair, 2007; van Honk & Schutter, 2006). These system-specific deficits may be observed by diffusion tensor imaging and tractography measurements. For example, the uncinate fasciculus is a white-matter tract connecting the amygdala and neighboring anterior temporal lobe with the orbitofrontal cortex and it thus may be involved in facilitating empathy, emotion regulation and socio-cognitive processes (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Such models would for example explain why local changes in brain structure cannot always be inferred from purely functional models. For example, in individuals with reactive aggression aberrant amygdala activity but intact amygdala structure is observed (Bobes et al., 2013). In such cases it is possible that impaired fiber connections (e.g. reduced functional anisotropy in the uncinate fasciculus) to and from this area cause the neuronal differences observed (Bobes et al., 2013). In line with evidence in AB (Bobes et al., 2013) significant differences in the fractional anisotropy (FA) measures of the uncinate fasciculus have been demonstrated in adolescents with conduct disorder (Passamonti et al., 2010; Sarkar et al., 2013) as well as in adult psychopathy (M. C. Craig et al., 2009; Motzkin, Newman, Kiehl, & Koenigs, 2011). Similarly, studies of intrinsic connectivity (resting state) explore functional networks that are non-stimulus driven and may inform about the basic functional brain architecture while implicating anatomical connectivity of the regions involved (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011). In individuals with antisocial personality disorder this intrinsic connectivity between highly interconnected brain centers is disrupted (Tang, Jiang, Liao, Wang, & Luo, 2014).

Independent of the precise neurophysiological nature of structure-function associations, our results have indicated co-localized structural and functional deficits in right dmPFC and left insular cortex. Based on today's structure-function knowledge we thus hypothesize that decreased synaptic density may have led to a co-localized decrease within the BOLD response measured through fMRI. However, it has to be noted that here we only investigate co-localized structure-function findings that are based on gray matter volume reductions and functional hypoactivations in AB. This limitation (no volume increases or hyperactivity investigated) is due to the nature of the existing neuroimaging evidence, with only five studies reporting gray matter volume increases and six studies providing evidence for

functional hyperactivations in individuals with AB. Further studies comparing adolescents with AB compared to controls are needed in order to examine functional hypoactivations and gray matter volume increases more extensively. Furthermore, only longitudinal research studies will be able to show the precise developmental trajectory of these alterations in detail.

Limitations

Meta-analytic approaches such as the current one have a number of limitations in need for discussion. The presented analyses are first of all limited by the detail and quality of the original research studies. This includes problems of variations within the significance threshold of data reported, insufficient information on possible coordinate transformations and variation in group sizes. Additionally, even though psychosocial factors have been significantly linked to brain structure in AB, none of the studies to date systematically studied the influence of these within their designs. Furthermore, only a small number of studies to date have examined brain structure and function in youths with AB on a whole brain level. We decided that a more stringent inclusion criterion is beneficial over the absolute number of studies entering the analyses, especially in regards to the attempt to truly capture the neuronal and structural phenotype of adolescents with AB. The number of studies entering each analysis therefore is on the lower limit. Contrast analyses are ideally contain a minimum of 15 studies in each dataset to obtain sufficient statistical power (http://brainmap.org/ale/ (Eickhoff et al., 2012; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2012)). Therefore, the current analysis runs the risk of being under-powered.

Most of the studies included here consisted of only, or majority of, male participants (see **Tables 1, 2**). Some of the included study designs considered sex-matched clinical and control groups, while others applied a gender covariate within their design (e.g. (Stevens & Haney-Caron, 2012; Wallace et al., 2014)). Two VBM (Dalwani et al., 2015; Fairchild, Hagan, et al., 2013) and one fMRI (Fairchild et al., 2014) study included only female participants. These studies were nevertheless included in the current meta-analyses because the structural alterations observed in girls with CD broadly overlapped with those previously reported in male samples only (Fairchild, Hagan, et al., 2013). But while the current population included mirrors the occurrence of AB in the general population (e.g. higher number of males with AB (Loeber et al., 2000)), research has shown that it may be crucial to differentiate clinical cases based on gender in future research studies (e.g. (Berkout, Young, & Gross, 2011)). Specifically, to determine possible gender related differences of structural and functional characteristics in individuals with AB, a comparison between meta-analyses of studies examining females and those examining males separately would have been of interest, but was not possible due to the small number of studies that are available for each group individually.

Another potential caveat is the fact that clinical and subclinical forms of aggressive behavior are often associated with comorbid diagnoses, most prominently attention-deficit hyperactivity disorder (ADHD; reported in up to 69% of CD patients (Klein et al., 1997)) and anxiety (Loeber et al., 2000). To date there is no neuroimaging evidence investigating pure diagnosis of clinical manifestations of aggressive behavior (e.g. CD or ODD) (Banaschewski et al., 2005). Researchers argue whether aggressive behavior in combination with ADHD even posits a distinct subtype or not (Banaschewski et al., 2003) and common neurobiological pathways are considered (Banaschewski et al., 2005). Overall it can be concluded that neuroimaging research studies on aggressive behavior in children and adolescents to date are characterized by diverse approaches in regards to the sample selection and definition, all of which have their justification and pitfalls (Sterzer & Stadler, 2009). Ultimately, only a comparison of both, pure and comorbid groups will be able to inform about the specificity and predictive value of either definition. Here we included adolescents with clinical and subclinical forms of aggressive behavior, most of which have comorbid ADHD symptoms (e.g. (Dalwani et al., 2011; De Brito et al., 2009; Fairchild et al., 2014; Fairchild, Hagan, et al., 2013; Fairchild et al., 2011; Huebner et al., 2008; Lockwood et al., 2013; Marsh et al., 2013; Marsh et al., 2011; O'Nions et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014; Sterzer et al., 2005; Wallace et al., 2014; White et al., 2012). Many of the included studies report no differences in results when controlling for ADHD (through exclusion or a covariate within the study design; (Fairchild et al., 2014; Marsh et al., 2013; O'Nions et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014; Sterzer et al., 2005; White et al., 2013)).

Similar problems are IQ differences, drug use or socioeconomic status, all of which are a characteristic of populations with aggressive behavior. Studies included in the current meta-analysis have all matched their participants according to IQ measures (Fahim et al., 2011; Fairchild et al., 2014; Fairchild et al., 2011; Huebner et al., 2008; Lockwood et al., 2013; Marsh et al., 2013; Marsh et al., 2011; O'Nions et al., 2014; Passamonti et al., 2010; Sebastian et al., 2014; Stevens & Haney-Caron, 2012; White et al., 2012) or used IQ as a covariate within their study design (Dalwani et al., 2011; De Brito et al., 2009; Fairchild, Hagan, et al., 2013; Hyatt et al., 2012; Sterzer et al., 2005; Wallace et al., 2014). Drug use and socio-economic status were controlled for in some, but not all, studies and further research is needed using a more careful sample characterization in order to inform about the impact of these variables on brain structure and function.

It is also to consider that the diagnosis of conduct disorder (clinical manifestation of AB) may encompass at least two clinically relevant subgroups. While the first group exhibits callous-unemotional traits (e.g. reduced guilt, callousness, uncaring behavior and reduced empathy) and

heightened risk of persistent antisocial behavior, the second group is characterized by heightened threat sensitivity and reactive aggression (R. J. Blair et al., 2014; Euler et al., 2014). Callous-unemotional traits are highly heritable (Viding, Seara-Cardoso, & McCrory, 2014), expressed as early as at two years of age (Waller et al., 2012) and are predictive of the most severe and persistent variant of conduct disorder (Dandreaux & Frick, 2009; Rowe et al., 2010). Studies also indicate that this severity may significantly impact the neuronal alterations observed (Ducharme et al., 2011; Fairchild et al., 2014; Fairchild et al., 2011; Passamonti et al., 2010). To summarize, while we were unable to constrain the current meta-analysis based on potential subtypification and gender variables, these factors may pose an exciting view on data analysis strategies and interpretations for future studies. For all the reasons noted, the current results have to be interpreted with caution. However, multimodal neuroimaging methods combining two or more functional (fMRI and/or EEG) and structural (MRI and/or DTI) approaches are suggested to provide a more sensitive measure in comparison to unimodal imaging for disease classification (Sui, Huster, Yu, Segall, & Calhoun, 2014). Furthermore, we think that the confounding variables discussed here have influenced the functional and structural meta-analyses similarly.

Overall, we could demonstrate that structural and functional alterations in adolescents with AB co-localize within key regions of the emotion processing and regulation network (e.g. prefrontal and insular cortex). Thus, our current analysis, using an activation likelihood estimation approach, provides an important step towards a more focused method of neuroimaging in AB. Future studies need to determine whether the here identified convergent clusters of neuronal and structural alterations may be applicable for clinical purposes (for example an improved pathophysiological description of individuals with AB) or whether a further specification (e.g. based on subtypes and gender) may be needed. However, the coordinates presented here can serve as non-independent regions of interest for future studies in AB, conduct disorder or in individuals with AB or antisocial/psychopathic tendencies.

Summary and conclusion

Aggressive behavior constitutes a major issue of public health and increased knowledge about the behavioral and neuronal underpinnings of AB are crucial for the development of novel and implementation of existing treatment strategies. However, single site studies often suffer problems of small sample size and thus power issues. Quantitative meta-analysis techniques using activation likelihood estimations as implemented here offer a unique opportunity to investigate consistency of results between several studies investigating the same research question and population. We have implicated several brain regions of the emotion processing and regulation network to show hypoactivations and gray matter volume reductions in adolescents with AB (including prefrontal brain

regions, amygdala, insular and cingulate cortex) and demonstrated that functional and structural alterations in AB co-localize within right dmPFC and left insular cortex.

Overall, we are in line with meta-analytic work as well as structural, functional and connectivity findings that make a strong point for the involvement of a network of brain areas responsible for emotion processing and regulations. This network is impacted in individuals with AB and antisocial personality disorder/psychopathy. However, much still needs to be investigated. For example, study findings differ in regards to hypo- or hyperactivations and gray matter volume reductions or increases in different regions of the emotion processing and regulation network. Due to power constraints, the current meta-analysis only investigated hypoactivations and gray matter volume reductions in youths with AB and no hyperactivations or increases in brain structure. Future studies implementing longitudinal designs may be able to shed more light on the developmental pathway as well as onto typical and atypical trajectories within the regions reported. Such longitudinal designs will further allow the investigation of the bidirectional influence of biological and psychosocial influences in AB.

Acknowledgements

We thank Kübra Özoglu and Lea Klüwer for their help during the manuscript preparation.

References

Afif, A., Bouvier, R., Buenerd, A., Trouillas, J., & Mertens, P. (2007). Development of the human fetal insular cortex: study of the gyration from 13 to 28 gestational weeks. *Brain Struct Funct, 212*(3-4), 335-346. doi: 10.1007/s00429-007-0161-1

American Psychiatric Association, (APA). (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

Anderson, N. E., & Kiehl, K. A. (2014). Psychopathy: developmental perspectives and their implications for treatment. *Restor Neurol Neurosci, 32*(1), 103-117. doi: 10.3233/RNN-139001

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2003). Association of ADHD and conduct disorder--brain electrical evidence for the existence of a distinct subtype. *J Child Psychol Psychiatry, 44*(3), 356-376.

Banaschewski, T., Hollis, C., Oosterlaan, J., Roeyers, H., Rubia, K., Willcutt, E., & Taylor, E. (2005). Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD. *Dev Sci, 8*(2), 132-140. doi: 10.1111/j.1467-7687.2005.00400.x

Bar, K. J., Berger, S., Schwier, C., Wutzler, U., & Beissner, F. (2013). Insular dysfunction and descending pain inhibition in anorexia nervosa. *Acta Psychiatrica Scandinavica, 127*(4), 269-278. doi: DOI 10.1111/j.1600-0447.2012.01896.x

Bardone, A. M., Moffitt, T. E., Caspi, A., Dickson, N., Stanton, W. R., & Silva, P. A. (1998). Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety. *J Am Acad Child Adolesc Psychiatry, 37*(6), 594-601. doi: 10.1097/00004583-199806000-00009

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., & Williams, S. C. (1999). Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci, 11*(6), 1891-1898.

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex, 10*(3), 295-307.

Beer, J. S., John, O. P., Scabini, D., & Knight, R. T. (2006). Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. *J Cogn Neurosci, 18*(6), 871-879. doi: 10.1162/jocn.2006.18.6.871

Berkout, O. V., Young, J. N., & Gross, A. M. (2011). Mean girls and bad boys: Recent research on gender differences in conduct disorder. *Aggression and Violent Behavior, 16*(6), 503-511. doi: DOI 10.1016/j.avb.2011.06.001

Beyer, F., Munte, T. F., Gottlich, M., & Kramer, U. M. (2014). Orbitofrontal Cortex Reactivity to Angry Facial Expression in a Social Interaction Correlates with Aggressive Behavior. *Cereb Cortex*. doi: 10.1093/cercor/bhu101

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., & Flor, H. (2005). Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Arch Gen Psychiatry, 62*(7), 799-805. doi: 10.1001/archpsyc.62.7.799

Blair, K. S., Smith, B. W., Mitchell, D. G. V., Morton, J., Vythilingam, M., Pessoa, L., . . . Blair, R. J. R. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage, 35*(1), 430-440. doi: DOI 10.1016/j.neuroimage.2006.11.048

Blair, R. J. (2003). Neurobiological basis of psychopathy. *Br J Psychiatry, 182*, 5-7.

Blair, R. J. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends Cogn Sci, 11*(9), 387-392. doi: 10.1016/j.tics.2007.07.003

Blair, R. J. (2010). Neuroimaging of psychopathy and antisocial behavior: a targeted review. *Curr Psychiatry Rep, 12*(1), 76-82. doi: 10.1007/s11920-009-0086-x

Blair, R. J., Leibenluft, E., & Pine, D. S. (2014). Conduct disorder and callous-unemotional traits in youth. *N Engl J Med, 371*(23), 2207-2216. doi: 10.1056/NEJMra1315612

Bobes, M. A., Ostrosky, F., Diaz, K., Romero, C., Borja, K., Santos, Y., & Valdes-Sosa, M. (2013). Linkage of functional and structural anomalies in the left amygdala of reactive-aggressive men. *Soc Cogn Affect Neurosci, 8*(8), 928-936. doi: 10.1093/scan/nss101

Boccardi, M., Frisoni, G. B., Hare, R. D., Cavedo, E., Najt, P., Pievani, M., . . . Tiihonen, J. (2011). Cortex and amygdala morphology in psychopathy. *Psychiatry Res, 193*(2), 85-92. doi: 10.1016/j.pscychresns.2010.12.013

Bora, E., Fornito, A., Pantelis, C., & Yucel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord, 138*(1-2), 9-18. doi: 10.1016/j.jad.2011.03.049

Botvinick, M. M. (2007). Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci, 7*(4), 356-366.

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., & Yeo, B. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol, 106*(5), 2322-2345. doi: 10.1152/jn.00339.2011

Cappadocia, M. C., Desrocher, M., Pepler, D., & Schroeder, J. H. (2009). Contextualizing the neurobiology of conduct disorder in an emotion dysregulation framework. *Clin Psychol Rev, 29*(6), 506-518. doi: 10.1016/j.cpr.2009.06.001

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A, 100*(9), 5497-5502. doi: 10.1073/pnas.0935845100

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70. doi: 10.1038/nrn2555

Craig, M. C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., . . . Murphy, D. G. (2009). Altered connections on the road to psychopathy. *Mol Psychiatry, 14*(10), 946-953, 907. doi: 10.1038/mp.2009.40

Crowe, S. L., & Blair, R. J. R. (2008). The development of antisocial behavior: What can we learn from functional neuroimaging studies? *Development and Psychopathology, 20*(4), 1145-1159. doi: Doi 10.1017/S0954579408000540

D'Argembeau, A., Ruby, P., Collette, F., Degueldre, C., Balteau, E., Luxen, A., . . . Salmon, E. (2007). Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective taking. *J Cogn Neurosci, 19*(6), 935-944. doi: 10.1162/jocn.2007.19.6.935

Dalwani, M., Sakai, J. T., Mikulich-Gilbertson, S. K., Tanabe, J., Raymond, K., McWilliams, S. K., . . . Crowley, T. J. (2011). Reduced cortical gray matter volume in male adolescents with substance and conduct problems. *Drug Alcohol Depend, 118*(2-3), 295-305. doi: 10.1016/j.drugalcdep.2011.04.006

Dalwani, M. S., McMahon, M. A., Mikulich-Gilbertson, S. K., Young, S. E., Regner, M. F., Raymond, K. M., . . . Sakai, J. T. (2015). Female adolescents with severe substance and conduct problems have substantially less brain gray matter volume. *PLoS One, 10*(5), e0126368. doi: 10.1371/journal.pone.0126368

Dalwani, M. S., Tregellas, J. R., Andrews-Hanna, J. R., Mikulich-Gilbertson, S. K., Raymond, K. M., Banich, M. T., . . . Sakai, J. T. (2014). Default mode network activity in male adolescents with conduct and substance use disorder. *Drug Alcohol Depend, 134*, 242-250. doi: 10.1016/j.drugalcdep.2013.10.009

Dandreaux, D. M., & Frick, P. J. (2009). Developmental pathways to conduct problems: a further test of the childhood and adolescent-onset distinction. *J Abnorm Child Psychol, 37*(3), 375-385. doi: 10.1007/s10802-008-9261-5

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci, 3*(1), 11-21.

Davidson, R. J., Jackson, D. C., & Kalin, N. H. (2000). Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. *Psychol Bull, 126*(6), 890-909.

De Brito, S. A., Mechelli, A., Wilke, M., Laurens, K. R., Jones, A. P., Barker, G. J., . . . Viding, E. (2009). Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain, 132*(Pt 4), 843-852. doi: 10.1093/brain/awp011

Decety, J., Michalska, K. J., Akitsuki, Y., & Lahey, B. B. (2009). Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. *Biol Psychol, 80*(2), 203-211. doi: 10.1016/j.biopsycho.2008.09.004

Decety, J., Skelly, L. R., & Kiehl, K. A. (2013). Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. *JAMA Psychiatry, 70*(6), 638-645. doi: 10.1001/jamapsychiatry.2013.27

Derbyshire, S. W. (2000). Exploring the pain "neuromatrix". *Curr Rev Pain, 4*(6), 467-477.

Dolan, M. C. (2010). What imaging tells us about violence in anti-social men. *Crim Behav Ment Health, 20*(3), 199-214. doi: 10.1002/cbm.771

Dolan, M. C., & Fullam, R. S. (2009). Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. *Biol Psychiatry, 66*(6), 570-577. doi: 10.1016/j.biopsych.2009.03.019

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: changes in grey matter induced by training. *Nature, 427*(6972), 311-312. doi: 10.1038/427311a

Driemeyer, J., Boyke, J., Gaser, C., Buchel, C., & May, A. (2008). Changes in gray matter induced by learning--revisited. *PLoS One, 3*(7), e2669. doi: 10.1371/journal.pone.0002669

Ducharme, S., Hudziak, J. J., Botteron, K. N., Ganjavi, H., Lepage, C., Collins, D. L., . . . Brain Development Cooperative, G. (2011). Right anterior cingulate cortical thickness and bilateral striatal volume correlate with child behavior checklist aggressive behavior scores in healthy children. *Biol Psychiatry, 70*(3), 283-290. doi: 10.1016/j.biopsych.2011.03.015

Dupont, S., Bouilleret, V., Hasboun, D., Semah, F., & Baulac, M. (2003). Functional anatomy of the insula: new insights from imaging. *Surg Radiol Anat, 25*(2), 113-119. doi: 10.1007/s00276-003-0103-4

Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., & Fox, P. T. (2012). Activation likelihood estimation meta-analysis revisited. *Neuroimage, 59*(3), 2349-2361. doi: 10.1016/j.neuroimage.2011.09.017

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp, 30*(9), 2907-2926. doi: 10.1002/hbm.20718

Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *J Abnorm Psychol, 121*(3), 649-658. doi: 10.1037/a0026371

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron, 51*(6), 871-882. doi: 10.1016/j.neuron.2006.07.029

Euler, F., Jenkel, N., Stadler, C., Schmeck, K., Fegert, J. M., Kolch, M., & Schmid, M. (2014). Variants of Girls and Boys with Conduct Disorder: Anxiety Symptoms and Callous-Unemotional Traits. *J Abnorm Child Psychol*. doi: 10.1007/s10802-014-9946-x

Euston, D. R., Gruber, A. J., & McNaughton, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron, 76*(6), 1057-1070. doi: 10.1016/j.neuron.2012.12.002

Fahim, C., He, Y., Yoon, U., Chen, J., Evans, A., & Perusse, D. (2011). Neuroanatomy of childhood disruptive behavior disorders. *Aggress Behav, 37*(4), 326-337. doi: 10.1002/ab.20396

Fairchild, G., Hagan, C. C., Passamonti, L., Walsh, N. D., Goodyer, I. M., & Calder, A. J. (2014). Atypical neural responses during face processing in female adolescents with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 53*(6), 677-687 e675. doi: 10.1016/j.jaac.2014.02.009

Fairchild, G., Hagan, C. C., Walsh, N. D., Passamonti, L., Calder, A. J., & Goodyer, I. M. (2013). Brain structure abnormalities in adolescent girls with conduct disorder. *J Child Psychol Psychiatry, 54*(1), 86-95. doi: 10.1111/j.1469-7610.2012.02617.x

Fairchild, G., Passamonti, L., Hurford, G., Hagan, C. C., von dem Hagen, E. A., van Goozen, S. H., . . . Calder, A. J. (2011). Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. *Am J Psychiatry, 168*(6), 624-633. doi: 10.1176/appi.ajp.2010.10081184

Fairchild, G., van Goozen, S. H., Calder, A. J., & Goodyer, I. M. (2013). Research review: evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. *J Child Psychol Psychiatry, 54*(9), 924-940. doi: 10.1111/jcpp.12102

Finger, E. C., Marsh, A., Blair, K. S., Majestic, C., Evangelou, I., Gupta, K., . . . Blair, R. J. (2012). Impaired functional but preserved structural connectivity in limbic white matter tracts in youth with conduct disorder or oppositional defiant disorder plus psychopathic traits. *Psychiatry Res, 202*(3), 239-244. doi: 10.1016/j.pscychresns.2011.11.002

Finger, E. C., Marsh, A. A., Blair, K. S., Reid, M. E., Sims, C., Ng, P., . . . Blair, R. J. (2011). Disrupted reinforcement signaling in the orbitofrontal cortex and caudate in youths with conduct disorder or oppositional defiant disorder and a high level of psychopathic traits. *Am J Psychiatry, 168*(2), 152-162. doi: 10.1176/appi.ajp.2010.10010129

Frick, P. J., & Viding, E. (2009). Antisocial behavior from a developmental psychopathology perspective. *Dev Psychopathol, 21*(4), 1111-1131. doi: 10.1017/S0954579409990071

Fusar-Poli, P., Borgwardt, S., Crescini, A., Deste, G., Kempton, M. J., Lawrie, S., . . . Sacchetti, E. (2011). Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev, 35*(5), 1175-1185. doi: 10.1016/j.neubiorev.2010.12.005

Gao, Y., Glenn, A. L., Schug, R. A., Yang, Y., & Raine, A. (2009). The neurobiology of psychopathy: a neurodevelopmental perspective. *Can J Psychiatry, 54*(12), 813-823.

Garavan, H. (2010). Insula and drug cravings. *Brain Struct Funct, 214*(5-6), 593-601. doi: 10.1007/s00429-010-0259-8

Garavan, H., Pendergrass, J. C., Ross, T. J., Stein, E. A., & Risinger, R. C. (2001). Amygdala response to both positively and negatively valenced stimuli. *Neuroreport, 12*(12), 2779-2783.

Gasquoine, P. G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychol Rev, 24*(2), 77-87. doi: 10.1007/s11065-014-9246-9

Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., . . . Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol Psychiatry, 64*(9), 774-781. doi: 10.1016/j.biopsych.2008.03.031

Glenn, A. L., & Raine, A. (2008). The neurobiology of psychopathy. *Psychiatr Clin North Am, 31*(3), 463-475, vii. doi: 10.1016/j.psc.2008.03.004

Glenn, A. L., Raine, A., & Schug, R. A. (2009). The neural correlates of moral decision-making in psychopathy. *Mol Psychiatry, 14*(1), 5-6. doi: 10.1038/mp.2008.104

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., . . . Ohman, A. (2012). Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. *PLoS One, 7*(11), e48107. doi: 10.1371/journal.pone.0048107

Hamann, S. B., Ely, T. D., Hoffman, J. M., & Kilts, C. D. (2002). Ecstasy and agony: activation of the human amygdala in positive and negative emotion. *Psychol Sci, 13*(2), 135-141.

Haney-Caron, E., Caprihan, A., & Stevens, M. C. (2014). DTI-measured white matter abnormalities in adolescents with Conduct Disorder. *J Psychiatr Res, 48*(1), 111-120. doi: 10.1016/j.jpsychires.2013.09.015

Herpertz, S. C., Huebner, T., Marx, I., Vloet, T. D., Fink, G. R., Stoecker, T., . . . Herpertz-Dahlmann, B. (2008). Emotional processing in male adolescents with childhood-onset conduct disorder. *J Child Psychol Psychiatry, 49*(7), 781-791. doi: 10.1111/j.1469-7610.2008.01905.x

Huebner, T., Vloet, T. D., Marx, I., Konrad, K., Fink, G. R., Herpertz, S. C., & Herpertz-Dahlmann, B. (2008). Morphometric brain abnormalities in boys with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 47*(5), 540-547. doi: 10.1097/CHI.0b013e3181676545

Hyatt, C. J., Haney-Caron, E., & Stevens, M. C. (2012). Cortical thickness and folding deficits in conduct-disordered adolescents. *Biol Psychiatry, 72*(3), 207-214. doi: 10.1016/j.biopsych.2011.11.017

Ilg, R., Wohlschlager, A. M., Gaser, C., Liebau, Y., Dauner, R., Woller, A., . . . Muhlau, M. (2008). Gray matter increase induced by practice correlates with task-specific activation: a combined functional and morphometric magnetic resonance imaging study. *J Neurosci, 28*(16), 4210-4215. doi: 10.1523/JNEUROSCI.5722-07.2008

Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., & Turski, P. A. (1996). Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport, 7*(11), 1765-1769.

Jiang, W., Liu, H., Liao, J., Ma, X., Rong, P., Tang, Y., & Wang, W. (2013). A Functional Mri Study of Deception among Offenders with Antisocial Personality Disorders (Vol 244, Pg 90, 2013). *Neuroscience, 252*, 125-125. doi: DOI 10.1016/j.neuroscience.2013.08.007

Jones, A. P., Laurens, K. R., Herba, C. M., Barker, G. J., & Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *Am J Psychiatry, 166*(1), 95-102. doi: 10.1176/appi.ajp.2008.07071050

Kensinger, E. A., & Schacter, D. L. (2006). Processing emotional pictures and words: effects of valence and arousal. *Cogn Affect Behav Neurosci, 6*(2), 110-126.

Kiehl, K. A., Smith, A. M., Hare, R. D., Mendrek, A., Forster, B. B., Brink, J., & Liddle, P. F. (2001). Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry, 50*(9), 677-684.

Klein, R. G., Abikoff, H., Klass, E., Ganeles, D., Seese, L. M., & Pollack, S. (1997). Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry, 54*(12), 1073-1080.

Koenigsberg, H. W., Siever, L. J., Lee, H., Pizzarello, S., New, A. S., Goodman, M., . . . Prohovnik, I. (2009). Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res, 172*(3), 192-199. doi: 10.1016/j.pscychresns.2008.07.010

Kollndorfer, K., Krajnik, J., Woitek, R., Freiherr, J., Prayer, D., & Schopf, V. (2013). Altered likelihood of brain activation in attention and working memory networks in patients with multiple sclerosis: an ALE meta-analysis. *Neurosci Biobehav Rev, 37*(10 Pt 2), 2699-2708. doi: 10.1016/j.neubiorev.2013.09.005

Lahey, B. B., Loeber, R., Burke, J. D., & Applegate, B. (2005). Predicting future antisocial personality disorder in males from

a clinical assessment in childhood. *J Consult Clin Psychol, 73*(3), 389-399. doi: 10.1037/0022-006X.73.3.389

Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., . . . Fox, P. T. (2005). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Hum Brain Mapp, 25*(1), 155-164. doi: 10.1002/hbm.20136

Laird, A. R., Robinson, J. L., McMillan, K. M., Tordesillas-Gutierrez, D., Moran, S. T., Gonzales, S. M., . . . Lancaster, J. L. (2010). Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. *Neuroimage, 51*(2), 677-683. doi: 10.1016/j.neuroimage.2010.02.048

Lancaster, J. L., Rainey, L. H., Summerlin, J. L., Freitas, C. S., Fox, P. T., Evans, A. C., . . . Mazziotta, J. C. (1997). Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. *Hum Brain* Mapp, 5(4), 238-242. doi: 10.1002/(SICI)1097-0193(1997)5:4<238::AID-HBM6>3.0.CO;2-4

Lancaster, J. L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., . . . Fox, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum Brain Mapp, 28(11), 1194-1205. doi: 10.1002/hbm.20345

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., . . . Fox, P. T. (2000). Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp, 10*(3), 120-131.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184. doi: 10.1146/annurev.neuro.23.1.155

Li, T. Q., Mathews, V. P., Wang, Y., Dunn, D., & Kronenberger, W. (2005). Adolescents with disruptive behavior disorder investigated using an optimized MR diffusion tensor imaging protocol. *Ann N Y Acad Sci, 1064*, 184-192. doi: 10.1196/annals.1340.034

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav Brain Sci, 35*(3), 121-143. doi: 10.1017/S0140525X11000446

Linkersdorfer, J., Lonnemann, J., Lindberg, S., Hasselhorn, M., & Fiebach, C. J. (2012). Grey matter alterations co-localize with functional abnormalities in developmental dyslexia: an ALE meta-analysis. *PLoS One, 7*(8), e43122. doi: 10.1371/journal.pone.0043122

Liu, H., Liao, J., Jiang, W., & Wang, W. (2014). Changes in low-frequency fluctuations in patients with antisocial personality disorder revealed by resting-state functional MRI. *PLoS One, 9*(3), e89790. doi: 10.1371/journal.pone.0089790

Lockwood, P. L., Sebastian, C. L., McCrory, E. J., Hyde, Z. H., Gu, X., De Brito, S. A., & Viding, E. (2013). Association of callous traits with reduced neural response to others' pain in children with conduct problems. *Curr Biol, 23*(10), 901-905. doi: 10.1016/j.cub.2013.04.018

Loeber, R., Burke, J. D., Lahey, B. B., Winters, A., & Zera, M. (2000). Oppositional defiant and conduct disorder: a review of the past 10 years, part I. *J Am Acad Child Adolesc Psychiatry, 39*(12), 1468-1484. doi: 10.1097/00004583-200012000-00007

Luo, Q., Nakic, M., Wheatley, T., Richell, R., Martin, A., & Blair, R. J. (2006). The neural basis of implicit moral attitude--an IAT study using event-related fMRI. *Neuroimage, 30*(4), 1449-1457. doi: 10.1016/j.neuroimage.2005.11.005

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A, 97*(8), 4398-4403. doi: 10.1073/pnas.070039597

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., . . . Sorg, C. (2014). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience, 7*. doi: DOI 10.3389/fnhum.2013.00930

Manoliu, A., Riedl, V., Doll, A., Bauml, J. G., Muhlau, M., Schwerthoffer, D., . . . Sorg, C. (2013). Insular Dysfunction Reflects Altered Between-Network Connectivity and Severity of Negative Symptoms in Schizophrenia during Psychotic Remission. *Frontiers in Human Neuroscience, 7*, 216. doi: 10.3389/fnhum.2013.00216

Marsh, A. A., Finger, E. C., Fowler, K. A., Adalio, C. J., Jurkowitz, I. T., Schechter, J. C., . . . Blair, R. J. (2013). Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. *J Child Psychol Psychiatry, 54*(8), 900-910. doi: 10.1111/jcpp.12063

Marsh, A. A., Finger, E. C., Fowler, K. A., Jurkowitz, I. T. N., Schechter, J. C., Yu, H. H., . . . Blair, R. J. R. (2011). Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. *Psychiatry Research-Neuroimaging, 194*(3), 279-286. doi: DOI 10.1016/j.pscychresns.2011.07.008

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., . . . Blair, R. J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry, 165*(6), 712-720. doi: 10.1176/appi.ajp.2007.07071145

Mathews, V. P., Kronenberger, W. G., Wang, Y., Lurito, J. T., Lowe, M. J., & Dunn, D. W. (2005). Media violence exposure and frontal lobe activation measured by functional magnetic resonance imaging in aggressive and nonaggressive adolescents. *J Comput Assist Tomogr, 29*(3), 287-292.

May, A., Hajak, G., Ganssbauer, S., Steffens, T., Langguth, B., Kleinjung, T., & Eichhammer, P. (2007). Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb Cortex, 17*(1), 205-210. doi: 10.1093/cercor/bhj138

McEwen, B. S. (2003). Early life influences on life-long patterns of behavior and health. *Ment Retard Dev Disabil Res Rev, 9*(3), 149-154. doi: 10.1002/mrdd.10074

Mitchell, D. G., Nakic, M., Fridberg, D., Kamel, N., Pine, D. S., & Blair, R. J. (2007). The impact of processing load on emotion. *Neuroimage, 34*(3), 1299-1309. doi: 10.1016/j.neuroimage.2006.10.012

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ, 339*, b2535. doi: 10.1136/bmj.b2535

Morris, J. S., Friston, K. J., Buchel, C., Frith, C. D., Young, A. W., Calder, A. J., & Dolan, R. J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121 (Pt 1)*, 47-57.

Motzkin, J. C., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2011). Reduced Prefrontal Connectivity in Psychopathy. *Journal of Neuroscience, 31*(48), 17348-17357. doi: Doi 10.1523/Jneurosci.4215-11.2011

Nunn, K., Frampton, I., Fuglset, T. S., Torzsok-Sonnevend, M., & Lask, B. (2011). Anorexia nervosa and the insula. *Med Hypotheses, 76*(3), 353-357. doi: 10.1016/j.mehy.2010.10.038

O'Nions, E., Sebastian, C. L., McCrory, E., Chantiluke, K., Happe, F., & Viding, E. (2014). Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. *Dev Sci, 17*(5), 786-796. doi: 10.1111/desc.12167

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci, 1251*, E1-24. doi: 10.1111/j.1749-6632.2012.06751.x

Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I. M., Nimmo-Smith, I., Hagan, C. C., & Calder, A. J. (2012). Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. *PLoS One, 7*(11), e48789. doi: 10.1371/journal.pone.0048789

Passamonti, L., Fairchild, G., Goodyer, I. M., Hurford, G., Hagan, C. C., Rowe, J. B., & Calder, A. J. (2010). Neural abnormalities in early-onset and adolescence-onset conduct

disorder. *Arch Gen Psychiatry, 67*(7), 729-738. doi: 10.1001/archgenpsychiatry.2010.75

Pawliczek, C. M., Derntl, B., Kellermann, T., Gur, R. C., Schneider, F., & Habel, U. (2013). Anger under Control: Neural Correlates of Frustration as a Function of Trait Aggression. PLoS One, 8(10). doi: UNSP e78503

Pedersen, W., & Mastekaasa, A. (2011). Conduct disorder symptoms and subsequent pregnancy, child-birth and abortion: a population-based longitudinal study of adolescents. J Adolesc, 34(5), 1025-1033. doi: 10.1016/j.adolescence.2010.11.005

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348. doi: 10.1006/nimg.2002.1087

Phan, K. L., Wager, T. D., Taylor, S. F., & Liberzon, I. (2004). Functional neuroimaging studies of human emotions. *CNS Spectr, 9*(4), 258-266.

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Gore, J. C., Grillon, C., & Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nat Neurosci, 4*(4), 437-441. doi: 10.1038/86110

Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., . . . David, A. S. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature, 389*(6650), 495-498. doi: 10.1038/39051

Potegal, M. (2012). Temporal and frontal lobe initiation and regulation of the top-down escalation of anger and aggression. *Behav Brain Res, 231*(2), 386-395. doi: 10.1016/j.bbr.2011.10.049

Prehn, K., Schlagenhauf, F., Schulze, L., Berger, C., Vohs, K., Fleischer, M., . . . Herpertz, S. C. (2013). Neural correlates of risk taking in violent criminal offenders characterized by emotional hypo- and hyper-reactivity. *Soc Neurosci, 8*(2), 136-147. doi: 10.1080/17470919.2012.686923

Raemaekers, M., du Plessis, S., Ramsey, N. F., Weusten, J. M., & Vink, M. (2012). Test-retest variability underlying fMRI measurements. *Neuroimage, 60*(1), 717-727. doi: 10.1016/j.neuroimage.2011.11.061

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry, 57*(2), 119-127; discussion 128-119.

Raine, A., & Yang, Y. (2006). Neural foundations to moral reasoning and antisocial behavior. *Soc Cogn Affect Neurosci, 1*(3), 203-213. doi: 10.1093/scan/nsl033

Ravens-Sieberer, U., Wille, N., Erhart, M., Bettge, S., Wittchen, H. U., Rothenberger, A., . . . group, B. s. (2008). Prevalence of mental health problems among children and adolescents in Germany: results of the BELLA study within the National Health Interview and Examination Survey. *Eur Child Adolesc Psychiatry, 17 Suppl 1*, 22-33. doi: 10.1007/s00787-008-1003-2

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443-447. doi: 10.1126/science.1100301

Rowe, R., Maughan, B., Moran, P., Ford, T., Briskman, J., & Goodman, R. (2010). The role of callous and unemotional traits in the diagnosis of conduct disorder. *J Child Psychol Psychiatry, 51*(6), 688-695. doi: 10.1111/j.1469-7610.2009.02199.x

Rubia, K. (2011). "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. *Biol Psychiatry, 69*(12), e69-87. doi: 10.1016/j.biopsych.2010.09.023

Rubia, K., Halari, R., Smith, A. B., Mohammed, M., Scott, S., Giampietro, V., . . . Brammer, M. J. (2008). Dissociated functional brain abnormalities of inhibition in boys with pure conduct disorder and in boys with pure attention deficit hyperactivity disorder. *Am J Psychiatry, 165*(7), 889-897. doi: 10.1176/appi.ajp.2008.07071084

Rubia, K., Smith, A. B., Halari, R., Matsukura, F., Mohammad, M., Taylor, E., & Brammer, M. J. (2009). Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. *Am J Psychiatry, 166*(1), 83-94. doi: 10.1176/appi.ajp.2008.08020212

Sarkar, S., Craig, M. C., Catani, M., Dell'acqua, F., Fahy, T., Deeley, Q., & Murphy, D. G. (2013). Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. *Psychol Med, 43*(2), 401-411. doi: 10.1017/S003329171200116X

Schmidt-Wilcke, T., Rosengarth, K., Luerding, R., Bogdahn, U., & Greenlee, M. W. (2010). Distinct patterns of functional and structural neuroplasticity associated with learning Morse code. *Neuroimage, 51*(3), 1234-1241. doi: 10.1016/j.neuroimage.2010.03.042

Schwindt, G. C., & Black, S. E. (2009). Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. *Neuroimage, 45*(1), 181-190. doi: 10.1016/j.neuroimage.2008.11.024

Scott, S., Knapp, M., Henderson, J., & Maughan, B. (2001). Financial cost of social exclusion: follow up study of antisocial children into adulthood. *BMJ, 323*(7306), 191.

Sebastian, C. L., McCrory, E. J., Cecil, C. A., Lockwood, P. L., De Brito, S. A., Fontaine, N. M., & Viding, E. (2012). Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. *Arch Gen Psychiatry, 69*(8), 814-822. doi: 10.1001/archgenpsychiatry.2011.2070

Sebastian, C. L., McCrory, E. J., Dadds, M. R., Cecil, C. A., Lockwood, P. L., Hyde, Z. H., . . . Viding, E. (2014). Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits. *Psychol Med, 44*(1), 99-109. doi: 10.1017/S0033291713000482

Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T. F., Nugent, A. C., . . . McIntosh, A. M. (2012). Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. *Bipolar Disord, 14*(2), 135-145. doi: 10.1111/j.1399-5618.2012.01000.x

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci, 12*(3), 154-167. doi: 10.1038/nrn2994

Stadler, C., Sterzer, P., Schmeck, K., Krebs, A., Kleinschmidt, A., & Poustka, F. (2007). Reduced anterior cingulate activation in aggressive children and adolescents during affective stimulation: association with temperament traits. *J Psychiatr Res, 41*(5), 410-417. doi: 10.1016/j.jpsychires.2006.01.006

Stark, C. E., & Squire, L. R. (2001). When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proc Natl Acad Sci U S A, 98*(22), 12760-12766. doi: 10.1073/pnas.221462998

Sterzer, P., & Stadler, C. (2009). Neuroimaging of aggressive and violent behaviour in children and adolescents. *Front Behav Neurosci, 3*, 35. doi: 10.3389/neuro.08.035.2009

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., & Poustka, F. (2005). Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biol Psychiatry, 57*(1), 7-15. doi: 10.1016/j.biopsych.2004.10.008

Sterzer, P., Stadler, C., Poustka, F., & Kleinschmidt, A. (2007). A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage, 37*(1), 335-342. doi: 10.1016/j.neuroimage.2007.04.043

Stevens, M. C., & Haney-Caron, E. (2012). Comparison of brain volume abnormalities between ADHD and conduct disorder in adolescence. *J Psychiatry Neurosci, 37*(6), 389-398. doi: 10.1503/jpn.110148

Sui, J., Huster, R., Yu, Q., Segall, J. M., & Calhoun, V. D. (2014). Function-structure associations of the brain: evidence from multimodal connectivity and covariance studies. *Neuroimage, 102 Pt 1*, 11-23. doi: 10.1016/j.neuroimage.2013.09.044

Tang, Y., Jiang, W., Liao, J., Wang, W., & Luo, A. (2014). Identifying Individuals with Antisocial Personality Disorder Using Resting-State fMRI (vol 8, e60652, 2013). *PLoS One*, *9*(4). doi: ARTN e96962

Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum Brain Mapp, 33(1), 1-13. doi: 10.1002/hbm.21186

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, *15*(1), 273-289. doi: 10.1006/nimg.2001.0978

van Honk, J., & Schutter, D. J. (2006). Unmasking feigned sanity: a neurobiological model of emotion processing in primary psychopathy. *Cogn Neuropsychiatry*, *11*(3), 285-306. doi: 10.1080/13546800500233728

Viding, E., & McCrory, E. J. (2012). Genetic and neurocognitive contributions to the development of psychopathy. *Dev Psychopathol*, *24*(3), 969-983. doi: 10.1017/S095457941200048X

Viding, E., Seara-Cardoso, A., & McCrory, E. J. (2014). Antisocial and callous behaviour in children. *Curr Top Behav Neurosci*, *17*, 395-419. doi: 10.1007/7854_2013_266

Vloet, T. D., Konrad, K., Huebner, T., Herpertz, S., & Herpertz-Dahlmann, B. (2008). Structural and functional MRI- findings in children and adolescents with antisocial behavior. *Behav Sci Law*, *26*(1), 99-111. doi: 10.1002/bsl.794

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci*, *6*(7), 533-544. doi: 10.1038/nrn1704

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain*, *136*(Pt 6), 1692-1707. doi: 10.1093/brain/awt094

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron*, *30*(3), 829-841.

Wallace, G. L., White, S. F., Robustelli, B., Sinclair, S., Hwang, S., Martin, A., & Blair, R. J. (2014). Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. *J Am Acad Child Adolesc Psychiatry*, *53*(4), 456-465 e451. doi: 10.1016/j.jaac.2013.12.008

Waller, R., Gardner, F., Hyde, L. W., Shaw, D. S., Dishion, T. J., & Wilson, M. N. (2012). Do harsh and positive parenting predict parent reports of deceitful-callous behavior in early childhood? *J Child Psychol Psychiatry*, *53*(9), 946-953. doi: 10.1111/j.1469-7610.2012.02550.x

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci*, *18*(1), 411-418.

White, S. F., Pope, K., Sinclair, S., Fowler, K. A., Brislin, S. J., Williams, W. C., . . . Blair, R. J. (2013). Disrupted expected value and prediction error signaling in youths with disruptive behavior disorders during a passive avoidance task. *Am J Psychiatry*, *170*(3), 315-323. doi: 10.1176/appi.ajp.2012.12060840

White, S. F., Williams, W. C., Brislin, S. J., Sinclair, S., Blair, K. S., Fowler, K. A., . . . Blair, R. J. (2012). Reduced activity within the dorsal endogenous orienting of attention network to fearful expressions in youth with disruptive behavior disorders and psychopathic traits. *Dev Psychopathol*, *24*(3), 1105-1116. doi: 10.1017/S0954579412000569

Wu, D. X., Zhao, Y., Liao, J., Yin, H. F., & Wang, W. (2011). White matter abnormalities in young males with antisocial personality disorder Evidence from voxel-based morphometry-diffeomorphic anatomical registration using exponentiated lie algebra analysis. *Neural Regeneration Research*, *6*(25), 1965-1970. doi: DOI 10.3969/j.issn.1673-5374.2011.25.008

Yeh, P. H., Zhu, H. T., Nicoletti, M. A., Miles, G. A., Baloch, H., Hatch, J. P., . . . Scares, J. C. (2009). Different Regional Patterns of Gray Matter Volume and Cortical Thickness between Adolescent Bipolar and Major Depressive Disorders. *Biol Psychiatry*, *65*(8), 241s-241s.

Zald, D. H. (2007). Orbital versus dorsolateral prefrontal cortex: anatomical insights into content versus process differentiation models of the prefrontal cortex. *Ann N Y Acad Sci*, *1121*, 395-406. doi: 10.1196/annals.1401.012

Zhang, J., Gao, J., Shi, H., Huang, B., Wang, X., Situ, W., . . . Yao, S. (2014). Sex differences of uncinate fasciculus structural connectivity in individuals with conduct disorder. *Biomed Res Int*, *2014*, 673165. doi: 10.1155/2014/673165

Zhang, J., Zhu, X., Wang, X., Gao, J., Shi, H., Huang, B., . . . Yao, S. (2014). Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. *J Am Acad Child Adolesc Psychiatry*, *53*(4), 466-475 e461. doi: 10.1016/j.jaac.2013.12.015

Supplement

Table S1. Checklist for PRISMA items.

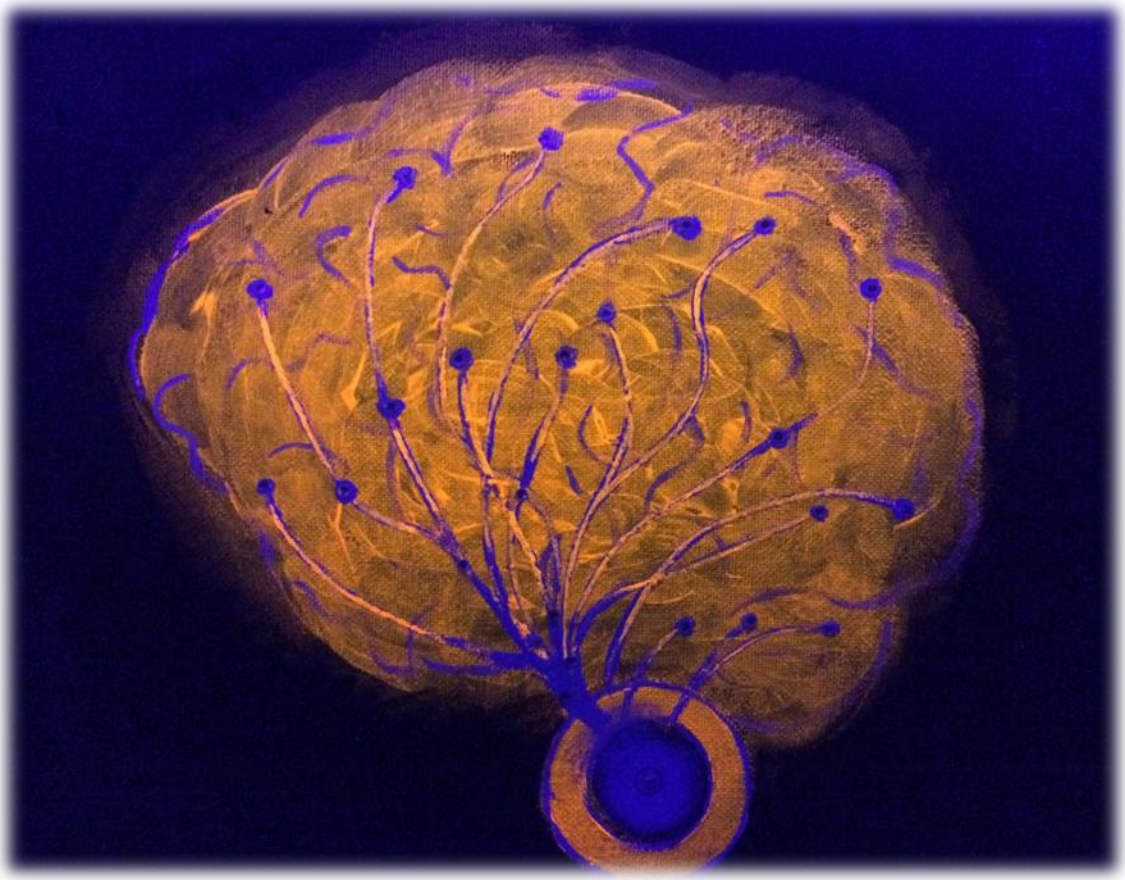
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9, 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-8 Table S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8 Table1+ 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-8 Table1+ 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Chapter 3. Callous-Unemotional Traits and Brain Structure: Sex-Specific Effects in Typically-Developing Youths



Nora M Raschle[1], **Willeke M Menks[1]**, Lynn V Fehlbaum[1], Martin Steppan[1], Areti Smaragdi[2], Karen Gonzalez[2], Jack Rogers[3], Roberta Clanton[3], Gregor Kohls[4], Anne Martinelli[6], Anka Bernhard[6], Graeme Fairchild[2], Stephane de Brito[3], Kerstin Konrad[4,5], Beate Herpertz-Dahlmann[4], Christine M Freitag[6], & Christina Stadler[1]

[1] Department of Child and Adolescent Psychiatry, University of Basel, Psychiatric University Hospital, Basel, Switzerland, [2] Academic Unit of Psychology, University of Southampton, Southampton, England, [3] School of Psychology, University of Birmingham, Birmingham, England [4] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of the RWTH Aachen, Germany, [5] JARA-Brain Institute II, Molecular Neuroscience and Neuroimaging, RWTH Aachen & Research Centre Juelich, Germany, [6] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany

Submitted: Neuroimage Clinical (under review)

Abstract

Aggressive and antisocial behaviors are common reasons for referral to youth mental health services, and result in adverse psychological, clinical and societal consequences. However, aggressive and antisocial youths are heterogeneous with respect to etiology, behavior, treatment responsiveness and neurobiology. Callous-unemotional traits differentiate meaningful subgroups, and callousness has been linked to neuroanatomical correlates in clinical samples. Nevertheless, it is unknown whether callous-unemotional traits are associated with neuroanatomical correlates within normative populations without clinical forms of aggression. Here we investigated the relationship between callous-unemotional traits and gray matter volume using voxel-based morphometry in typically-developing boys and girls (N=189). Whole-brain multiple regression analyses controlling for site, total intracranial volume and age were conducted in the whole sample and in boys/girls individually. Results revealed that callous-unemotional traits were positively correlated with bilateral anterior insula volume in boys, but not girls. Insula volume explained 19% of the variance in callous-unemotional traits for boys. Our results demonstrate that callous-unemotional traits have a neurobiological basis beyond psychiatric samples. This association was sex-specific, underlining the importance to consider sex in future research designs. Longitudinal studies will need to determine whether these results persist over time and whether neural correlates of callous-unemotional traits are predictive of future psychiatric vulnerability.

Introduction

Aggressive and antisocial behavior during childhood and adolescence are amongst the most common reasons for a childhood referral to mental health services (Kazdin et al., 2006). While the prevalence of aggressive and antisocial behavior is higher in boys than girls, for both genders adverse psychological, clinical and societal consequences may result (Kessler et al., 2012). Clinically, severe aggression and antisocial behaviors in youths are subsumed under the term disruptive behavior disorders (DBD), which includes oppositional defiant and conduct disorder (American Psychiatric Association, 2013). Notably, children and adolescents with DBD form a very heterogeneous group in regard to etiology, associated behavioral symptoms, developmental trajectories, future risk for impairment or response to treatment (Moffitt et al., 2008). Thus devising a meaningful approach to subtyping antisocial behavior has been of long-lasting clinical interest (Frick et al., 2014). Various procedures have been adapted, including the distinction between proactive and reactive aggression, childhood- or adolescent-onset conduct problems, socialized versus under-socialized youths or high versus low callous-unemotional (CU) traits (see also Diagnostic and Statistical Manual of Mental Disorders (DSM-III to DSM-5) (Kruesi et al., 2004; Frick et al., 2006; Fairchild et al., 2011; American Psychiatric Association, 2013)). Overall, behavioral, genetic and neurobiological data indicate the potential of CU-traits in explaining heterogeneity within antisocial populations (Frick et al., 2006; Bezdjian et al., 2011; Rogers and De Brito, 2016). This was likewise recognized within the latest version of the DSM-5 by an additional specifier to the diagnosis of conduct disorder termed 'Limited Prosocial Emotions' (American Psychiatric Association, 2013). However, to date there is only little evidence focusing on the neurobiological correlates of CU-traits in typically-developing youths and no study has yet focused on sex-specific effects by studying males and females individually.

Descriptively, CU-traits are defined by lack of empathy, reduced guilt or limited prosocial emotions (Blair, 2013; Fairchild et al., 2013). In DBDs high CU-traits are indicative for the development of particularly severe, persistent and treatment-resistant forms of aggression (Frick and White, 2008). While CU-traits have most commonly been studied in clinical populations that display antisocial behavior (i.e. DBD) there is increasing evidence for the relevance of CU-traits in community samples without clinical levels of antisocial behavior (Frick et al., 2006; Kumsta et al., 2012; Viding and McCrory, 2012). Children who experienced early deprivation have for example been shown to display high levels of CU-traits in the absence of antisocial behavior. CU-traits in youths without DBD have again been related to antisocial behavior (subclinical levels), impairments affecting peer relationships, prosocial behavior, hyperactivity increased risk-taking and reduced emotional responsiveness in some studies (Frick et al., 2003; Barker et al., 2011; Kumsta et al., 2012; Viding and McCrory, 2012). Emotion processing deficits in high CU-community youths are not consistently reported though and it

has been suggested that CU individuals may further be subtyped according to conduct problems and/or anxiety levels (Fanti et al., 2013). CU-traits in aggressive and non-aggressive youths are likewise highly heritable and may carry independent diagnostic value (Frick et al., 2003; Larsson et al., 2008; Rowe et al., 2010; Barker et al., 2011; Kumsta et al., 2012; Viding and McCrory, 2012).

Neuroimaging studies in DBDs have led to varying findings with respect to the direction and precise location of the observed neuronal alterations (Blair, 2013; Raschle et al., 2015; Rogers and De Brito, 2016). However, most commonly evidence has linked atypical brain structure and function to limbic and prefrontal regions (Kruesi et al., 2004; Fahim et al., 2011; Fairchild et al., 2011; Rogers and De Brito, 2016). Considering variations amongst DBDs has led to the identification of meaningful subgroups within DBD adolescents (e.g. differences between high/low CU-traits). Functional neuroimaging evidence revealed that while high CU-traits were negatively associated with activations of the threat or limbic system (insula, amygdala, caudate, anterior cingulate, and ventromedial prefrontal cortex) (Blair, 2013, 2015), low levels of CU-traits were positively linked to activations of the same areas (Viding et al., 2012; Blair, 2013). Notably, these findings have not been consistently replicated or even show an opposite pattern (White et al., 2012; Lozier et al., 2014; White et al., 2016). Furthermore, some studies have revealed that the degree of functional alteration in DBD may reflect the symptom severity of the associated disorder (Marsh et al., 2008), while others were not able to replicate this (Finger et al., 2012).

Investigating the unique associations between CU-traits in DBD youths and brain structure has generated exciting preliminary findings, but further evaluation is still needed (Blair, 2013; Cohn et al., 2016). Overall, areas of the limbic and threat system are again most commonly linked to variability in CU-traits. Elevated CU-traits have been linked to both increases and decreases in gray matter volume and concentration within orbitofrontal, anterior cingulate, para-/hippocampal and temporal cortices (De Brito et al., 2009; Fairchild et al., 2013; Cope et al., 2014; Wallace et al., 2014; Raschle et al., 2015; Cohn et al., 2016; Rogers and De Brito, 2016). Within the amygdala volume-decreases in DBD are linked to variations in CU-traits by some (Sterzer et al., 2007; Huebner et al., 2008; Fairchild et al., 2013; Cohn et al., 2016), but not all researchers (De Brito et al., 2009; Dalwani et al., 2011). In adulthood, psychopathic traits, subsuming callous-unemotional traits and impulsive antisocial tendencies, have shown to be negatively associated with gray matter volume in paralimbic and limbic areas as demonstrated in a large sample of incarcerated adults (N=191) (Ermer et al., 2013). Finally, a meta-regression study found a negative correlation between CU-traits and putamen gray matter volume in DBD youths (Rogers and De Brito, 2016). Overall, variations in the direction and precise location of altered regions in studies to date may be due to the use of different analysis tools and

strategies, as well as heterogeneity (e.g. differences in demographic and clinical features) of the groups studied.

To date, investigations on CU-traits in DBD have been limited by several factors: (1) By missing to study the neurobiological correlates of CU-traits in typically-developing youths, it remains open whether effects previously attributed to CU-traits were actually driven by the presence of DBD, or whether CU-traits only modulate brain structure within DBD populations; (2) While epidemiologic as well as longitudinal research indicate gender-specific developmental trajectories for neuropsychiatric disorders (Moffitt et al., 2008; Giedd and Rapoport, 2010), most studies on CU-traits have focused solely on males, limiting the generalizability of these findings to females; and (3) Contradictory findings may be due to the group classification employed or the questionnaires chosen to assess CU-traits (Essau et al., 2006; Viding and McCrory, 2012; Kimonis et al., 2016).
Therefore, the current study aimed at bridging this gap in knowledge by investigating CU-traits in typically-developing boys and girls without DBD-symptoms using whole brain multiple regression analyses. By studying typically-developing adolescents we aimed at characterizing the individual differences in CU-traits associated with brain structure independent of DBDs. Secondly, we aimed to test whether variations in CU-traits and brain structure are sex-specific for males and females. Finally, we aimed to implement a comprehensive measure of CU-traits by testing a composite score based on two sources of information for CU-traits variability (self and other taring). To date, limited neuronal evidence in typically-developing non-DBD youths hinders a concise hypothesis. However, based on evidence in DBD and community samples with varying degrees of aggression, we expect correlations between CU-traits and brain structure in typically-developing youths within limbic and prefrontal brain regions including amygdala, insula and prefrontal cortex.

Method

Participants

We recruited 223 typically-developing adolescents (9-18 years) within the average IQ range. All adolescents were tested in the context of an ongoing European multi-center study investigating female conduct disorder (FemNAT-CD) and were explicitly screened to be free of any psychiatric disorder, including DBDs. Participants underwent standardized clinical interviews and psychometric testing and took part in a neuroimaging session. On average, the two sessions took place within 8.2±7.7 weeks of each other. Data were acquired at five different sites, including the Universities of Frankfurt #01 and Aachen #02 in Germany; the Psychiatric University Hospital in Basel, Switzerland #05; and the Universities of Birmingham #07 and Southampton #04, England (only site numbers will consequently

be reported within the text). All participants and their caretakers provided verbal and written informed consent to take part in the study, as approved by all local ethics committees.

Clinical and psychometric testing

Based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL (Kaufman et al., 1997)) diagnostic interview, we ascertained that none of the youths met a current clinical diagnosis or a past history of DBDs according to DSM-5 (American Psychiatric Association, 2013). Behavioral and emotional problems within the past 6 months were assessed using the Child Behavior Checklist (CBCL: 120 items, using a three-point Likert scale (Achenbach, 1991)). Since we explicitly aimed to study CU-traits in non-aggressive individuals, participants scoring T≥70 within the aggression and/or the delinquency subscales of the CBCL were excluded from this study (see Supplement 1). IQ was assessed using the short-form of the Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler, 1999)) at English speaking sites (#04, #07) or the German version of the Wechsler Intelligence Scale for Children (WISC-IV/WAIS-IV (Petermann and Wechsler, 2008)) for sites #01, #02 and #05. All t- and standard scores were first z-transformed prior to any analysis.

CU-traits were measured using parent ratings of the Inventory of Callous-Unemotional traits (ICU (Essau et al., 2006)) and self-ratings of the Youth Psychopathic traits Inventory (YPI (Andershed et al., 2007)). The ICU (a 24-item parental report) has three subscales: callousness, uncaring, and unemotional, as well as a total score. Across previous samples, reliability reports for the ICU range from acceptable to good (Cronbach alpha range: 0.77-0.89) (Essau et al., 2006). The YPI (a 50-item self-report) comprises ten subscales, which generate the following three dimensions: callous-unemotional, grandiose-manipulative and impulsive-irresponsible (Andershed et al., 2007). Research based reliability scores of the YPI dimensions range from moderate to good (Cronbach's alphas of 0.36-0.71). While there is a validated short form of the YPI available for children 9-12 years, we used the original YPI for all ages because these versions differ only minimally and only the original YPI is available in all languages represented here (Andershed et al., 2007; van Baardewijk et al., 2008). A Cronbach's alpha for the ICU total of 0.79 (confidence interval: 0.74-0.83) and a Cronbach's alpha for the YPI callous-unemotional dimension of 0.79 (confidence interval: 0.74-0.83) was calculated in the present sample. We based CU-traits on multiple sources of information in order to maximize reliability, which is in line with suggestions by the American Psychiatric Association (American Psychiatric Association, 2013). However, it is noteworthy that we computed a composite score based on parent and child-ratings from two different instruments. Specifically, mean scores representing the YPI callous-unemotional dimension and the ICU total were z-transformed and a new composite score for 'CU-traits' was built by calculating the mean of the two resulting z-scores. The usefulness of this

new composite score was verified by: (1) Running a reliability analysis including all respective items (Cronbach's alpha of 0.83; CI: 0.79-0.87); (2) Investigating brain structure and correlations between ICU total, YPI callous-unemotional scale and composite CU-traits score; and (3) Testing significant differences between the old and new Cronbach alpha's (see Supplement 2). The new composite score showed significantly higher internal reliability as compared to the ICU total or YPI callous-unemotional dimension. The composite scores were normally distributed and showed sufficient variance to justify a dimensional approach (Supplement 3).

Table 1. *Group characteristics – psychometrics and clinical testing.*

	Girls (N=108) *Mean (±SD)*	**Boys** (N=81) *Mean (±SD)*	***p*-value** *Two-Sample T*	
Age in years	13.9 (±2.9)	13.2 (±2.5)	0.850	
IQ	105.5 (±10.4)	106.6 (±11.4)	0.486	
Psychopathic Traits (YPI)				
Psychopathy (YPI total)	87.6 (±17.0)	96.1 (±18.0)	0.001	***
Grandiose, Manipulative	32.0 (±8.4)	35.1 (±9.4)	0.020	*
Callous, Unemotional	25.3 (±5.7)	29.4 (±5.8)	<0.001	***
Impulsive, Irresponsible	30.2 (±6.1)	31.7 (±6.5)	0.115	
CU-Traits (ICU)				
ICU total	15.3 (±7.2)	18.3 (±7.5)	0.006	**
Uncaring	7.2 (±4.1)	8.6 (±4.2)	0.024	*
Unemotional	4.2 (±2.5)	5.1(±2.6)	0.019	*
Callousness	3.9 (±3.0)	4.6 (±2.5)	0.080	
Callous-unemotional traits				
Composite score	-0.2 (±0.8)	0.3 (±0.7)	0.001	***
CBCL				
Anxiety/Depression	55.5 (±6.2)	54.1 (±5.9)	0.121	
Attention Problems	53.4 (±4.9)	53.1 (±5.0)	0.677	
Delinquency	52.3 (±5.1)	52.3 (±3.9)	0.999	
Aggression	52.7 (±4.4)	51.7 (±5.4)	0.160	
Internal Problems	49.7 (±10.0)	49.7 (±10.0)	0.868	
External Problems	47.7 (±8.5)	46.6 (±8.1)	0.385	
Total Problems	48.4 (±9.6)	47.4 (±9.3)	0.472	

***significant at $p \leq 0.001$; **significant at $p \leq 0.01$; *significant at $p \leq 0.05$

IQ= Intelligence quotient (Z-scores); YPI= Youth Psychopathic Traits Inventory (mean scores); ICU= Inventory of Callous-Unemotional traits (mean scores); CBCL= Child Behavior Checklist (T-scores).

ICU and YPI as well as the new composite scores are presented in Table 1. Overall, scores observed in the present sample are comparable to those reported in community samples or control groups (Essau et al., 2006; Fairchild et al., 2013). Boys scored significantly higher than girls on several subscales of the YPI or ICU as analyzed using SPSSv23 (IBM Corp., Armonk, N.Y., USA).

Structural image acquisition

Participants completed between one and three functional neuroimaging tasks and/or diffusion tensor imaging in addition to structural T1-weighted MPRAGE data acquisition on Siemens 3T (#01/#04: Trio; #02/#05: Prisma) or Philips 3T (#07: Achieva) scanners. Each site underwent a site qualification procedure prior to starting data collection in which a radiological (ACR) phantom and healthy volunteers were scanned using multiple sequences (Chen et al., 2004). The resulting data were reviewed by an MR physicist, and scanning parameters were adjusted until the protocols were comparable (see acquisition parameters in Supplement 4).

Voxel-based morphometry (VBM) analysis and statistics

We utilized the computational anatomy toolbox (CAT12; http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) as implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and executed in MATLAB (Mathworks, Natick, MA). To account for the young age of the participants, we employed an adapted VBM-workflow that implemented customized tissue probability maps (TPM) as created through the template-o-matic toolbox (TOM8; https://irc.cchmc.org/software/tom/downloads.php) and a customized DARTEL template based on the gray and white matter tissue segments of all participants. Analysis steps included:

Quality control

Prior to preprocessing, all images passed a first visual quality check targeting motion, gross anatomical artifacts and assuring whole-brain coverage. After preprocessing, additional information about data-quality (resolution, noise and bias) was provided by CAT12. We assured that all data had a weighted average quality of B or higher, representing very good image quality (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). Finally, prior to statistical analysis we conducted another quality assessment by displaying the sample homogeneity using standard deviations through the CAT12 toolbox. Of the 223 scans reviewed, 14 had to be excluded due to motion artifacts and 2 individuals were excluded from the analysis due to significantly enlarged ventricles, resulting in N=207.

Customized tissue probability maps (TPMs) and Dartel Template creation

Customized TPMs were created using an average approach within TOM8 including vectors for age and gender, representing each of the 207 participants with useable T1 data based on the previous step (Wilke et al., 2008). All images were segmented into gray matter, white matter and cerebrospinal fluid (whereas customized TPMs were inputted during affine registration) and the affine registered tissue segments were used to construct a customized DARTEL template representing the entire study sample. Finally, the template was normalized to MNI and registered to MNI (ICBM) space.

Preprocessing and calculation of total intracranial volume

(TIV). Preprocessing was achieved through segmentation of all data using the custom template/TPMs and a Gaussian smoothing kernel of 8mm. Total intracranial volume (TIV) was calculated for each participant through CAT12. Since we were interested in group-based variations in the absolute tissue (gray matter volume), TIV was consequently incorporated in the statistical analysis to account for differences in brain size.

Statistical Analysis

Prior to analysis, we excluded two participants with high scores on the aggression and delinquency subscales of the CBCL (≥70; see methods section for further explanation). Additionally, 16 individuals missed either an YPI or ICU subscale and were thus excluded. The total N entering statistical analysis was therefore 189 participants (108 female, 81 male). The DARTEL-normalized gray matter volumes entered multiple regression models linking CU-traits with brain structure. Scanning site, age and TIV were added as covariates (and gender for the whole sample) and statistics were conducted for gray matter volume only. Results are reported at a whole brain cluster-level FWE correction for multiple comparisons of $p<0.05$.

Results

Voxel-based morphometry results

In line with previous findings, girls and boys significantly differed in total intracranial volume (TIV: [girls/boys] = [1414.4±112.9 / 1580.6±126.2]), white (WM: [girls/boys] = [470.3±49.8 / 529.3±48.5]) and gray matter volume (GM: [girls/boys] = [702.3±57.8 / 790.1±71.3]; all $p<0.001$). Thus, along with age and site, TIV was included as a covariate in all analyses.

Multiple regression analysis across the whole sample

Across all girls and boys, there were no significant positive or negative correlations between CU-traits and gray matter volume. To exclude the influence of unequal group sizes between boys and girls, we

employed a stratified random sampling approach and created two age, gender and site-controlled groups of equal size (81:81). The analysis was then repeated, resulting in similar outcome.

Multiple regression analysis in girls

Within females there were no significant positive or negative relationships between CU-traits and gray matter volume.

Multiple regression analysis in boys

For boys, CU-traits were significantly positively correlated with gray matter volume in bilateral anterior insular cortex ($p<0.05$, cluster level corrected; see Table 2 and Figure 1).

Table 2. *Montreal Neurological Institute neuroanatomical coordinates, cluster size and Z-scores (Zo) representing the peak coordinates for significant positive associations between callous-unemotional traits and gray matter volume in typically-developing boys, but not girls.*

	K	**(Zo)**	**x**	**y**	**z**
Boys (N=81)					
Left anterior insula, inferior frontal cortex	1069	4.16	-28	22	3
Right anterior insula, putamen, inferior frontal cortex	958	4.51	30	21	0
Girls (N=108)					
No significant correlations	-	-	-	-	-

Post-hoc region of interest analyses

Post-hoc region of interest and partial correlation analyses were conducted using the marsbar toolbox (http://marsbar.sourceforge.net/) to extract gray matter volume and SPSS-23 to run statistical analyses. Bilateral anterior insula regions of interest were created using 5mm-radius spheres around the MNI coordinates (x=-32, y=22, z=-2) and (x=36, y=22, z=-6) as derived from a coordinate-based meta-analysis (Rottschy et al., 2012). The averaged mean gray matter volume indices for these regions of interest were extracted and scaled by each individual's TIV, in order to avoid multicollinearity and adjust for unmodulated scores. Resulting values were used to address two post-hoc aims, namely: (1) Investigate the specific CU-traits-bilateral insula associations for boys and girls separately; and (2) Investigate the amount of variance in CU-traits accounted for by bilateral insula volume variations in boys, as was done previously in adult studies (Ermer et al., 2013; Cope et al., 2014). Post-hoc results revealed significant positive correlations between left (Figure 1d) and right (e) insula volumes and CU-traits in males, but not girls. In girls, a trend even indicates an opposite (negative) association between insular volume and CU-traits. Finally, the scaled mean gray matter bilateral insula volumes

were entered as predictors into a multiple regression model with CU-traits scores as the dependent variable. The resulting model for boys, excluding the influence of the covariate, reached significance ($p<0.001$) and indicated that variations in bilateral anterior volume explained 19.4% of the variance in CU- traits.

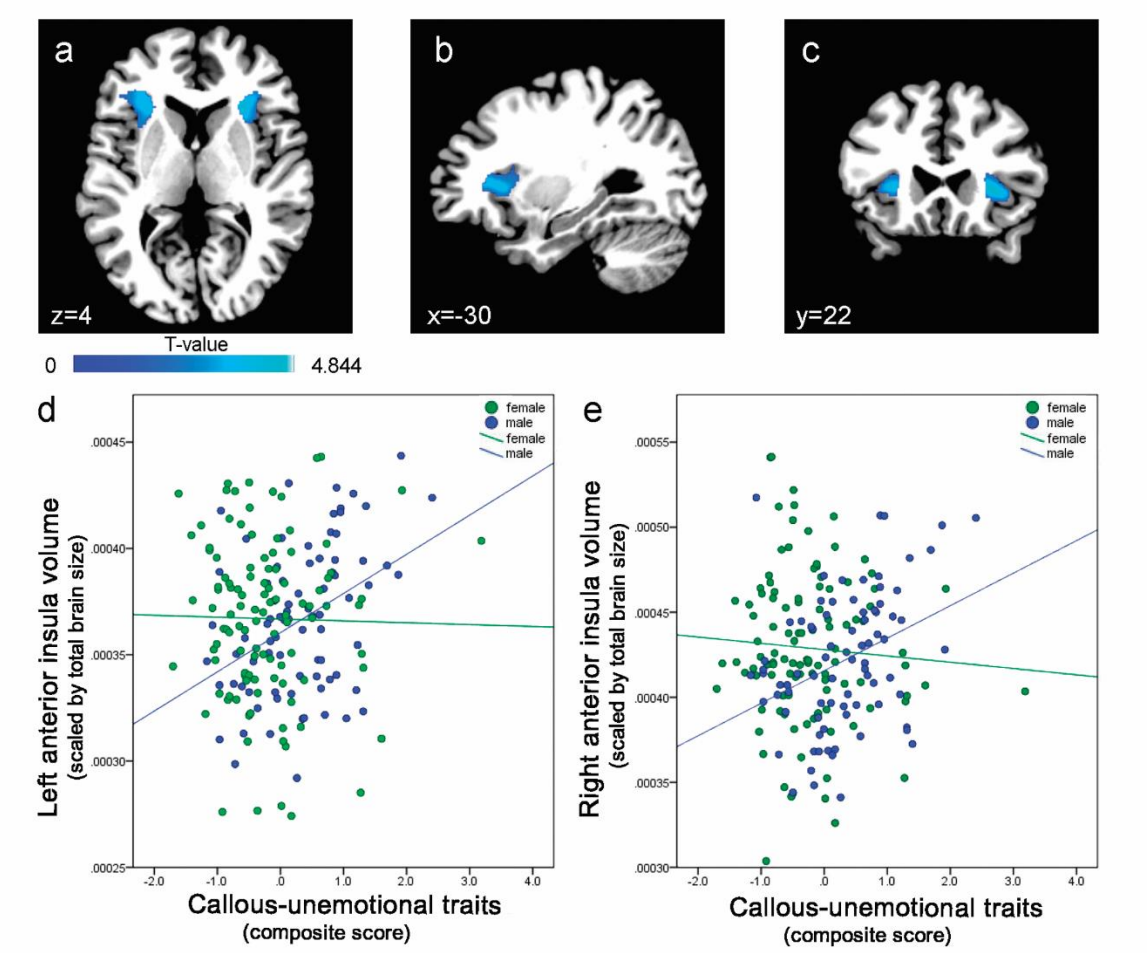


Figure 1. *Statistical parametric maps showing a significant positive correlation between callous-unemotional traits and bilateral anterior insula volume in boys (in blue; displayed a=axial, b=sagittal, c=coronal views using the Multi-image Analysis GUI, available at http://ric.uthscsa.edu/mango/mango.html; p<0.05, FWE cluster level corrected) and correlations between callous-unemotional traits and gray matter volume in the left (d) and right (e) anterior insula regions of interest for boys (blue) and girls (green).*

Discussion

In a sample of typically-developing community boys and girls, we show for the first time that callous-unemotional (CU) traits correlate with brain volume of the anterior insula, independent of disruptive behavior disorders (DBDs). This association was sex-specific, with CU-traits showing a positive correlation with bilateral anterior insula volume in boys only. Overall, anterior insula volume

accounted for 19.1% of the variance in CU-traits amongst boys; this is comparable to the informative value of structural associations in adult psychopathy (Ermer et al., 2013; Cope et al., 2014). The present study generated a composite CU-score based on multiple sources of information. In line with others before and according to psychometric evaluations, we consider this a potential strength (Essau et al., 2006; American Psychiatric Association, 2013). However, through the use of a newly created score, comparability with previous findings may be impacted.

Callous-unemotional traits and brain structure in boys

Our analysis identified the bilateral anterior insula as a structural correlate of CU-traits in typically-developing boys, but not girls. Previous studies point towards a functionally plausible parcellation of the insula into at least three distinct sub-regions, subserving chemosensory and socioemotional processing (ventro-anterior), higher cognitive processing (dorso-anterior) and pain or sensorimotor processing (posterior) (Chang et al., 2013). The here observed correlation between CU-traits and brain structure was strongest in bilateral anterior insula extending to the inferior frontal gyrus. This area has consistently been linked to emotion processing and empathy tasks and has further been associated to cognitive control mechanisms (Phan et al., 2002; Fan et al., 2011; Sundermann and Pfleiderer, 2012).

Past research has revealed structural and functional alterations in individuals with DBDs (Sterzer et al., 2007; Fahim et al., 2011; White et al., 2012; Blair, 2013; Raschle et al., 2015; Rogers and De Brito, 2016; White et al., 2016). Thereby, empathic responding, emotional learning and decision-making are for instance all linked to the anterior insula and impacted in DBD (White et al., 2012; Blair, 2013; White et al., 2016). However, while some DBD studies identified gray matter increases in insular cortex (De Brito et al., 2009), others found reduced anterior insula volume, cortical thinning or folding deficits (Fahim et al., 2011; Hyatt et al., 2012; Fairchild et al., 2013). Additionally, DBD-related structural and functional insula alterations were shown to correlate with CU-traits in some (Blair, 2013; Frick et al., 2014), but not all previous work (White et al., 2012; White et al., 2016). In line with a previous study in DBD boys (De Brito et al., 2009), it could be hypothesized that differences in reports of increased or decreased gray matter in anterior insula in community boys with heightened CU-traits, may reflect maturational effects (i.e. delayed maturation of this region in males). Reports of an inverted U-shaped development for the insular cortex and differences in rates of cortical maturation between girls and boys of about 1-3 years supports this hypothesis(Giedd and Rapoport, 2010; Viding et al., 2012). Notably, our findings diverge from those of Sterzer and colleagues (2007), who identified decreases in bilateral anterior insula volume in DBD and a negative association to empathy scores. Within this line, our findings may appear surprising given several previous studies in DBD suggested a negative association between CU-traits and brain structure (Rogers and De Brito, 2016). This could suggest that the association between CU-traits and brain structures differs in

typically-developing youths and those with DBDs. However, differences may also be based on group selection (number of participants, clinical criteria) or construct employed (e.g. measuring CU-traits versus empathy more specifically).

CU-traits and brain structure in girls: gender differences?

Unlike previous clinical findings across boys and girls, we found no significant relationships between CU-traits and gray matter volume in a large sample of girls (N=108). Sexual dimorphism in insula structure and function, as well as sex-difference in gray matter volume trajectories may explain this (Lenroot et al., 2007; Giedd and Rapoport, 2010). Studies on the impact of CU-traits in DBD populations have almost exclusively focused on males, not allowing a validation of the constructs employed in females (Rogstad and Rogers, 2008). It is a matter of ongoing debate whether differences in CU-traits between boys and girls represent true sex differences or whether the instruments, which have predominantly been developed in male samples, do not likewise apply to females (Rogstad and Rogers, 2008). Nevertheless, we suggest that the sex-specific effects identified here do not result from measurement issues since the variance in CU-traits within each group is similar. While the consideration of sex-differences in brain imaging studies is a controversial issue, bearing in mind the implications of incorrect conclusions (Cosgrove et al., 2007), future studies should include both genders to enhance our understanding of sex differences and apply this information to study neurodevelopmental disorders (i.e. DBDs) that are more prevalent in males. Ultimately, longitudinal studies are needed in order to answer the question whether the observed neuroanatomical differences are of developmental (e.g. through a time-specific shift in the cortical growth curve of boys and girls) or fundamental nature (e.g. present across development).

Limitations

This study had several limitations that should be considered when interpreting the results. First, previous evidence suggests that volumetric brain alterations derive from changes in both cortical thickness and surface area (Panizzon et al., 2009). Investigating gray matter volume indices in relation to CU-traits cannot indicate which factor(s) have uniquely contributed to the results. For example, in conduct disorder cortical thickness and folding deficits were demonstrated to localize to different (posterior versus anterior) brain structures (Hyatt et al., 2012). Secondly, while we excluded adolescents scoring high on aggression or delinquency, we cannot eliminate the possibility that subclinical variations of these measures have contributed to the present findings. Third, future studies will need to assess more complex developmental questions, which the present sample could not answer (e.g. stability of the observed associations across age). And finally, while we employed a

dimensional analysis approach in each sex individually, it is still possible that extreme scores in one group have driven the effects observed.

CU-traits as a dimensional construct

We here demonstrate the usefulness of CU-traits as a potential neurobiological specifier in adolescent boys beyond clinical populations. More specifically, CU-traits showed associations with brain structure in typically-developing boys, without diagnosable levels of antisocial behavior. Our findings thus support a dimensional approach characterizing mental health as implemented within the Research Domain Criteria framework (Blair, 2015). Moving away from categorical classifications, variations in traits are used to describe individual phenotypes. Frameworks assessing such traits must be able to differentiate not only across the clinical spectrum, but also within samples of typically-developing youths. While our findings in typically-developing boys complement findings in DBDs linking the anterior insula to CU-traits (De Brito et al., 2009; Fairchild et al., 2013), the direction of findings across studies varies (i.e. increases/decreases of gray matter volume). This may indicate a different relationship between CU-traits and brain structures in DBD and typically-developing youths. Within these lines, a recent voxel-based morphometry study in at-risk adolescents demonstrated a positive correlation between CU-traits and insular cortex volume in individuals with low, but not high, CD symptoms (Cohn et al., 2016). Future studies will need to examine the relationship between CU-traits and brain structure, not only in typically-developing individuals, strictly at-risk children or those with DBDs, but across the whole spectrum. Large-scale neuroimaging studies including both genders may likewise explore interaction effects of age, gender and CU-traits. Finally, it remains to be investigated whether the structural variations accompanying CU-traits identified here predict future psychiatric illness or psychosocial maladjustment (Viding and McCrory, 2012).

References

Achenbach, T. M. (1991) Manual for the Child Behavior Checklist/4-18 and 1991 Profile, Department of Psychiatry, University of Vermont.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

Andershed, H., Hodgins, S. & Tengstrom, A. (2007) Convergent validity of the Youth Psychopathic Traits Inventory (YPI): association with the Psychopathy Checklist: Youth Version (PCL:YV), Assessment, 14, p. 144-154.

Barker, E. D., Oliver, B. R., Viding, E., Salekin, R. T. & Maughan, B. (2011) The impact of prenatal maternal risk, fearless temperament and early parenting on adolescent callous-unemotional traits: a 14-year longitudinal investigation, J Child Psychol Psychiatry, 52, p. 878-888.

Bezdjian, S., Raine, A., Baker, L. A. & Lynam, D. R. (2011) Psychopathic personality in children: genetic and environmental contributions, Psychol Med, 41, p. 589-600.

Blair, R. J. (2013) The neurobiology of psychopathic traits in youths, Nat Rev Neurosci, 14, p. 786-799.

Blair, R. J. (2015) Psychopathic traits from an RDoC perspective, Curr Opin Neurobiol, 30, p. 79-84.

Chang, L. J., Yarkoni, T., Khaw, M. W. & Sanfey, A. G. (2013) Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference, Cereb Cortex, 23, p. 739-749.

Chen, C. C., Wan, Y. L., Wai, Y. Y. & Liu, H. L. (2004) Quality assurance of clinical MRI scanners using ACR MRI phantom: Preliminary results, Journal of Digital Imaging, 17, p. 279-284.

Cohn, M. D., Viding, E., McCrory, E., Pape, L., van den Brink, W., Doreleijers, T. A., et al. (2016) Regional grey matter volume and concentration in at-risk adolescents: Untangling associations with callous-unemotional traits and conduct disorder symptoms, Psychiatry Res, 254, p. 180-187.

Cope, L. M., Ermer, E., Nyalakanti, P. K., Calhoun, V. D. & Kiehl, K. A. (2014) Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits, J Abnorm Child Psychol, 42, p. 659-668.

Cosgrove, K. P., Mazure, C. M. & Staley, J. K. (2007) Evolving knowledge of sex differences in brain structure, function, and chemistry, Biol Psychiatry, 62, p. 847-855.

Dalwani, M., Sakai, J. T., Mikulich-Gilbertson, S. K., Tanabe, J., Raymond, K., McWilliams, S. K., et al. (2011) Reduced cortical gray matter volume in male adolescents with substance and conduct problems, Drug Alcohol Depend, 118, p. 295-305.

De Brito, S. A., Mechelli, A., Wilke, M., Laurens, K. R., Jones, A. P., Barker, G. J., et al. (2009) Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits, Brain, 132, p. 843-852.

Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D. & Kiehl, K. A. (2013) Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits, J Am Acad Child Adolesc Psychiatry, 52, p. 94-103 e103.

Essau, C. A., Sasagawa, S. & Frick, P. J. (2006) Callous-unemotional traits in a community sample of adolescents, Assessment, 13, p. 454-469.

Fahim, C., He, Y., Yoon, U., Chen, J., Evans, A. & Perusse, D. (2011) Neuroanatomy of childhood disruptive behavior disorders, Aggress Behav, 37, p. 326-337.

Fairchild, G., Hagan, C. C., Walsh, N. D., Passamonti, L., Calder, A. J. & Goodyer, I. M. (2013) Brain structure abnormalities in adolescent girls with conduct disorder, J Child Psychol Psychiatry, 54, p. 86-95.

Fairchild, G., Passamonti, L., Hurford, G., Hagan, C. C., von dem Hagen, E. A., van Goozen, S. H., et al. (2011) Brain structure abnormalities in early-onset and adolescent-onset conduct disorder, Am J Psychiatry, 168, p. 624-633.

Fan, Y., Duncan, N. W., de Greck, M. & Northoff, G. (2011) Is there a core neural network in empathy? An fMRI based quantitative meta-analysis, Neuroscience and Biobehavioral Reviews, 35, p. 903-911.

Fanti, K. A., Demetriou, C. A. & Kimonis, E. R. (2013) Variants of Callous-Unemotional Conduct Problems in a Community Sample of Adolescents, Journal of Youth and Adolescence, 42, p. 964-979.

Finger, E. C., Marsh, A., Blair, K. S., Majestic, C., Evangelou, I., Gupta, K., et al. (2012) Impaired functional but preserved structural connectivity in limbic white matter tracts in youth with conduct disorder or oppositional defiant disorder plus psychopathic traits, Psychiatry Res, 202, p. 239-244.

Frick, P. J., Cornell, A. H., Bodin, S. D., Dane, H. E., Barry, C. T. & Loney, B. R. (2003) Callous-unemotional traits and developmental pathways to severe conduct problems, Dev Psychol, 39, p. 246-260.

Frick, P. J., Marsee, M. A. & Patrick, C. (2006) Psychopathy and developmental pathways to antisocial behavior in youth, Handbook of psychopathy, p. 353-374.

Frick, P. J., Ray, J. V., Thornton, L. C. & Kahn, R. E. (2014) Can callous-unemotional traits enhance the understanding, diagnosis, and treatment of serious conduct problems in children and adolescents? A comprehensive review, Psychol Bull, 140, p. 1-57.

Frick, P. J. & White, S. F. (2008) Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior, J Child Psychol Psychiatry, 49, p. 359-375.

Giedd, J. N. & Rapoport, J. L. (2010) Structural MRI of pediatric brain development: what have we learned and where are we going?, Neuron, 67, p. 728-734.

Huebner, T., Vloet, T. D., Marx, I., Konrad, K., Fink, G. R., Herpertz, S. C., et al. (2008) Morphometric brain abnormalities in boys with conduct disorder, J Am Acad Child Adolesc Psychiatry, 47, p. 540-547.

Hyatt, C. J., Haney-Caron, E. & Stevens, M. C. (2012) Cortical thickness and folding deficits in conduct-disordered adolescents, Biol Psychiatry, 72, p. 207-214.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997) Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data, J Am Acad Child Adolesc Psychiatry, 36, p. 980-988.

Kazdin, A. E., Whitley, M. & Marciano, P. L. (2006) Child-therapist and parent-therapist alliance and therapeutic change in the treatment of children referred for oppositional, aggressive, and antisocial behavior, J Child Psychol Psychiatry, 47, p. 436-445.

Kessler, R. C., Avenevoli, S., Costello, E. J., Georgiades, K., Green, J. G., Gruber, M. J., et al. (2012) Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement, Arch Gen Psychiatry, 69, p. 372-380.

Kimonis, E. R., Fanti, K. A., Anastassiou-Hadjicharalambous, X., Mertan, B., Goulter, N. & Katsimicha, E. (2016) Can Callous-Unemotional Traits be Reliably Measured in Preschoolers?, Journal of Abnormal Child Psychology, 44, p. 625-638.

Kruesi, M. J., Casanova, M. F., Mannheim, G. & Johnson-Bilder, A. (2004) Reduced temporal lobe volume in early onset conduct disorder, Psychiatry Res, 132, p. 1-11.

Kumsta, R., Sonuga-Barke, E. & Rutter, M. (2012) Adolescent callous-unemotional traits and conduct disorder in adoptees exposed to severe early deprivation, Br J Psychiatry, 200, p. 197-201.

Larsson, H., Viding, E. & Plomin, R. (2008) Callous-unemotional traits and antisocial behavior - Genetic, environmental, and early parenting characteristics, Criminal Justice and Behavior, 35, p. 197-211.

Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., et al. (2007) Sexual dimorphism of brain developmental trajectories during childhood and adolescence, Neuroimage, 36, p. 1065-1073.

Lozier, L. M., Cardinale, E. M., VanMeter, J. W. & Marsh, A. A. (2014) Mediation of the Relationship Between Callous-Unemotional Traits and Proactive Aggression by Amygdala Response to Fear Among Children With Conduct Problems, JAMA Psychiatry, 71, p. 627-636.

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., et al. (2008) Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders, Am J Psychiatry, 165, p. 712-720.

Moffitt, T. E., Arseneault, L., Jaffee, S. R., Kim-Cohen, J., Koenen, K. C., Odgers, C. L., et al. (2008) Research review: DSM-V conduct disorder: research needs for an evidence base, J Child Psychol Psychiatry, 49, p. 3-33.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., et al. (2009) Distinct genetic influences on cortical surface area and cortical thickness, Cereb Cortex, 19, p. 2728-2735.

Petermann, F. & Wechsler, D. (2008) HAWIK-IV: Hamburg-Wechsler-Intelligenztest für Kinder-IV, Verlag Hans Huber, Hogrefe, Testverlag.

Phan, K. L., Wager, T., Taylor, S. F. & Liberzon, I. (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI, Neuroimage, 16, p. 331-348.

Raschle, N. M., Menks, W. M., Fehlbaum, L. V., Tshomba, E. & Stadler, C. (2015) Structural and Functional Alterations in Right Dorsomedial Prefrontal and Left Insular Cortex Co-Localize in Adolescents with Aggressive Behaviour: An ALE Meta-Analysis, PLoS One, 10, p. e0136553.

Rogers, J. C. & De Brito, S. A. (2016) Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis, JAMA Psychiatry, 73, p. 64-72.

Rogstad, J. E. & Rogers, R. (2008) Gender differences in contributions of emotion to psychopathy and antisocial personality disorder, Clin Psychol Rev, 28, p. 1472-1484.

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., et al. (2012) Modelling neural correlates of working memory: a coordinate-based meta-analysis, Neuroimage, 60, p. 830-846.

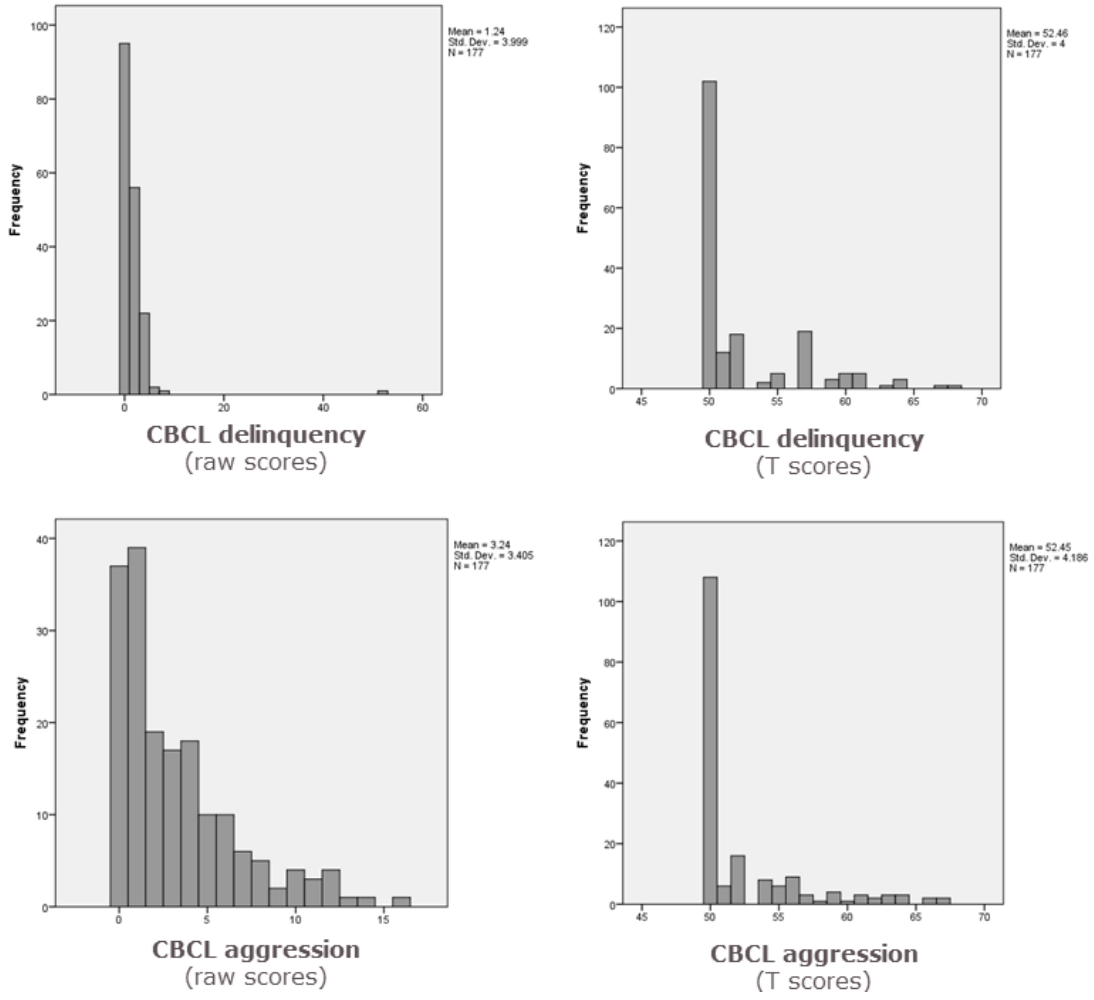
Rowe, R., Maughan, B., Moran, P., Ford, T., Briskman, J. & Goodman, R. (2010) The role of callous and unemotional

traits in the diagnosis of conduct disorder, J Child Psychol Psychiatry, 51, p. 688-695.
Sterzer, P., Stadler, C., Poustka, F. & Kleinschmidt, A. (2007) A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy, Neuroimage, 37, p. 335-342.
Sundermann, B. & Pfleiderer, B. (2012) Functional connectivity profile of the human inferior frontal junction: involvement in a cognitive control network, BMC Neurosci, 13, p. 119.
van Baardewijk, Y., Stegge, H., Andershed, H., Thomaes, S., Scholte, E. & Vermeiren, R. (2008) Measuring psychopathic traits in children through self-report. The development of the Youth Psychopathic traits Inventory-Child Version, Int J Law Psychiatry, 31, p. 199-209.
Viding, E. & McCrory, E. J. (2012) Why should we care about measuring callous-unemotional traits in children?, Br J Psychiatry, 200, p. 177-178.
Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A., De Brito, S. A., et al. (2012) Amygdala response to preattentive masked fear in children with conduct problems: the role of callous-unemotional traits, Am J Psychiatry, 169, p. 1109-1116.
Wallace, G. L., White, S. F., Robustelli, B., Sinclair, S., Hwang, S., Martin, A., et al. (2014) Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits, J Am Acad Child Adolesc Psychiatry, 53, p. 456-465 e451.
Wechsler, D. (1999) Wechsler abbreviated scale of intelligence, Psychological Corporation.
White, S. F., Marsh, A. A., Fowler, K. A., Schechter, J. C., Adalio, C., Pope, K., et al. (2012) Reduced amygdala response in youths with disruptive behavior disorders and psychopathic traits: decreased emotional response versus increased top-down attention to nonemotional features, Am J Psychiatry, 169, p. 750-758.
White, S. F., Tyler, P. M., Erway, A. K., Botkin, M. L., Kolli, V., Meffert, H., et al. (2016) Dysfunctional representation of expected value is associated with reinforcement-based decision-making deficits in adolescents with conduct problems, J Child Psychol Psychiatry, 57, p. 938-946.
Wilke, M., Holland, S. K., Altaye, M. & Gaser, C. (2008) Template-O-Matic: a toolbox for creating customized pediatric templates, Neuroimage, 41, p. 903-913.

Supplementary material

Supplement 1

Distribution of the delinquency and aggression subscale from the CBCL (left: raw scores; right T-scores).



Supplement 2

Here we present evidence for the usefulness of the newly built composite score reflecting CU traits: (**1**) Cronbach Alpha scores and confidence intervals (CI) for the YPI callous-unemotional dimension, ICU total and the new composite score representing CU-traits; (**2**) Between-assessment correlations; (**3**) Changes in Cronbach's alpha between assessments; and (**4**) replication of correlational findings in boys for ICU total, YPI callous-unemotional and composite score.

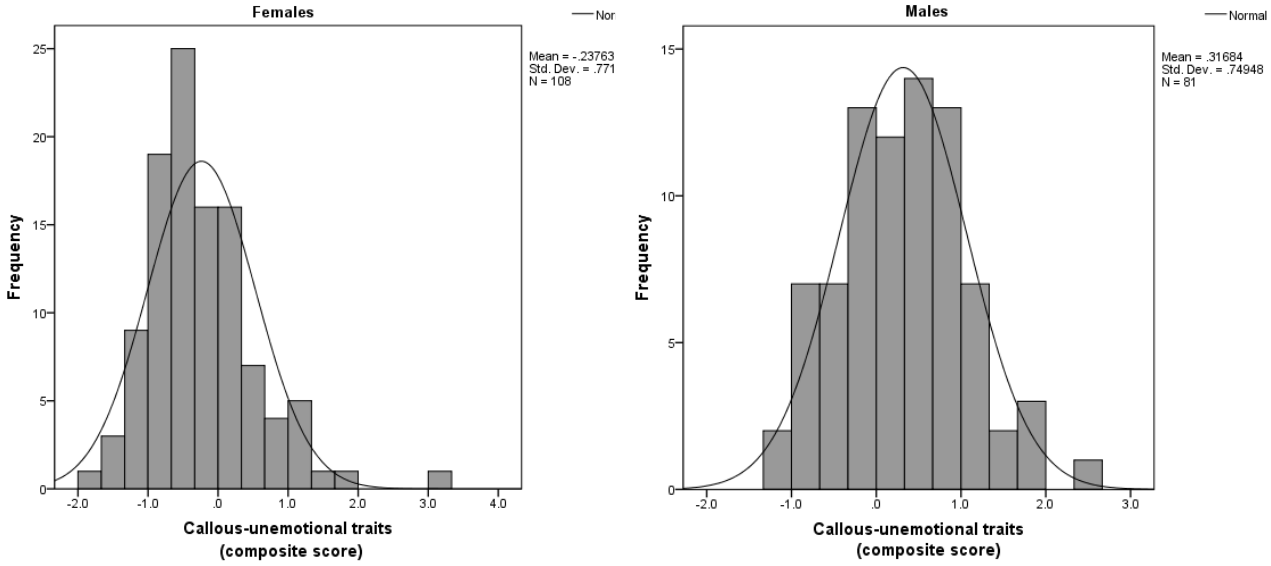
(1) Reliability of Scales - Cronbach's alpha scores

Group	Assessment	Cronbach's Alpha	Confidence Interval
All	YPI (callous-unemotional)	0.785	0.737 to 0.828
	ICU (total)	0.791	0.744 to 0.833
	CU-traits (composite)	0.832	0.794 to 0.866
Girls	YPI (callous-unemotional)	0.765	0.694 to 0.825
	ICU (total)	0.774	0.705 to 0.833
	CU-traits (composite)	0.803	0.743 to 0.854
Boys	YPI (callous-unemotional)	0.752	0.662 to 0.827
	ICU (total)	0.791	0.717 to 0.853
	CU-traits (composite)	0.823	0.759 to 0.877

Note. 95% Confidence Intervals.

Supplement 3

Graphs show the distribution of callous-unemotional traits, for girls and boys respectively. Plots demonstrate that the data falls into a wide range and that a sufficient number of high, medium and low scores represent our groups.



Supplement 4
Site-specific acquisition parameters and numbers of subjects tested.

Site #	**01**	**02**	**04**	**05**	**07**
#of participants	36	41	44	18	50
[girls/boys]	[16/20]	[22/19]	[22/22]	[18/0]	[30/20]
scanner model	Siemens Trio	Siemens Prisma	Siemens Trio	Siemens Prisma	Phillips
#of slices	192	192	192	192	192
TR	1900ms	1900ms	1900ms	1900ms	1900ms
TE	2.74ms	3,42ms	4.1ms	3.42ms	3.7ms
TI	900ms	900ms	900ms	900ms	900ms
flip angle (°)	9	9	9	9	9
field of view	256mm	256mm	256mm	256mm	256mm
voxel size	1×1×1mm	1×1×1mm	1×1×1mm	1×1×1mm	1×1×1mm

01=Frankfurt; 02=Aachen; 04=Southampton; 05=Basel; 07=Birmingham; TR=repetition time; TE=echo time; TI=inversion time.

Chapter 4. Microstructural White Matter Alterations in the Corpus Callosum of Girls with Conduct Disorder.

Willeke M. Menks, Reto Furger, Claudia Lenz, Lynn V. Fehlbaum, Christina Stadler, & Nora M. Raschle

25 December 2016.

JACAAP, DOI: http://dx.doi.org/10.1016/j.jaac.2016.12.006

Abstract

Diffusion tensor imaging (DTI) studies in adolescent conduct disorder (CD) have demonstrated white matter alterations of tracts connecting functionally distinct fronto-limbic regions, but only in boys or mixed-gender samples. So far, no study has investigated white matter integrity in CD girls on a whole-brain level. Therefore, our aim was to investigate white matter alterations in adolescent girls with CD. We collected high resolution DTI data from 24 girls with CD and 20 typically developing control girls using a 3T MR imaging system. Fractional anisotropy (FA) and mean diffusivity (MD) were analyzed for whole brain as well as a priori defined regions of interest, while controlling for age and intelligence, using a voxel-based analysis and an age-appropriate customized template. Whole-brain findings revealed white matter alterations (i.e. increased FA) in CD girls bilaterally within the body of the corpus callosum, expanding towards the right cingulum and left corona radiata. The FA and MD results in a priori defined regions of interest were more widespread and included changes in the cingulum, corona radiata, fornix and uncinate fasciculus. These results were not driven by age, intelligence or ADHD comorbidity. This paper provides the first evidence of white matter alterations in female adolescents with CD as indicated through white matter reductions in callosal tracts. This finding enhances current knowledge about the neuropathological basis of female CD. An increased understanding of gender-specific neuronal characteristics in CD may influence diagnosis, early detection and successful intervention strategies.

Introduction

Conduct disorder (CD) is a mental disorder of childhood and adolescence and is characterized by repeated patterns of rule-breaking and aggressive or defiant behavior which is outside the appropriate age norm (DSM-5 312.8; American Psychiatric Association, 2013). A clinical diagnosis of CD affects familial, academic or occupational functioning and can thus result in substantial societal costs. Clinically, CD and oppositional defiant disorder are subsumed under the diagnosis disruptive behavior disorder (American Psychiatric Association, 2013). The estimated life time prevalence of CD corresponds to about 7% in girls and 12% in boys (Nock, Kazdin, Hiripi, & Kessler, 2006). Consequently, the majority of research studies investigating CD almost exclusively included male participants. However, considering the known sex differences in the prevalence and progression of CD, the importance of including gender as a critical factor within CD studies remains indispensable (Nock et al., 2006). Sixteen to thirty percent of adolescents with CD display comorbid attention deficit hyperactivity disorder (ADHD), resulting in a possible influence (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). However, research has indicated that CD specific deficits persist beyond the presence of comorbid ADHD symptoms (Pape et al., 2015; Passamonti et al., 2012).

Behaviorally, reduced empathy, emotion processing and regulation skills are key deficits in the behavioral symptomatology of CD. Likewise, impulsivity, decision making and reinforcement learning, are commonly impacted (Blair, 2013). In line with the known behavioral phenotype, functional neuroimaging studies in CD have revealed neuronal characteristics affecting the emotion processing, regulation and threat circuitries of the brain, as indicated by neuronal alterations in amygdala, insula, prefrontal, superior temporal and cingulate cortex (Marsh et al., 2008; Passamonti et al., 2010; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005; Viding et al., 2012). In line with functional evidence, changes in gray and white matter structure in brain areas of the frontal, limbic and temporal lobe have been identified when comparing CD to typically developing youths (Baker, Clanton, Rogers, & De Brito, 2015; De Brito et al., 2009; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007). For example, by using voxel-, surface- or cortical thickness-based morphometry analysis structural alterations in CD have been linked to the amygdala, insula, precuneus, prefrontal cortex, cingulate cortex and corpus callosum (Baker et al., 2015; Fairchild et al., 2013; Raine et al., 2003; Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015). Structural and functional brain alterations are further dependent on age of onset, CD symptom severity or the level of callous-unemotional traits displayed. Heightened scores are thereby predictive of a negative disease progression and the development of antisocial behavior later in life (Fairchild et al., 2013; Marsh et al., 2008; Passamonti et al., 2010; Viding et al., 2012). Regionally specific structural changes have been linked to alterations

within the white matter tracts, or neural circuitries, connecting these regions, for example the prefrontal-limbic circuit.

Neural circuits such as the prefrontal-limbic system may be investigated using diffusion tensor imaging (DTI), a technique measuring structural connectivity. DTI can inform about the fiber consistency and microstructural integrity of white matter tracts (e.g. fractional anisotropy (FA) or mean diffusivity (MD)). Previous DTI studies in male or mixed-gender groups of adolescents with disruptive behavior disorders have reported white matter increases and decreases in tracts comprising the corpus callosum, corona radiata, superior longitudinal fasciculus, fronto-occipital fasciculus, uncinate fasciculus, stria terminalis and cerebellar peduncle (Breeden, Cardinale, Lozier, VanMeter, & Marsh, 2015; Haney-Caron, Caprihan, & Stevens, 2014; Passamonti et al., 2012; Zhang et al., 2014b).

To date it is unclear whether previously identified white matter alterations in CD boys are also present in CD girls. Two studies, one using a region of interest approach, the second based on post-hoc examinations of adult females with a prior CD diagnosis provide first evidence about potentially unique white-matter characteristics in female CD (Zhang et al., 2014a; Lindner et al., 2016). However, no study to date has investigated whole-brain white matter alterations in female adolescents with a clinical diagnosis of CD using diffusion tensor imaging. Therefore, the present paper aims at bridging this gap in knowledge by comparing white matter tracts in CD girls compared to typically developing controls through voxel-based DTI-TK using both a whole-brain and a region-of-interest approach. By employing a more conservative whole brain approach as well as investigations within a priori defined regions of interest method we aim to gain novel insights into white matter alteration in CD girls, but also allowing comparability to past studies. Based on previous evidence implicating white matter alterations within the neurobiology of CD, we hypothesize that in a group of only girls with CD alterations in white matter structures are likewise observed (i.e. in the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum and fronto-occipital fasciculus) (Breeden et al., 2015; Haney-Caron et al., 2014; Pape et al., 2015; Passamonti et al., 2012; Zhang et al., 2014b). Comorbid ADHD symptoms will be accounted for by the repetition of analysis in CD girls without ADHD comorbidity. Finally, using correlational analyses we will investigate whether callous-unemotional traits, which are known to increase the symptom severity and disease progression of CD, may be linked to the observed microstructural alterations (Frick, Cornell, Barry, Bodin, & Dane, 2003).

Method

Participants

Forty-four average intelligent female adolescents, 24 with CD (age range: 12-18 years) and 20 typically developing controls (age range: 12-19 years), were recruited through healthcare institutions and schools within this Swiss National Foundation study investigating adolescent CD. Some participants were part of FemNAT-CD, a project across Europe (http://www.femnat-cd.eu/). All patients fulfilled the DSM-5 criteria for CD using the semi-structured diagnostic interview K-SADS-PL(Kaufman et al., 1997); Healthy controls were free of any psychiatric or neurological disorder. In line with the known overlap between CD and ADHD, we here identified nine CD patients with comorbid ADHD symptoms (Maughan et al., 2004). Furthermore, two patients were diagnosed with a present alcohol abuse and five patients with a present substance abuse. Handedness was assessed using the Edinburgh Handedness Inventory (Caplan & Mendoza, 2011). All participants completed two testing sessions, including clinical interview/psychometric testing and one MRI appointment. The MRI session occurred on average 2.6 months (±2.3 for CD; ±2.9 for controls) after the clinical interview. All participants and caretakers provided verbal and written informed consent to take part in the study as approved by the local ethics committee in Basel, Switzerland (Ethikkommission Nordwest- und Zentralschweiz).

Table 1. *Group characteristics of girls with conduct disorder (CD) and typically developing controls (TD).*

Variable		CD Mean (±SD)	TD Mean (±SD)	*p*-value	N (CD/TD)
Age in years		15.8 (±1.4)	16.3 (±1.8)	.262	(24/20)
Age of CD onset				-	
	Child-onset (<10 years)	5	-		
	Adolescent-onset (≥10 years)	19	-		
Handedness				.319	(22/20)
	Left-handed	2	4		
	Right-handed	20	16		
Intelligence quotient (IQ; WISC-IV)*		99.5 (±10.5)	108.1 (±10.9)	.011	(24/20)
	*Verbal IQ**	96.9 (±13.3)	111.3 (±13.5)	.001	(24/20)
	Performance IQ	102.1 (±11.1)	105.0 (±11.5)	.398	(24/20)
Aggression (RPQ)		13.1 (±9.3)	8.6 (±4.3)	.127[1]	(20/20)
Psychopathic Traits (YPI)*		107.5 (±22.1)	92.2 (±18.6)	.019	(23/20)
Callous-Unemotional Traits (ICU)*		28.6 (±10.8)	17.0 (±6.1)	.001	(16/17)
Puberty status		3.9 (±0.4)	4.2 (±0.7)	.233[1]	(18/19)
Socioeconomic status		5.0 (±1.8)	5.5 (±1.4)	.502	(13/12)

* significant group difference ($p < 0.05$), two-tailed T-test. [1] Mann-Whitney U test; For all tests, mean scores and standard deviations (SD) are reported. RPQ= Reactive-Proactive Questionnaire; YPI= Youth Psychopathic Traits Inventory; ICU= Inventory of Callous-Unemotional Traits.

Psychometric testing

Participants completed a battery of standardized psychometric tests measuring psychopathic traits (Youth Psychopathic Traits Inventory self-report, based on 10 dimensions/50 items rated on a four-point Likert scale (Andershed, Kerr, Stattin, & Levander, 2002)), callous-unemotional traits (Inventory of Callous-Unemotional traits parent-report, based on 24 items rated on a four-point Likert scale (Essau, Sasagawa, & Frick, 2006)), aggressive behavior (Reactive–Proactive Aggression Questionnaire, a 26-items self-report (Raine et al., 2006)) and pubertal status (Petersen, Crockett, Richards, & Boxer, 1988). Additionally, behavioral problems were recorded through parental reports (Child Behavior Checklist (Achenbach & Rescorla, 2001)). Furthermore, parental socioeconomic status was estimated using a six point educational-scale based on the International Standard Classification of Education (OECD/Eurostat/UNESCO Institute for Statistics). Clinical and psychometric data analyses were based on the homogeneity of variance (Levene's) test and parametric (two-sample *t*-test) or non-parametric testing (Mann-Whitney U test) as implemented in SPSSv23 (IBM Corp., Armonk, N.Y., USA). Group characteristics are presented in Table 1. There were no significant differences in respect to age, handedness, puberty status, socioeconomic status or performance IQ. The present group of CD girls is comparable in scores to previously described CD samples, including heightened aggression, callousness and psychopathy scores (Passamonti et al., 2012; Zhang et al., 2014a). Compared to controls, total and verbal but not performance IQ was significantly lower in CD girls.

DTI acquisition

Whole-brain neuroimaging data was acquired using a 3T MR imaging system (Siemens Prisma, Erlangen, Germany) and a 20-channel phased-array radio frequency head coil. A single-shot echo planar imaging (EPI) sequence was used with the following acquisition parameters: A>>P phase encoding direction; echo spacing of 0.65ms, GRAPPA parallel imaging with an acceleration factor of two, phase partial Fourier 6/8 acquisition, matrix 128 × 128, field of view 256mm, 2 x 2 mm2 in-plane resolution, slice thickness of 2.0mm, no slice gap, 62 contiguous axial slices, TR = 7500ms, TE = 71ms and bandwidth of 1776 Hz/Pixel. Diffusion-sensitive gradients were applied along 64 directions (b=800 s/mm^2), and two additional images were collected without a diffusion gradient (b0=0 s/mm^2) with A>>P and P>>A phase encoding directions, necessary for distortion corrections of the EPI imaging data during analysis.

DTI data processing

Prior to preprocessing, all images underwent quality control using DTIPrep in addition to visual checks through two independent reviewers (WMM, RF) in order to exclude artifact-influenced

gradient directions. EPI distortions were corrected using eddy and TopUp in FSL5.0 and the brain fMRI software library.(Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Oguz et al., 2014) With FSL-BET individual brain masks were created. Subsequently FA and MD values were obtained by using the FSL-DTIfit algorithm. Again, visual checks were applied to assure good coherence between individual FA- and MD- maps and corresponding diffusion tensor eigenvectors.

To increase specificity, particularly for smaller tracts a voxel-based analysis as opposed to tract based statistics was employed (Bach et al., 2014; Schwarz et al., 2014). Most importantly, by using DTI-TK and an existing tensor template (the IXI aging template v3.0 in standard space) a study-specific customized adolescent brain template was created based on our study population (H. Zhang, Yushkevich, Alexander, & Gee, 2006). Subsequently, all subjects' DTI volumes were aligned to our customized template, using the affine and diffeomorphic alignment of DTI-TK. DTI-TK uses a deformable registration algorithm optimizing the white matter alignment of DTI images between participants based on the tensors itself (Zhang et al., 2006). Therefore an advantage of using DTI-TK is the more precise spatial normalization of the DTI data. Consequently, a higher sensitivity for white matter alterations is achieved (Bach et al., 2014; Schwarz et al., 2014). After normalization, the FA and MD data were smoothed using a Gaussian kernel with full width at half maximum of 6 mm.

Statistical whole brain and region of interest analysis

Statistical analyses were performed using both, a whole-brain and a region of interest approach. All analyses were based on a permutation inference (n=5000), with demeaned age and total IQ-scores as covariates. Results are based on between-group two sample-*t*-tests (two-tailed) and presented using a threshold-free cluster enhancement, $p \leq 0.05$ FWE-corrected. The ICBM-DTI-81 atlas was implemented for determining tracts that lie within the clusters resulting from the analysis. In order to evaluate specific white matter tracts previously identified in males with disruptive behavior disorder, we further chose to investigate six tracts using an a-priori defined region of interest approach (Breeden et al., 2015; Haney-Caron et al., 2014; Pape et al., 2015; Passamonti et al., 2012). More specifically, these regions were generated from the ICBM-DTI-81 atlas for white matter tracts that were altered in previous studies investigating CD: the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum, fronto-occipital fasciculus (Breeden et al., 2015; Haney-Caron et al., 2014; Mori et al., 2008; Pape et al., 2015; Passamonti et al., 2012; Zhang et al., 2014b).

Post-hoc region of interest analysis

Evidence indicates that CD adolescents can be further dissociated depending on the level (high versus low) of callous-unemotional traits displayed (Andersson, Skare, & Ashburner, 2003; Fairchild et al.,

2013; Lockwood et al., 2013; Viding et al., 2012; Wallace et al., 2014). There were not enough girls with high/low callous-unemotional traits allowing further subgroup analysis. However, post-hoc correlation analysis comparing the mean FA and MD values in anatomically defined areas of interest to callous-unemotional traits (corrected for IQ and age) were conducted in order to assess the influence of callousness on white matter alterations in CD girls. Correlational analyses were conducted using the ICU questionnaire, as well as the callous-unemotional subscale of the YPI. Both questionnaires are commonly used to distinguish relevant subgroups of CD individuals based on callous-unemotional traits (Fairchild et al., 2013; Lockwood et al., 2013; Wallace et al., 2014). Additionally, we planned to investigate the effect of comorbid ADHD symptoms, present in nine CD girls, on our findings by (**1**.) re-estimation of DTI analysis excluding the nine CD/ADHD girls; (**2**.) multiple linear regression analyses using CD and ADHD symptoms as independent variables (with age and intelligence as covariates) and clusters of significant whole brain FA changes in CD girls as dependent variables.

Results

Whole brain DTI findings in female CD

On a whole-brain level, DTI analysis identified one significant cluster of FA increases centered in the body of the corpus callosum expanding towards the right cingulum and the left corona radiata when comparing CD girls to healthy controls (Table 2; Figure 1).

Region of interest based DTI findings in female CD

Further analyses within six a-priori based regions of interest derived from the literature on male CD (i.e. the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum, fronto-occipital fasciculus) likewise confirmed several significant clusters of FA and MD alterations in girls with CD (Table 2). When compared to their typically developing peers, girls with CD displayed increased FA within the body of the corpus callosum, the right cingulate and the left anterior part of the corona radiata, but lower MD in the callosal body and right cingulate. The opposite pattern was observed for the left hippocampal part of the cingulum and the right hemispherical fornix, where FA was found to be significantly decreased in CD girls, but MD was increased in the fornix. Finally, within the right uncinate fasciculus girls with CD had lower MD, but no differences in FA, compared to typically developing girls.

Table 2. *MNI peak coordinates of microstructural white matter alterations in female conduct disorder (CD) compared to typically developing controls (TD).*

				coordinates of peak location[a]			Cluster size (number of voxels)	
	#	Brain region	L/R	X	Y	Z		*p*-value[b]
Fractional Anisotropy								
CD>TD								
	1	Bilateral corpus callosum (body)	L	-1	-26	24	2291	.038
	2	Corpus callosum (body)[c]	R	1	-26	24	5926	.005
	3	Cingulum (cingulate)[c]	R	12	-23	34	544	.011
	4	Corona radiata (anterior)[c]	L	-15	31	-3	91	.047
TD>CD								
	5	Cingulum (hippocampal)[c]	L	-20	-18	-27	196	.040
	6	Fornix[c]	R	2	-2	8	69	.046
Mean Diffusivity								
CD>TD								
	1	Fornix[c]	R	3	-3	8	109	.040
TD>CD								
	2	Corpus callosum (body)[c]	R	4	-24	26	5490	.010
	3	Cingulum (cingulate)[c]	R	7	-14	33	1197	.004
	4	Uncinate fasciculus[c]	R	38	-1	-18	156	.040

[a] MNI space. [b] Threshold-free cluster enhancement, $p \leq 0.05$ FWE-corrected. [c] Region of interest

Post-hoc region of interest analysis

Correlation analyses indicated no significant relationship between callous-unemotional traits (either ICU or YPI) and the MD or FA values within anatomically defined regions of interest in the group of CD girls. Furthermore, results of an additional DTI analysis excluding nine CD/ADHD girls remained significant (see Supplement 2). Additionally, multiple linear regression analysis indicated that ADHD symptoms do not explain any additional variance observed within the results (R^2 change = .019; $F_{(1.39)}$=1.09; p=.303).

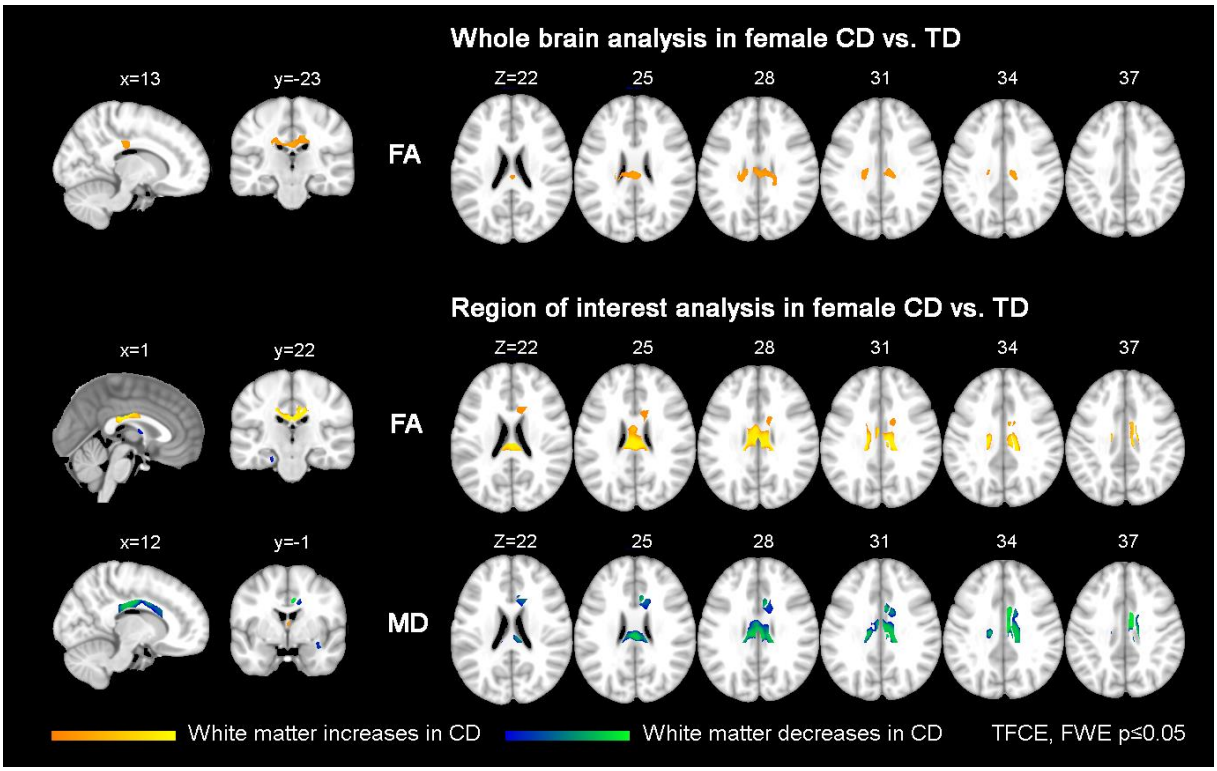


Figure 1 *(**top**). Increased fractional anisotropy (FA) values in the body of the corpus callosum in conduct disorder (CD) girls compared to controls (TD). In a priori defined regions of interest increased FA (**middle**) and mean diffusivity (MD) (**bottom**) alterations in CD were detected in areas including right corpus callosum, cingulum, left anterior corona radiate, right fornix and uncinate fasciculus.*

Discussion

For the first time, we here describe white matter alterations in female adolescents with conduct disorder (CD) using a whole-brain DTI analysis. More specifically, female CD is characterized by increased fractional anisotropy (FA) scores within the body of the corpus callosum, expanding towards the right cingulum and the left corona radiata. Further investigations within a-priori defined regions of interest reveal additional clusters of significantly altered white matter integrity in brain areas including the bilateral cingulum, left anterior corona radiata, right uncinate fasciculus and the right fornix. Overall, these findings align with findings in male CD or adolescents with aggressive behavior (Baker et al., 2015; Breeden et al., 2015; Haney-Caron et al., 2014; Passamonti et al., 2012; Sarkar et al., 2013; Sobhani, Baker, Martins, Tuvblad, & Aziz-Zadeh, 2015; Zhang et al., 2014a; Zhang et al., 2014b). These findings were corrected for age and IQ and proven independent of ADHD symptoms, which is in line with previous studies indicating that characteristic CD alterations remain after removal/control for ADHD comorbidity (Pape et al., 2015; Passamonti et al., 2012).

The here observed white matter alterations within the body of the corpus callosum are in line with previous research in CD. For example, Zhang and colleagues (2014b) used tract-based spatial statistics in order to demonstrate FA increases within the body and genu of the corpus callosum of male adolescents with CD. The corpus callosum is the largest white matter tract of the brain and crucial for interhemispheric communication. It has abundant projections (so called callosal radiations) to and from the cortices of both hemispheres and is generally subdivided into three distinct areas: the genu, the body and the splenium. Each part thereby connects functionally distinct brain regions. While the genu connects parts of the frontal lobes (executive and higher order cognitive processing) and the splenium temporal/occipital regions (visual processing), the body of the corpus callosum as identified here is specifically thought to connect motor, parietal and temporal areas important for motoric and emotion processing tasks (Schulte & Muller-Oehring, 2010). Interhemispheric processing is known to become progressively relevant with increasing cognitive demand. An intact connectivity through the body of the corpus callosum may thus be critical for enabling higher order skills such as emotion regulation (Raine et al., 2003). Furthermore, fibers of the callosal body connect to the insula, a structure associated with emotion processing and commonly altered in CD (Raybaud, 2010; Raschle et al., 2015). We therefore conclude that changes in the body of the corpus callosum of girls with CD may result in reduced interhemispheric processing and consequent lower emotion regulation abilities. In line with our finding, callosal alterations are linked to several childhood onset neuropsychiatric disorders (e.g. attention deficit hyperactivity disorder or developmental dyslexia (Catherine, 1994; Hasan et al., 2012)).

It is to note, that corpus callosum alterations are commonly identified, however, reports differ in regards to the precise underlying neuroanatomical variations. For example, two studies including mixed-gender groups of adolescents with and without CD reported no FA differences, but reduced radial diffusivity, which is the DTI measure for the transverse component of diffusion direction (Finger et al., 2012). Such inconsistencies may result from differences in the DTI methods or analysis approaches applied, small sample sizes or missing group heterogeneity (e.g. clinical criteria), variation in accompanying traits (e.g. high/low callous-unemotional traits), unbalanced gender or differences in the age of participants tested. For instance, previous studies have either used voxel-based analysis or tract-based spatial statistics (but rarely a combination), which may explain differences in results observed. Since DTI-TK has shown to enhance the specificity of the normalization of DTI data, we overall recommend using this tool (also prior to tract-based approaches) in order to increase the sensitivity in future studies (Bach et al., 2014).

Developmentally, the corpus callosum matures throughout childhood and adolescence, with a peak typically expected around 20 to 35 years of age (Lebel et al., 2012). Based on this knowledge, three possible explanations for FA increases in CD may be used: (**1**) accelerated maturation, causing the FA peak to shift to an earlier age; (**2**) an earlier degeneration following the initial over-proliferation (Passamonti et al., 2012; Zhang et al., 2014b); or (**3**) compensatory processes following an initial under-myelination (Markham, Herting, Luszpak, Juraska, & Greenough, 2009). These explanations would be in line with the finding that adults with a antisocial personality disorder or previous diagnosis of CD display FA reductions within the corpus callosum (Lindner et al., 2016; Sundram et al., 2012), while increases are more commonly detected in younger individuals (e.g. the here presented findings or Zhang et al., 2014b). Therefore, we agree with previous suggestions and hypothesize that an initial over-acceleration of white matter maturation, either due to excessive stimulation following early life stress or as a consequence of compensatory mechanism cause the characteristic changes in the corpus callosum in adolescents with CD and may potentially be followed by the onset of an earlier degeneration. However, future studies implementing longitudinal designs are needed in order to test whether differences in white matter trajectories within the corpus callosum are origin or result of the behavioral challenges observed. Furthermore, it would be interesting for future studies to analyze the eigenvalues (i.e. $\lambda 1$, $\lambda 2$, $\lambda 3$) of FA results separately in order to investigate which component is driving the observed findings (Passamonti et al., 2012).

Investigating a-priori defined regions of interest based data in males (Breeden et al., 2015; Haney-Caron et al., 2014; Pape et al., 2015; Zhang et al., 2014b), additional FA increases (i.e. in the right cingulum, left anterior corona radiate) but also decreases (i.e. in the left hippocampal part of the cingulum and right fornix) were detected. One area identified is the cingulum, a large c-shaped white matter tract positioned directly above the corpus callosum and connecting frontal, temporal and limbic brain regions. Particularly its anterior part is linked to cognitive and emotion processing (Bush, Luu, & Posner, 2000; Catani, Howard, Pajevic, & Jones, 2002). In line with our results, structural (i.e. voxel-based morphometry, DTI, surface-based morphometry) and functional (e.g. emotion, empathy and pain processing) cingulum alterations have been identified in CD (De Brito et al., 2009; Haney-Caron et al., 2014; Lindner et al., 2016; Sterzer et al., 2005). In line with previous findings (Haney-Caron et al., 2014; Raine et al., 2003; Sundram et al., 2012; Zhang et al., 2014b), we identified the corona radiate to distinguish girls with CD from healthy controls (Haney-Caron et al., 2014; Fergusson, Horwood, & Ridder, 2007; Caplan & Mendoza, 2011; Andershed et al., 2002). Containing a fan-shaped array of ascending and descending projection fibers and fanning out widely (Catani et al., 2002), the position of white matter alterations within this structure varies and remains debated. However, alterations within the left anterior corona radiata were linked to increased impulsivity.

Finally, we here identified the fornix a white matter tract connecting the hippocampus with the mammillary body, medial temporal lobe and the anterior thalamic nuclei (Catani et al., 2002; Thomas, Koumellis, & Dineen, 2011). Being part of the limbic system, the fornix and hippocampus are crucial for learning and memory processes (Tsivilis et al., 2008). Reduced FA in the fornix and the uncinate fasciculus have been associated with early life stress (Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Lindner et al., 2016), which is common in the etiology of CD. It is mentionable, that we did not observe FA alterations in the uncinated fasciculus in CD girls, but only reduced MD values. A reduction in MD may indicate increased myelination or more compact white matter tracts, however, various factors (e.g. fiber crossings) may play a role (Beaulieu, 2002). While reduced FA are consistently reported in male psychopaths (Craig et al., 2009; Motzkin, Newman, Kiehl, & Koenigs, 2011; Sobhani et al., 2015; Sundram et al., 2012), findings in adolescent CD show decreases (Breeden et al., 2015; Haney-Caron et al., 2014), increases or no changes in FA at all (Finger et al., 2012; Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014a). Differences may be due to variations in study designs, small sample sizes, unbalanced or single sex studies, age/developmental differences or no control for comorbidities.

Limitations

A potential limitation of the present work is that the overall intelligence score was significantly lower in girls with CD. While we used the overall intelligence score as a covariate of no interest within the analysis conducted, it is still possible that intelligence may have influenced the data. Interestingly, only verbal IQ differentiated CD girls from controls, but performance IQ was comparable between the groups. Furthermore, past DTI studies focusing on intelligence have indicated that FA values are unrelated to variations in IQ.(Meier et al., 2012) According to past research age of CD onset may distinguish meaningful neurobiological subgroups (Passamonti et al., 2012). This study included both child- (N=5) and adolescent-onset (N=19) CD girls which may have affected the final results. While no study has yet demonstrated differences in white matter integrity between child- and adolescent onset CD groups, it is recommendable to investigate this topic further. Lastly, some of the girls with CD had a diagnosis of alcohol and/or substance abuse, which was shown to strongly correlate with CD severity (Crowley, Mikulich, Ehlers, Whitmore, & MacDonald, 2001; Fergusson, Horwood, & Ridder, 2007), and consequent brain activation (Castellanos-Ryan et al., 2014). Therefore, we cannot exclude potential effects on the presented results.

Conclusion

Research has suggested that boys have an increased propensity to develop disruptive behavior disorders as opposed to girls who require a higher loading of biological risk factors to develop CD (Cloninger, Christiansen, Reich, & Gottesman, 1978). An increased understanding of the

neurobiological basis of CD across both sexes is crucial in order to improve individualized diagnostics and facilitate early detection of children at risk. Particularly, because a timely start of intervention program precedes success (Pardini & Frick, 2013). Here we have identified structural white matter changes specific for the corpus callosum in girls with a diagnosis of CD. Our findings align with results in male adolescents with CD displaying corpus callosum deficits, but being on average about two years younger (Zhang et al., 2014b). Thus it could be hypothesized that these alterations may be indeed a characteristic of both, males and females with CD, however, linked to different sensitive periods. Continuous developmental research of the uniqueness and shared features of both female and male individuals with CD is needed in order to draw conclusions adaptable for both genders.

References

Achenbach, T., & Rescorla, L. (2001). Manual for the ASEBA School-Age Forms & Profiles: Burlington, VT: University of Vermont, Research Center for Children, Youth, and Familie.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Press.

Andershed, H. A., Kerr, M., Stattin, H., & Levander, S. (2002). Psychopathic traits in non-referred youths : a new assessment tool. In E. Blaauw & L. Sheridan (Eds.), *Psychopaths : current international perspectives* (pp. 131-158). The Hague, The Netherlands: Elsevier.

Andersson, J. L., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage, 20*(2), 870-888. doi: 10.1016/S1053-8119(03)00336-7

Bach, M., Laun, F. B., Leemans, A., Tax, C. M., Biessels, G. J., Stieltjes, B., & Maier-Hein, K. H. (2014). Methodological considerations on tract-based spatial statistics (TBSS). *Neuroimage, 100*, 358-369. doi: 10.1016/j.neuroimage.2014.06.021

Baker, R. H., Clanton, R. L., Rogers, J. C., & De Brito, S. A. (2015). Neuroimaging findings in disruptive behavior disorders. *CNS Spectr, 20*(4), 369-381. doi: 10.1017/S1092852914000789

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR in Biomedicine, 15*(7-8), 435-455.

Blair, R. J. (2013). The neurobiology of psychopathic traits in youths. *Nat Rev Neurosci, 14*(11), 786-799. doi: 10.1038/nrn3577

Breeden, A. L., Cardinale, E. M., Lozier, L. M., VanMeter, J. W., & Marsh, A. A. (2015). Callous-unemotional traits drive reduced white-matter integrity in youths with conduct problems. *Psychol Med, 45*(14), 3033-3046. doi: 10.1017/S0033291715000987

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci, 4*(6), 215-222.

Caplan, B., & Mendoza, J. E. (2011). Edinburgh handedness inventory *Encyclopedia of Clinical Neuropsychology* (pp. 928-928): Springer.

Castellanos-Ryan, N., Struve, M., Whelan, R., Banaschewski, T., Barker, G. J., Bokde, A. L., . . . Conrod, P. J. (2014). Neural and cognitive correlates of the common and specific variance across externalizing problems in young adolescence. *Am J Psychiatry, 171*(12), 1310-1319. doi: 10.1176/appi.ajp.2014.13111499

Catani, M., Howard, R. J., Pajevic, S., & Jones, D. K. (2002). Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage, 17*(1), 77-94.

Catherine, A. (1994). Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. *Am J Psychiatry, 151*, 665-669.

Choi, J., Jeong, B., Rohan, M. L., Polcari, A. M., & Teicher, M. H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biol Psychiatry, 65*(3), 227-234. doi: 10.1016/j.biopsych.2008.06.022

Cloninger, C. R., Christiansen, K. O., Reich, T., & Gottesman, II. (1978). Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission. *Arch Gen Psychiatry, 35*(8), 941-951.

Craig, M. C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., . . . Murphy, D. G. (2009). Altered connections on the road to psychopathy. *Mol Psychiatry, 14*(10), 946-953, 907. doi: 10.1038/mp.2009.40

Crowley, T. J., Mikulich, S. K., Ehlers, K. M., Whitmore, E. A., & MacDonald, M. J. (2001). Validity of structured clinical evaluations in adolescents with conduct and substance problems. *J Am Acad Child Adolesc Psychiatry, 40*(3), 265-273. doi: 10.1097/00004583-200103000-00005

De Brito, S. A., Mechelli, A., Wilke, M., Laurens, K. R., Jones, A. P., Barker, G. J., . . . Viding, E. (2009). Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain, 132*(Pt 4), 843-852. doi: 10.1093/brain/awp011

Essau, C. A., Sasagawa, S., & Frick, P. J. (2006). Callous-unemotional traits in a community sample of adolescents. *Assessment, 13*(4), 454-469. doi: 10.1177/1073191106287354

Fairchild, G., Hagan, C. C., Walsh, N. D., Passamonti, L., Calder, A. J., & Goodyer, I. M. (2013). Brain structure abnormalities in adolescent girls with conduct disorder. *J Child Psychol Psychiatry, 54*(1), 86-95. doi: 10.1111/j.1469-7610.2012.02617.x

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. *Drug Alcohol Depend, 88 Suppl 1*, S14-26. doi: 10.1016/j.drugalcdep.2006.12.011

Finger, E. C., Marsh, A., Blair, K. S., Majestic, C., Evangelou, I., Gupta, K., . . . Blair, R. J. (2012). Impaired functional but preserved structural connectivity in limbic white matter tracts in youth with conduct disorder or oppositional defiant disorder plus psychopathic traits. *Psychiatry Res, 202*(3), 239-244. doi: 10.1016/j.pscychresns.2011.11.002

Frick, P. J., Cornell, A. H., Barry, C. T., Bodin, S. D., & Dane, H. E. (2003). Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and

self-report of delinquency. *J Abnorm Child Psychol, 31*(4), 457-470.

Haney-Caron, E., Caprihan, A., & Stevens, M. C. (2014). DTI-measured white matter abnormalities in adolescents with Conduct Disorder. *J Psychiatr Res, 48*(1), 111-120. doi: 10.1016/j.jpsychires.2013.09.015

Hasan, K. M., Molfese, D. L., Walimuni, I. S., Stuebing, K. K., Papanicolaou, A. C., Narayana, P. A., & Fletcher, J. M. (2012). Diffusion tensor quantification and cognitive correlates of the macrostructure and microstructure of the corpus callosum in typically developing and dyslexic children. *NMR in Biomedicine, 25*(11), 1263-1270.

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage, 62*(2), 782-790. doi: 10.1016/j.neuroimage.2011.09.015

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry, 36*(7), 980-988. doi: 10.1097/00004583-199707000-00021

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., & Beaulieu, C. (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage, 60*(1), 340-352.

Lindner, P., Savic, I., Sitnikov, R., Budhiraja, M., Liu, Y., Jokinen, J., . . . Hodgins, S. (2016). Conduct disorder in females is associated with reduced corpus callosum structural integrity independent of comorbid disorders and exposure to maltreatment. *Transl Psychiatry, 6*, e714. doi: 10.1038/tp.2015.216

Lockwood, P. L., Sebastian, C. L., McCrory, E. J., Hyde, Z. H., Gu, X., De Brito, S. A., & Viding, E. (2013). Association of callous traits with reduced neural response to others' pain in children with conduct problems. *Curr Biol, 23*(10), 901-905. doi: 10.1016/j.cub.2013.04.018

Markham, J. A., Herting, M. M., Luszpak, A. E., Juraska, J. M., & Greenough, W. T. (2009). Myelination of the corpus callosum in male and female rats following complex environment housing during adulthood. *Brain research, 1288*, 9-17.

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., . . . Blair, R. J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry, 165*(6), 712-720. doi: 10.1176/appi.ajp.2007.07071145

Maughan, B., Rowe, R., Messer, J., Goodman, R., & Meltzer, H. (2004). Conduct disorder and oppositional defiant disorder in a national sample: developmental epidemiology. *J Child Psychol Psychiatry, 45*(3), 609-621.

Meier, I. B., Manly, J. J., Provenzano, F. A., Louie, K. S., Wasserman, B. T., Griffith, E. Y., . . . Brickman, A. M. (2012). White matter predictors of cognitive functioning in older adults. *J Int Neuropsychol Soc, 18*(3), 414-427. doi: 10.1017/S1355617712000227

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., . . . Mazziotta, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage, 40*(2), 570-582. doi: 10.1016/j.neuroimage.2007.12.035

Motzkin, J. C., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2011). Reduced prefrontal connectivity in psychopathy. *J Neurosci, 31*(48), 17348-17357. doi: 10.1523/JNEUROSCI.4215-11.2011

Nock, M. K., Kazdin, A. E., Hiripi, E., & Kessler, R. C. (2006). Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol Med, 36*(5), 699-710.

OECD/Eurostat/UNESCO Institute for Statistics. (2015). *ISCED 2011 Operational Manual: Guidelines for Classifying National Education Programmes and Related Qualifications*. Paris: OECD Publishing.

Oguz, I., Farzinfar, M., Matsui, J., Budin, F., Liu, Z., Gerig, G., . . . Styner, M. (2014). DTIPrep: quality control of diffusion-weighted images. *Front Neuroinform, 8*, 4. doi: 10.3389/fninf.2014.00004

Pape, L. E., Cohn, M. D., Caan, M. W., van Wingen, G., van den Brink, W., Veltman, D. J., & Popma, A. (2015). Psychopathic traits in adolescents are associated with higher structural connectivity. *Psychiatry Res, 233*(3), 474-480. doi: 10.1016/j.pscychresns.2015.07.023

Pardini, D., & Frick, P. J. (2013). Multiple developmental pathways to conduct disorder: current conceptualizations and clinical implications. *J Can Acad Child Adolesc Psychiatry, 22*(1), 20-25.

Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I. M., Nimmo-Smith, I., Hagan, C. C., & Calder, A. J. (2012). Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. *PLoS One, 7*(11), e48789. doi: 10.1371/journal.pone.0048789

Passamonti, L., Fairchild, G., Goodyer, I. M., Hurford, G., Hagan, C. C., Rowe, J. B., & Calder, A. J. (2010). Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry, 67*(7), 729-738. doi: 10.1001/archgenpsychiatry.2010.75

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *J Youth Adolesc, 17*(2), 117-133. doi: 10.1007/bf01537962

Raine, A., Dodge, K., Loeber, R., Gatzke-Kopp, L., Lynam, D., Reynolds, C., . . . Liu, J. (2006). The Reactive-Proactive Aggression Questionnaire: Differential Correlates of Reactive and Proactive Aggression in Adolescent Boys. *Aggress Behav, 32*(2), 159-171. doi: 10.1002/ab.20115

Raine, A., Lencz, T., Taylor, K., Hellige, J. B., Bihrle, S., Lacasse, L., . . . Colletti, P. (2003). Corpus callosum abnormalities in psychopathic antisocial individuals. *Arch Gen Psychiatry, 60*(11), 1134-1142. doi: 10.1001/archpsyc.60.11.1134

Raschle, N. M., Menks, W. M., Fehlbaum, L. V., Tshomba, E., & Stadler, C. (2015). Structural and Functional Alterations in Right Dorsomedial Prefrontal and Left Insular Cortex Co-Localize in Adolescents with Aggressive Behaviour: An ALE Meta-Analysis. *PLoS One, 10*(9), e0136553. doi: 10.1371/journal.pone.0136553

Raybaud, C. (2010). The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. *Neuroradiology, 52*(6), 447-477. doi: 10.1007/s00234-010-0696-3

Sarkar, S., Craig, M. C., Catani, M., Dell'acqua, F., Fahy, T., Deeley, Q., & Murphy, D. G. (2013). Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. *Psychol Med, 43*(2), 401-411. doi: 10.1017/S003329171200116X

Schulte, T., & Muller-Oehring, E. M. (2010). Contribution of callosal connections to the interhemispheric integration of visuomotor and cognitive processes. *Neuropsychol Rev, 20*(2), 174-190. doi: 10.1007/s11065-010-9130-1

Schwarz, C. G., Reid, R. I., Gunter, J. L., Senjem, M. L., Przybelski, S. A., Zuk, S. M., . . . Kantarci, K. (2014). Improved DTI registration allows voxel-based analysis that outperforms tract-based spatial statistics. *Neuroimage, 94*, 65-78.

Sobhani, M., Baker, L., Martins, B., Tuvblad, C., & Aziz-Zadeh, L. (2015). Psychopathic traits modulate microstructural integrity of right uncinate fasciculus in a community population. *Neuroimage Clin, 8*, 32-38.

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., & Poustka, F. (2005). Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biol Psychiatry, 57*(1), 7-15. doi: 10.1016/j.biopsych.2004.10.008

Sterzer, P., Stadler, C., Poustka, F., & Kleinschmidt, A. (2007). A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage, 37*(1), 335-342. doi: 10.1016/j.neuroimage.2007.04.043

Sundram, F., Deeley, Q., Sarkar, S., Daly, E., Latham, R., Craig, M., . . . Murphy, D. G. (2012). White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex, 48*(2), 216-229. doi: 10.1016/j.cortex.2011.06.005

Thomas, A. G., Koumellis, P., & Dineen, R. A. (2011). The fornix in health and disease: an imaging review. *Radiographics, 31*(4), 1107-1121.

Tsivilis, D., Vann, S. D., Denby, C., Roberts, N., Mayes, A. R., Montaldi, D., & Aggleton, J. P. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nature neuroscience, 11*(7), 834-842.

Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A., De Brito, S. A., & McCrory, E. J. (2012). Amygdala response to preattentive masked fear in children with conduct problems: the role of callous-unemotional traits. *Am J Psychiatry, 169*(10), 1109-1116. doi: 10.1176/appi.ajp.2012.12020191

Wallace, G. L., White, S. F., Robustelli, B., Sinclair, S., Hwang, S., Martin, A., & Blair, R. J. (2014). Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. *J Am Acad Child Adolesc Psychiatry, 53*(4), 456-465 e451. doi: 10.1016/j.jaac.2013.12.008

Zhang, H., Yushkevich, P. A., Alexander, D. C., & Gee, J. C. (2006). Deformable registration of diffusion tensor MR images with explicit orientation optimization. *Med Image Anal, 10*(5), 764-785. doi: 10.1016/j.media.2006.06.004

Zhang, J., Gao, J., Shi, H., Huang, B., Wang, X., Situ, W., . . . Yao, S. (2014a). Sex differences of uncinate fasciculus structural connectivity in individuals with conduct disorder. *Biomed Res Int, 2014*, 673165. doi: 10.1155/2014/673165

Zhang, J., Zhu, X., Wang, X., Gao, J., Shi, H., Yi, J., . . . Yao, S. (2014b). Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 53*(4), 466-475. doi: 10.1016/j.jaac.2013.12.015

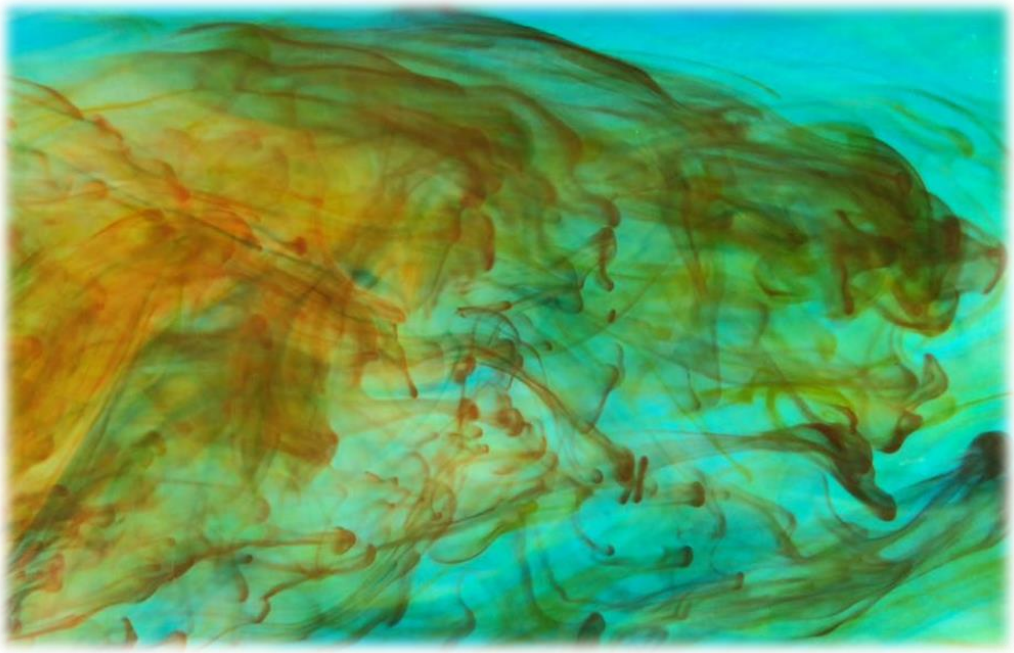
Supplementary material

Supplement 2. *Microstructural white matter alterations in 15 females with CD (CD) and without ADHD comorbidity compared to 20 typically developing controls (TD) using fractional anisotropy (FA) and mean diffusivity (MD).*

#	Brain region	L/R	coordinates of peak location[a] X	Y	Z	Cluster size (number of voxels)	*p*-value[b]
Fractional Anisotropy							
CD>TD							
1	Bilateral corpus callosum (body)	L	-1	-24	24	560	.046
2	Bilateral corpus callosum (body)	L	-13	-22	32	197	.050
3	Corpus callosum (body)[c]	R	1	-25	23	6725	.003
4	Cingulum (cingulate)[c]	R	12	-23	34	159	.022
TD>CD							
5	Cingulum (hippocampal)[c]	L	-22	-20	-27	628	.005
Mean Diffusivity							
CD>TD							
	-						
TD>CD							
1	Corpus callosum (body)[c]	R	4	-25	25	7644	.003
2	Cingulum (cingulate)[c]	R	7	-13	33	903	.008
3	Uncinate fasciculus[c]	R	37	3	-20	58	.047

[a] Neurological view (MNI space). [b] Threshold-free cluster enhancement, $p \leq 0.05$ FWE-corrected. [c] Region of interest

Chapter 5. Eye Gaze and Neural Activation Patterns during Face Processing in Adolescents with Conduct Disorder: An Eye-Tracking Paradigm.



Willeke M. Menks, Lynn V. Fehlbaum, Christina Stadler & Nora M. Raschle

Poster Submission OHBM 2016

Background. Antisocial behavior in adolescence, such as conduct disorder (CD) and oppositional defiant disorder, increases the risk for developing mental and physical health problems in adulthood. Behavioral and neuroimaging research has associated CD with deficits in facial expression recognition (e.g. fearful and angry faces) and altered neural activation during face/emotion processing (Dawel 2012; Fairchild 2014; Jones 2009). However, evidence for the neuronal basis of face processing is limited in CD, especially in relation to eye gaze/attention. Already, in 4- to 8-year-old children CD symptoms and callous-unemotional traits are linked to reduced eye contact (Dadds 2014). The eye-region plays an important role in the recognition of facial expressions. Thus, impaired eye contact could explain the observed dysfunctional face recognition and altered neuronal pattern in CD. So far, no fMRI study has investigated face processing and eye-tracking simultaneously. Our aim is to examine our adapted eye-tracking neuroimaging paradigm and investigate brain activation patterns during emotional face processing in youths with CD compared to typically developing controls.

Methods. We collected whole brain functional neuroimaging (fMRI) data using a 3T Siemens Prisma scanner in 81 youths (average age=15.5♂/15.5♀) with a clinical diagnosis of CD (DSM-5/N=42; 20♂,17♀) and their typically developing peers (N=39; 7♂,20♀) using an age appropriate neuroimaging protocol (Raschle 2012). All participants were behaviorally characterized using standardized clinical interviews/testing, including CU traits and aggression questionnaires. An emotional face processing paradigm (adapted from (Passamonti 2010) was used to investigate emotion processing. Participants have to indicate via button press the sex of angry, fearful, and neutral facial expressions posed by 30 different actors (50% female). Stimuli are presented in a blocked design where 5 faces from one category (angry, fearful or neutral) are pseudo randomly intermixed with 5 null events (fixation cross). Faces are presented for 2000ms, followed by a fixation cross of 750ms; null events consist of a presented fixation cross for 2750ms. During two scan sessions of 8.25min, the participants will view 18 blocks of each stimulus category (see Figure 1). Throughout the task reaction time and accuracy, as well as eye gaze are monitored.

A ViewPoint eye-tracking (Arrington Research®) system recorded real time (X- and Y-position) location and velocity of the right eye's pupil of all participants; from these data points the participant's eye gaze (i.e. fixations and saccades) can be calculated. The collected neuroimaging data was analyzed using SPM12. Preprocessing included realignment, coregistration, segmentation, normalization, smoothing, and artefact detection. Two-sample t-tests for the contrasts 'angry vs. neutral', and 'fear vs. neutral' were computed to compare youths with antisocial behavior with typically developing peers.

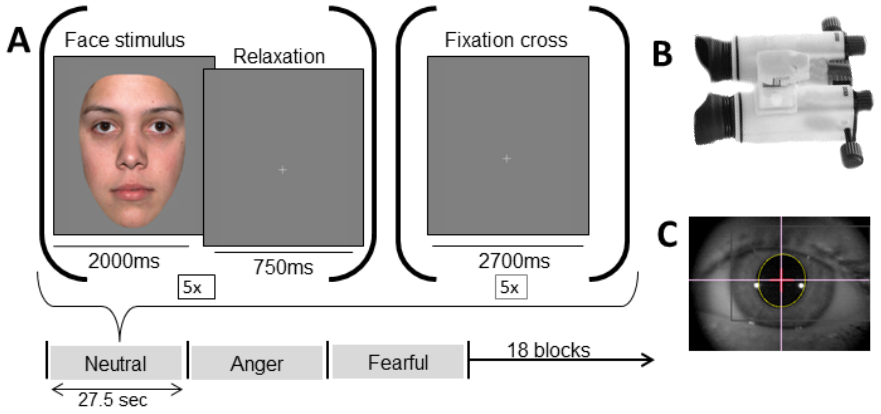


Figure 1. ***(A)*** *Emotion processing paradigm and* ***(B)*** *the Eyetracker system with* ***(C)*** *real-time pupil tracking.*

Results. Behaviorally, individuals with CD display significantly higher CU traits (total YPI (110.8/94.8), total ICU (27.0 /19.2), and the callousness (9.73/5.37) and uncaring (11.5/8.5) ICU subscales). Preliminary neuroimaging analyses indicated that both typically developing adolescents and adolescents with CD activate the emotional network of brain. However, adolescents with CD have more activation in the right caudate, left anterior cingulate, right fusiform area, and right amygdala for angry (angry>null) facial expressions in comparison to their typically developing peers (Figure 2A). Similarly, youths with CD display more activation in the right insula, left caudate, and right fusiform area for fearful (fearful>null) facial expressions (Figure 2B). Compared to the antisocial group, the control had no increased activation pattern on a whole brain level.

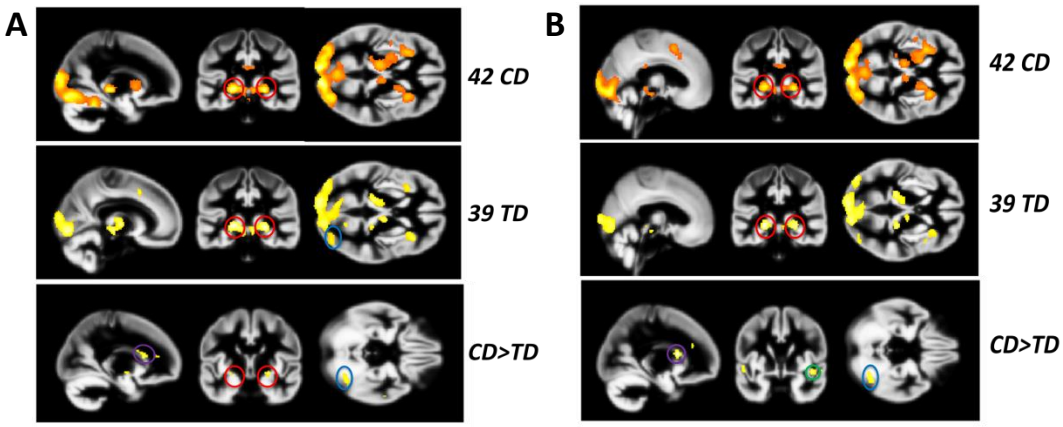


Figure 2. *Statistical parametric maps for looking at* ***(A)*** *angry facial expressions (angry>null) and* ***(B)*** *fearful facial expressions (Fear>null). TD: typical developing; CD: conduct disorder. Red: amygdala. Purple: left caudate. Blue: right fusiform area. Green: right insula. (p>0.005 unc.)*

Preliminary eye tracking data suggests that adolescents with conduct disorder have an atypical eye-gaze pattern –less fixations in the eye regions– compared to typically developed adolescents (see Figure 3.).

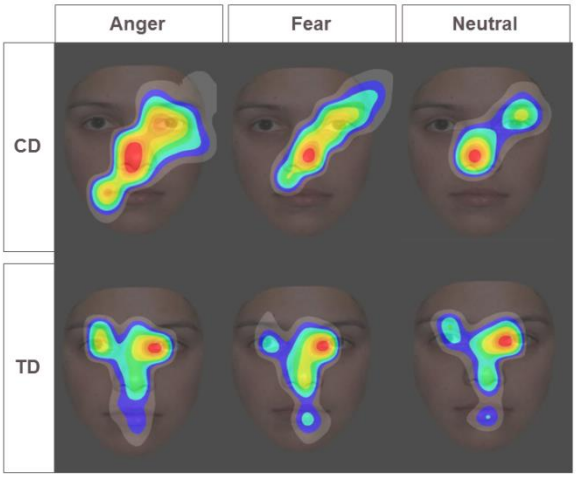


Figure 3. *Heatmaps during angry, fearful and neutral facial expression stimuli.*

Discussion. These whole-brain neuroimaging results demonstrate the effectiveness of our modified emotional-face processing paradigm, since several important regions involved in face (e.g. fusiform) and emotion processing (e.g. amygdala and insula) were activated in our sample of adolescents. Furthermore, youths with conduct disorder displayed altered neuronal activations during facial expression processing compared to controls. Our results will lay the foundation for investigating the neural activation pattern in larger groups (dependent on sex and symptom severity) and linking these activation patterns with eye gaze.

References

Dadds, M. R. (2014). Callous-unemotional traits in children and mechanisms of impaired eye contact during expressions of love: a treatment target? Journal of Child Psychology and Psychiatry, 55(7), 771-780.

Dawel, A. (2012). Not just fear and sadness: Meta-analytic evidence of pervasive emotion recognition deficits for facial and vocal expressions in psychopathy. Neuroscience & Biobehavioral Reviews, 36(10), 2288-2304.

Fairchild, G. (2014). Atypical neural responses during face processing in female adolescents with conduct disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 53(6), 677-687.

Jones, A. P. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. American Journal of Psychiatry, 166(1), 95-102.

Passamonti, L. (2010). Neural abnormalities in early-onset and adolescence-onset conduct disorder. Archives of General Psychiatry, 67(7), 729-738.

Raschle, N. (2012). Pediatric neuroimaging in early childhood and infancy: challenges and practical guidelines. Annals of the New York Academy of sciences, 1252(1), 43-50.

Chapter 6. Emotions and the Brain – or How to Master “the Force” –

Nora M. Raschle, Ebongo Tshomba, **Willeke M. Menks**, Lynn V. Fehlbaum, & Christina Stadler

Frontiers for Young Minds
NEUROSCIENCE
Published: 12 September 2016
doi:10.3389/frym.2016.00016

Abstract

Do you like science fiction? Have you heard of, or are you even a fan of, the famous “Star Wars” series? To summarize, there are rebels, emperors, princesses, robots, and many more fabulous creatures. There is also a power source called “The Force.” It is used by the Jedi (the good ones) but also by the dark side (the evil ones). Only the dark side uses the destructive power of “The Force,” which is based on negative emotions such as fear, anger, jealousy, or hate. A Jedi masters “The Force” and uses it for knowledge and defense by learning to control his emotions. Our research also looks at emotions and how to control them. We know that in our galaxy too, we have more success when we can control our feelings. Therefore, we want to find the brain regions responsible for allowing us to deal with our emotions and to help those children struggling with controlling negative emotions.

Introduction

Imagine walking down the school hall thinking about your next lesson. Suddenly, your best friend jumps out from a dark corner, right in front of you, wearing a silly mask and scaring you. This trick that was played on you immediately led to a reaction of your body. You can feel your heart beating and maybe you just screamed out loudly. A few seconds later though, you recognize your friend and notice there is no real threat. You may even start laughing about the joke. This is an example of how a person can react to an emotional situation. It also shows how our mind processes a situation using different clues. **Emotions** are feelings that (1) are caused by situations that are meaningful or important to you, (2) are something you feel or show through your body language, and (3) may compete with other important things (Gross & Barrett, 2011). In our example, the scary joke gave you the impression of being attacked, and it is important to you to stay unharmed. Your beating heart and the screaming is the reaction of your body. While you are scared and your first intention might be to run away quickly, you also noticed that this was simply your friend playing a joke on you. Being scared and knowing someone is your friend are two different clues that might compete with each other in your brain. One clue tells you to run away in order to stay unharmed, and the other tells you to stay with someone you like (competing reactions). Within a split second, you make a choice about which emotion you find important and which emotion you choose to control or suppress completely. Overall, people tend to choose to decrease negative emotions (anger, sadness, or fear) and increase positive emotions (happiness, love, and joyfulness). Changing or controlling your feelings is an action we call “**emotion regulation**.” The way that you control and change your emotions is called your “emotion regulation strategy.” Looking at data from many people, scientists were able to show that the way you regulate your emotions influences how you feel, but it also affects the people around you (Gross & Barrett, 2011). For example, if you have difficulties controlling your emotions when being angry you may end up cursing, punching, or even bullying the people around you. This is no fun for them either. Therefore, successful emotion processing and regulation is very important for humans. In fact, emotion regulation difficulties are a part of many mental health issues in children, teenagers, and adults.

Using An MRI Camera For Studying The Brain

The way the brain processes and regulates emotions can be studied using a technique called magnetic resonance imaging (MRI). An MRI scanner looks like a big tunnel (see Figure 1A). Actually, it is just a very fancy camera that is able to take images of all the parts inside your body. For example, an MRI camera can take an image of the bones in your leg, of your beating heart, or of the organ we are interested in – the brain. We can use the MRI camera to look at the structure (shape and size) of the brain. When we want to see how the brain works, then we can use an MRI

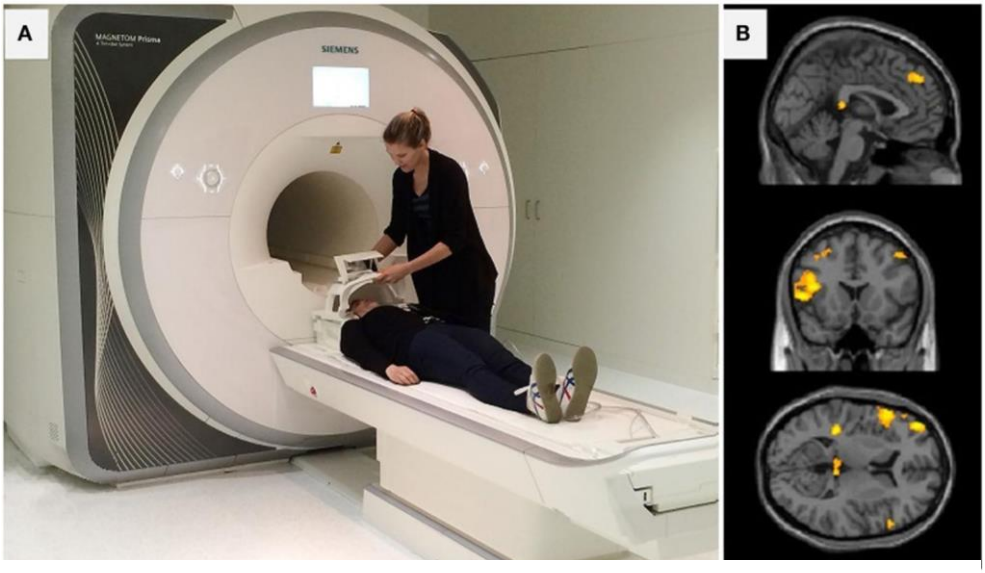


Figure 1. [A] *Two of our research team members showing you an MRI camera and how it is used.* ***[B]*** *Different views of a child’s brain as taken by an MRI camera. The areas that are colored yellow are important for emotion processing and regulation.*

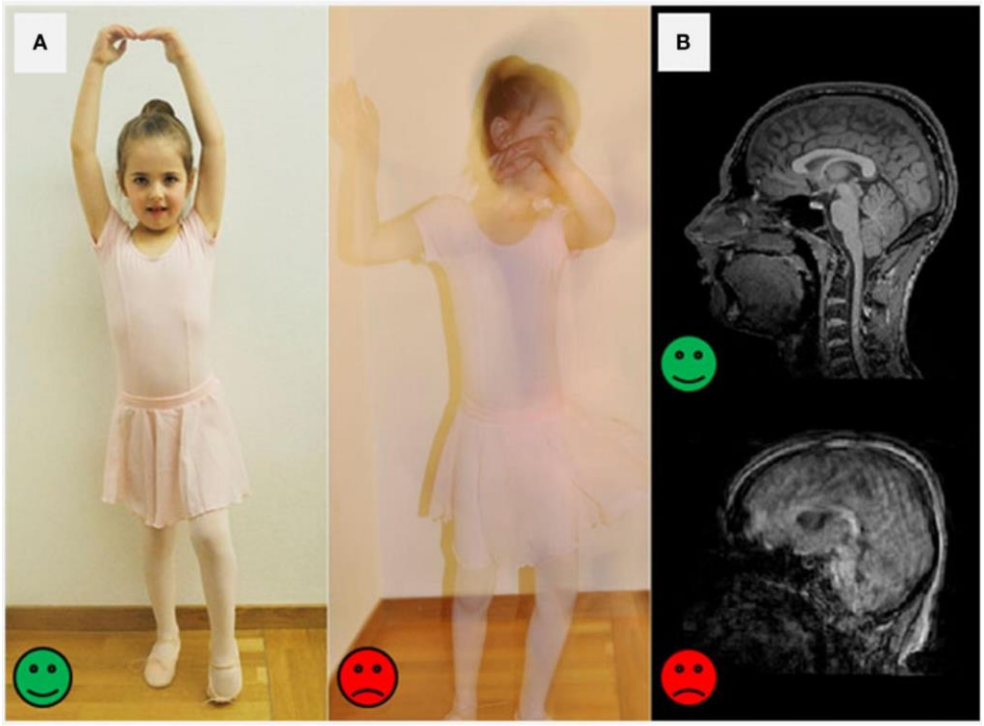


Figure 2. Why staying still during an MRI session is important: [A] *A picture taken by a regular camera can be very sharp when the person is standing super still (green happy face). But when the person is moving a lot, the picture becomes blurry (red sad face).* ***[B]*** *The same is true when taking brain pictures. The pictures can turn out super sharp when the person stays still (green happy face) or blurry and hard for scientists to read for when the person wiggles around (red sad face).*

camera to look at brain function. Just as you need more food when you do sports, your brain also needs more energy when it becomes active, but instead of food it needs oxygen. Therefore, when a specific region in the brain is hard at work, it will get more oxygen transported to it by the bloodstream. We call this blood oxygen-rich. Oxygen-rich blood gives different signals to the MRI camera compared with blood that has less oxygen. Using this knowledge, researchers can create an image of both the brain’s structure and function. With special computer programs, we can make pictures like the ones in Figure 1B. One of the most amazing things is that the MRI camera can take pictures of your brain at work without even touching you! But there are some challenges for people who take part in research studies using an MRI. Two of the biggest challenges are that (1) you have to stay super still while the pictures are taken or they become blurry (for an explanation, see Figure 2) and (2) you have to protect your ears against the noise. Big cameras such as an MRI can be quite loud, which is why you need to wear special headphones. Staying still can be practiced with fun games, such as the freezing game, where you have to stay still like an ice statue. If you want to know more and see what MRI experiments involving young children look like, you can watch the following video (http://www.jove.com/video/1309/ making-mr-imaging-child-s-play-pediatric-neuroimaging-protocol; Raschle et al., 2009).

What does the brain look like while processing and regulating emotions?

Now, in the first section, you learned about feelings, which scientists call emotions. You heard that emotions can lead to a reaction in your body. You also know that sometimes we experience several emotions at once and that sometimes it is necessary to control a feeling and not to act on it. This process is called emotion regulation. In the second section, you learned how an MRI camera works and how it can be used to take images of the structure and function of the brain. In the next section, we want to combine these two things and talk about the parts of the brain that are responsible for processing and regulating emotion.

Using MRI cameras, scientists have shown that emotions are processed by many different areas of the brain. There is not just one place that is responsible for processing an emotion. Several brain regions work together as a team. This is why scientists say that emotions are processed by a network of brain regions. A network of brain regions that process emotions is called an emotion- processing network (see Figure 3). Let us name some of those brain regions that are activated by emotions. They are the amygdala, the prefrontal cortex, the cingulate cortex, the hippocampus, and the basal ganglia (Phan et al., 2002). Fancy names, but it is not these names you need to remember. What is important to understand is that there are many brain regions involved during emotion processing. All the different regions have their own job and they all work together to identify and control an emotion. The

amygdala, for example, is a tiny part of the brain (it has the shape and size of an almond), and it is responsible for handling both positive and negative information. The amygdala is especially important when we experience the emotion of fear. Another region of the emotion processing network is the prefrontal cortex, which is named after its location: in the front of the brain. The prefrontal cortex is like a control center, helping to guide our actions, and therefore, this area is also involved during emotion regulation. Both the amygdala and the prefrontal cortex are part of the emotion network. Just like good friends, these different brain regions stay in touch and communicate frequently with each other. For example, the amygdala (the emotion center) can detect an important fearful event and transport that information to the prefrontal cortex (the control center). The prefrontal cortex gets the message that there is something scary happening. If necessary, this control center at the front of your head sends commands to other brain regions telling them to move your body and run away. To sum it up, many brain regions work together to process and react to an emotional situation (see Figure 3).

What happens in the brain when emotion processing fails?

By now, you understand that feelings are complicated and that emotions are represented and processed by many regions in the brain. You also remember that successful emotion regulation is important for a persons’ well-being and central for the people around them. As mentioned before, it can be really difficult to be around people that are constantly cursing, hitting, or bullying the people around them because they cannot control their negative emotions. Unfortunately, some children struggle more than others with their emotions. Imagine you have a classmate named Jamie, who has problems with regulating emotions, especially anger and fear. Now picture that you make a silly joke with Jamie, but instead of laughing, Jamie gets very upset and maybe even starts fighting with you. This is an example of someone who has emotion regulation difficulties. Such difficulties in handling emotions can often be observed in very aggressive (frequently fighting and bullying) and antisocial (breaking rules) teenagers. Research studies have shown that these teenagers cannot always successfully identify their emotions. It can also be very hard for these children to control their emotions, like in the case of Jamie. This is not fun for you, if you become a victim of Jamie when he wants to fight you. But it is also not fun for Jamie, who might be expelled from school for his behavior. It is no fun either for his parents or the people around him. You can see that many individuals are affected by Jamie’s difficulties controlling his emotions.

Because we are interested in how the brain processes and regulates emotions, we do a lot of work with children who can successfully handle their emotions. We also invite children who struggle with emotion processing and regulation to see whether their brain structure and function looks any different from the children who do not have trouble with emotion processing. So far, there have been several small studies, suggesting that there are differences in brain function and structure in children with aggressive behavior (Sterzer et al., 2007). But, as our MRI section describes, there are challenges when doing research studies with younger participants. For example, it is very hard for children to stay very still while the MRI takes pictures (Figure 2A). Because of this, most studies have a very small number of participants, and the results are not as clear. A method called "**meta-analysis**" helps to summarize the information from all of these very important small studies. Meta-analysis takes the results of many studies and combines them into one big finding. For example, we have combined all small studies done so far in children and teenagers with aggressive behavior (Raschle et al., 2015). While each study had a maximum size of about 40 participants, combining all of them into one meta-analysis allowed us to look at over 500 children at once. By doing so, we were able to show changes in both brain structure and brain activity (function) in the emotion processing network in aggressive teenagers (Figure 3).

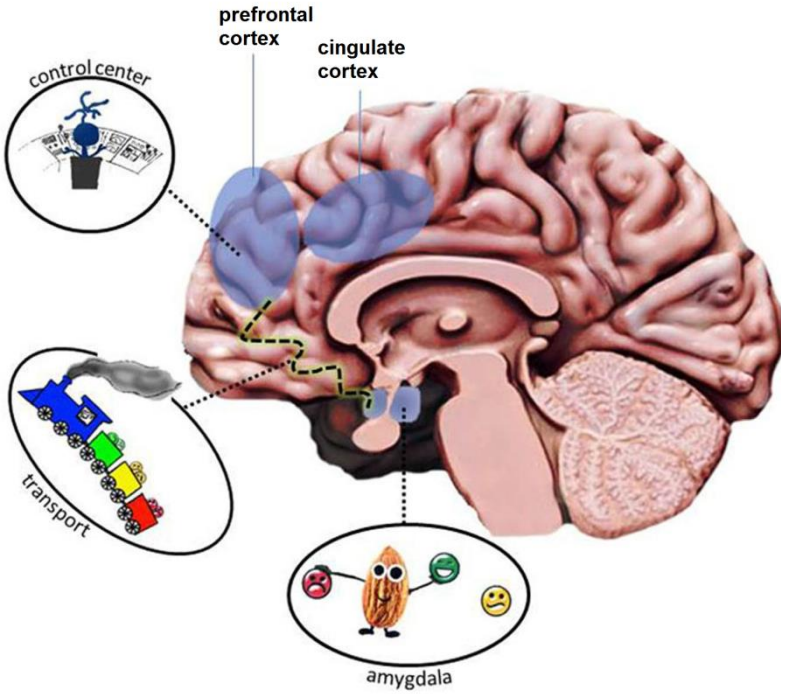


Figure 3. The emotion processing network includes several areas of the brain. *Some of these areas are shown here shaded in blue and you can see their different jobs: the amygdala (almond) recognizes and sorts the emotions before transporting them to other areas. In the picture, this transportation is visualized by a train driving along the dotted track line to the most frontal part of the brain. Once the information arrives there, the prefrontal cortex and the cingulate cortex act as a control center (little man behind desk), deciding what has to be done next with the incoming emotions. Many areas work together to process an emotion! (illustration by Menks).*

May “the force” be with you!

To summarize, emotions are feelings that are processed by a team of brain regions. Emotion processing is a complicated process, which sometimes does not work so well. Difficulties with emotion processing and regulation are found in children and teenagers with very aggressive and antisocial behavior. Using structural and functional neuroimaging techniques, we showed that areas of the emotion processing network of the brain are different in the youths with aggressive behavior. Luckily, the brain has the ability to change and adapt, especially when people are still young. The more we know about how our brain develops and how it processes and regulates emotions, the more we can help children with emotion processing problems. This knowledge also helps doctors to choose the most helpful treatment for these children. For example, if we know that a child struggles with recognizing an emotion, then that is what we teach them to practice. Or if we see that a child cannot control his emotions, we teach him ways to do so. In the end, we want to understand and teach others how to deal with feelings of anger, fear, and aggression in a good way. We hope that we can help those children struggling with their emotions and bring all of us a little closer to the “Jedi in us.”

Funding

CS has received funding through FemNAT-CD, a collaborative project by the European Union under the 7th Framework Program (grant agreement no. 602407). NR received funding through the Psychiatric University Clinics and the University of Basel.

References

Gross, J. J., and Barrett, L. F. 2011. Emotion generation and emotion regulation: one or two depends on your point of view. Emot. Rev. 3:8–16. doi:10.1177/ 1754073910380974

Raschle, N. M., Lee, M., Buechler, R., Christodoulou, J. A., Chang, M., Vakil, M., et al. 2009. Making MR imaging child’s play – pediatric neuroimaging protocol, guidelines and procedure. J. Vis. Exp. doi:10.3791/1309

Phan, K. L., Wager, T., Taylor, S. F., and Liberzon, I. 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16:331–48. doi:10.1006/nimg.2002.1087

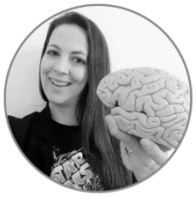
Sterzer, P., Stadler, C., Poustka, F., and Kleinschmidt, A. 2007. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. Neuroimage 37:335–42. doi:10.1016/j.neuroimage.2007.04.043

Raschle, N. M., Menks, W. M., Fehlbaum, L. V., Tshomba, E., and Stadler, C. 2015. Structural and functional alterations in right dorsomedial prefrontal and left insular cortex co-localize in adolescents with aggressive behaviour: an ALE meta-analysis. PLoS ONE 10:e0136553. doi:10.1371/journal.pone.0136553

Reviewers

Riverside Elementary School, 9–10 years old. Riverside Elementary School serves children from prekindergarten through fifth grade in Princeton, NJ, USA. Our diverse student body includes children from more than 23 different countries, and we all love to learn about brains! We also have a science lab, a courtyard with frogs and box turtles, a team of dedicated teachers and support staff, and a great principal who always supports new opportunities for learning. Fourth grade students are either in Ms. Levy’s or Mr. McGovern’s classroom, and Mr. Eastburn is their teacher in the science lab.

Authors



Nora Maria Raschle. I am a developmental neuroscientist, and I have always been fascinated by how the brain makes us tick. I am particularly interested in understanding how the brain develops, how it learns, and what might be going on if it does things a bit differently in one child compared to other children. You kids are the ones with all the answers for me, and I enjoy very much working and learning from you. I also like Star Wars, shooting stars, rock climbing, rock music, and Roquefort.

Ebongo Tshomba. I am a master’s student of psychology and work as an intern at the Department of Child and Adolescent Psychiatry in Basel. Two things are especially exciting about our research field: working with kids and looking at brains. I also enjoy dancing to Caribbean music, planning adventurous trips, and I just recently did a “Star Wars” puzzle with 2000 pieces.

Willeke Martine Menks. I am a biologist from the Netherlands, and I am intrigued by the brain and human behavior. I currently work in Switzerland where I study the brains of children with behavioral problems. With the help of my favorite machine (the MRI scanner), I try to answer difficult questions as: “How does our brain recognize emotions?” and “What happens in the brain when you have behavioral problems?” And besides all this science fun, I bake silly cakes, travel around the world, love to dance, and play basketball.

Lynn Valérie Fehlbaum. I am a PhD candidate at the Department of Child and Adolescent Psychiatry at the Psychiatric University Clinics in Basel, Switzerland. I like brains and enjoy working with children. In particular, I am interested in how the child’s brain develops and how it responds to different environmental settings and individual characteristics, such as aggressive behavior. I believe that an increased knowledge about the mechanisms of your brain can help us understand kids even better!

Christina Stadler. I am a professor working at the University Hospital for Child and Adolescent Psychiatry in Basel. I would like to better understand why some children sometimes become rapidly stressed and often react very aggressively. From my clinical work, I learnt that the reasons often lead back to negative living conditions in which the children grew up. It seems that because of these negative experiences, kids with aggressive behavior have developed a super sensor to detect signs of danger. Thus, one of my research interests is to investigate the biological mechanism of this super sensor in order to better understand those children who have problems inhibiting aggressive behavior.

Chapter 7. General Discussion

The central aim of this dissertation was to further the neuroscientific knowledge of antisocial behavior in children and adolescents by investigating the underlying structural and functional neurobiological characteristics, with an extra focus on possible sex differences and the neural correlates of callous-unemotional traits. **First**, we aimed to aggregate and summarize the current neuroimaging literature, through meta-analyses, with the purpose of overcoming the heterogeneity of antisocial behavior and generating a common "overlapping" pattern of structural and functional atypicalities in youths with antisocial behavior. **Secondly**, the relation between callous-unemotional traits and brain structure was investigated separately for sex and independently of psychiatric comorbidities. **Thirdly**, this work investigated white matter structures within a homogenous group of girls with conduct disorder –the severe variant of antisocial behavior– in comparison to typically developing girls. **Fourthly**, this dissertation presents preliminary neural and eye-gaze results from a novel-developed eye-tracking paradigm, which lays the foundation for studying the direct relationship between neural-activation patterns and attention to social cues (i.e. eye-region of faces) within a cohort of youths with antisocial behavior. **Additionally**, we have translated the results from our meta-analysis project to the general public using accessible language, attractive illustrations, and popular examples (e.g. Star Wars), in order to raise awareness about antisocial behavior and the importance of neuroscience research in youths. The following sections elaborate and summarize the key findings, strengths, and challenges of this dissertation, as well as the impact of this work on the current research field and future prospects.

7.1. Structural and functional neural patterns in gray matter

This dissertation presents novel evidence for distinct structural and functional neural patterns in children and adolescents with antisocial behavior. We observed a consistent pattern of gray matter reductions and hypoactivations in brain areas that are involved in the emotion processing and regulation network (e.g. prefrontal and limbic cortex). Our findings are in line with other recent meta-analyses investigating neural correlates of antisocial behavior in youths (Rogers & De Brito, 2016) and adults (Aoki, Cortese, & Tansella, 2015; Yang & Raine, 2009). Especially structural atypicalities within the insula were a recurring theme within this work. Insula volume was not only correlated with antisocial behavior throughout the preceding literature (chapter 2) but also positively correlated with callous-unemotional traits independent of clinical antisocial behavior (chapter 3). For this latter study, we have constructed a novel composite score for callous-unemotional traits based on multiple sources (i.e. parental and self-report) and instruments (i.e. ICU and YPI questionnaire). This new composite score had a higher internal reliability (Cronbach's alpha of 0.83; see chapter 3, supplement 2) than the two individual dimensions

commonly used, thus informing the importance to use several information sources when investigating callous-unemotional traits. In the following paragraphs we will shortly review the key areas found in this dissertation that contained atypical structural and functional gray matter in youths with antisocial behavior: amygdala, insula, and prefrontal cortex.

7.1.1. Amygdala

The amygdala is a key-player within the emotion processing network (see Figure 1.; Haxby, Hoffman, & Gobbini, 2000), hence this structure is crucial for the perception and encoding of emotionally loaded stimuli (Garavan et al., 2001; Irwin et al., 1996; LeDoux, 2000; Lindquist et al., 2012), empathy (Baron-Cohen et al., 1999; Carr et al., 2003), and moral reasoning (Luo et al., 2006). Empirical research has repeatedly connected altered amygdala functioning and structure to antisocial behavior in adulthood (Boccardi et al., 2011; Contreras-Rodriguez et al., 2014; Craig et al., 2009; Ermer et al., 2012; Glenn, Raine, & Schug, 2009; Kiehl et al., 2001; Marsh & Blair, 2008b; Osumi et al., 2012; Pardini et al., 2014; Raine & Yang, 2006; Yang et al., 2009b). Consequently, amygdala dysfunction is suggested to be one of the core features and possible marker in the symptomatology of antisocial behavior (Blair, 2003, 2008b; Boccardi et al., 2011; Carre et al., 2013; Craig et al., 2009; Crowe & Blair, 2008; Dadds et al., 2006; Gao et al., 2009; Glenn & Raine, 2008; Jones et al., 2009; Marsh et al., 2013a; Weber et al., 2008). Consistent with the literature, our meta-analyses have identified functional and structural abnormalities in the right and left-hemispheric amygdala in youths with antisocial behavior. These findings are in line with the proposed neurobiological model that associated amygdala dysfunction with impaired emotional empathy (Blair, 2013).

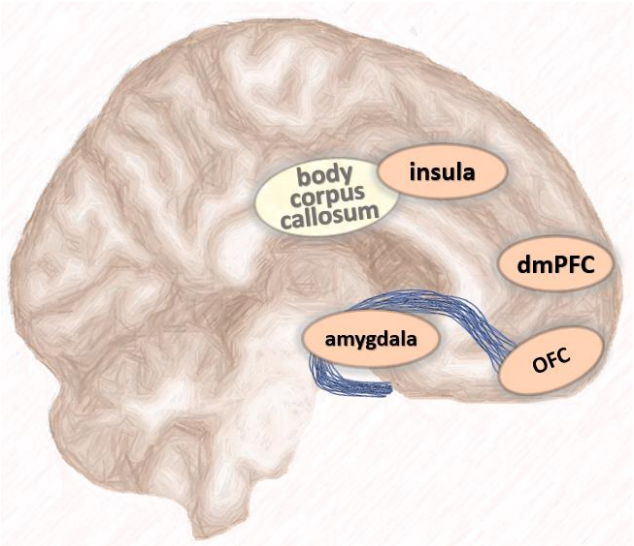


Figure 1. Schematic overview of major findings within this dissertation. *Gray matter reductions and/or hypoactivation within the insula, amygdala, orbitofrontal cortex (OFC), dorsomedial prefrontal cortex (dmPFC)) of youths with antisocial behavior. White matter alterations within the body of the corpus callosum (white) and uncinate fasciculus (blue lines) of girls with conduct disorder.*

7.1.2. Insula

The insula is part of the cerebral cortex and is bi-directionally connected to various brain regions, including the orbitofrontal cortex, anterior cingulate, parietal, temporal cortices, and the amygdala (see Figure 1.; Dupont et al., 2003). Neuroimaging evidence supports a generic role of the insula in the awareness of bodily sensations and affective feelings, but also during processing of emotions such as anger and disgust (Craig, 2009; Lindquist et al., 2012; Phan et al., 2002; Phillips et al., 1997). Both hypo- and hyperactivity of the insula are linked to antisocial behavior, especially during tasks of emotion processing and empathy (Anderson et al., 2017; Decety et al., 2013; Fairchild et al., 2014; Fan et al., 2011; Klapwijk et al., 2015; Lockwood et al., 2013; Phan et al., 2002; Rubia et al., 2009; Sundermann & Pfleiderer, 2012). Also thinning and reduced density of gray matter within the insula are commonly found in adults with psychopathy (Gregory et al., 2012; Ly et al., 2012; Schiffer et al., 2011) and negatively related to psychopathic traits (Cope et al., 2012; Ermer et al., 2012). In line with the literature of adult antisocial behavior and the proposed neurobiological model, our meta-analyses indicated several clusters of hypoactivations and gray matter reductions within the insula in youths with antisocial behavior. Furthermore, these functional and structural atypicalities were partly overlapping in the same part of the left insula, which could point towards a robust neural correlate of antisocial behavior in youths functioning as a potential neural marker (see chapter 2).

Interestingly, our whole-brain multiple regression analyses (chapter 3) indicated a strong positive correlation between callous-unemotional traits and increased gray matter density in the bilateral anterior insula of typically-developing boys. This is in contrast to previous studies in adults (Cope et al., 2012; de Oliveira-Souza et al., 2008; Ermer et al., 2012) that suggested an opposite -negative- relationship between callous-unemotional traits and the insula volume. So far, one study has observed decreased bilateral insula volume in youths with antisocial behavior that was negatively correlated with empathy scores (Sterzer et al., 2007). The discrepancy in correlation direction between Sterzer et al. (2007) and our results could be attributed to different sample selection (i.e. sample size, clinical diagnoses, ADHD comorbidities) or behavioral dimensions (i.e. callous-unemotional traits or empathy) assessed. No significant relationship was found between callous-unemotional traits and gray matter volume in girls. Research reporting sexual-dimorphism in the brain-development trajectories for both insula and whole-brain gray matter may explain the observed sex differences (Giedd & Rapoport, 2010; Lenroot et al., 2007). Thus, our findings highlight the importance of including both sexes for comparison in future studies.

7.1.3. Prefrontal cortex

The prefrontal cortex (PFC) consist of multiple regions, including the orbitofrontal and dorsomedial prefrontal cortex, that show aberrant brain function and structure in youths with antisocial behavior (see Figure 1.). The overall main function of the PFC is cognitive control, such as self-regulation, decision making, planning, and achieving goals/actions (Miller & Cohen, 2001). Particularly the medial prefrontal cortex (dmPFC) has been implicated in emotional self-regulation (Davidson, Putnam, & Larson, 2000), general self-referential activities (D'Argembeau et al., 2007) and emotion-related decision making (Euston, Gruber, & McNaughton, 2012). Empirical evidence has linked the prefrontal cortex to antisocial behavior in adults (Anderson et al., 1999; Beyer et al., 2014; Blair, 2003; Blair, 2007a, 2007b; Decety et al., 2013; Raine et al., 2000; Yang et al., 2009a). Our meta-analysis in chapter 2 has indicated several areas within the prefrontal cortex (i.e. OFC, dmPFC) with reduced gray matter density and hypoactivations in youths with antisocial behavior compared to healthy peers. Hence, our findings align with previous studies and recent meta-analytical findings (Aoki et al., 2015; Rogers & De Brito, 2016; Yang & Raine, 2009), but also partly correspond with the neurobiological model proposed by Blair (2013) that linked the dmPFC with impairments in decision making. Importantly, our functional and structural alterations overlap within the same region of the dmPFC; this point out the possibility of the OFC and dmPFC as future neural markers for antisocial behavior in youths.

7.2. Neural connectivity in antisocial behavior.

Research has suggested that the previous mentioned gray matter structures (i.e. the amygdala, insula, and prefrontal cortex) are interconnected through white matter tracts within the prefrontal-limbic circuitry, and thus it is proposed that one specific tract, i.e. the uncinate fasciculus (see Figure 1.), is altered in individuals with antisocial behavior (Blair, 2008a; Craig et al., 2009; Finger et al., 2012; Marsh et al., 2011a). In chapter 4, we described alterations within several white matter tracts including the uncinate fasciculus, which showed a small cluster of decreased mean diffusivity (MD) but not atypical fractional anisotropy (FA) as is observed in previous studies (Sarkar et al., 2013; Sobhani et al., 2015; Zhang et al., 2014a). Importantly, this dissertation presented the first whole-brain DTI analysis in girls with conduct disorder that had as outcome white matter alterations within the body of the corpus callosum (see Figure 1.). These findings, corrected for age and independent of ADHD symptoms, align with boys with antisocial behavior (Breeden et al., 2015; Passamonti et al., 2012; Sarkar et al., 2013; Sobhani et al., 2015; Zhang et al., 2014a; Zhang et al., 2014b). The corpus callosum is the largest white matter tract of the brain and crucial for interhemispheric communication, and thus critical for enabling higher order skills such as emotion regulation (Raine et al., 2003). Furthermore, fibers of the callosal body connect to the insula (Raybaud, 2010), this structure is associated with emotion processing and, as mentioned before,

commonly affected in youth presenting antisocial behavior (see chapter 2) and correlated with callous-unemotional traits (see chapter 3). We therefore hypothesize that our observed alterations within the corpus callosum may result in reduced interhemispheric processing within the limbic system and consequent lower emotion regulation abilities in girls with antisocial behavior.

7.3. Strengths and limitations

This dissertation has an overall important strength, namely the inclusion of homogenous samples to investigate the distinct neurobiological correlates of antisocial behavior in youths; this will not only benefit the results' accuracy but will also facilitate the interpretation and comparison of our results with past and future research. As mentioned before, antisocial behavior is a heterogeneous disorder composed of various psychiatric subdiagnoses (e.g. ODD and CD) or subtypes (e.g. CU traits, proactive or reactive aggression), each variant could distinctively influence brain structure and function (Fairchild et al., 2013b; Fanti, 2016; Klahr & Burt, 2014; Stadler, Poustka, & Sterzer, 2010). Thus, creating homogenous groups in neuroimaging studies is a necessity to avoid biased results in relation to antisocial behavior, and to incrementally understand the complex etiology of antisocial behavior. Consequently, to strengthen the results of this dissertation we have included solely patients with conduct disorder (the severe variant of antisocial behavior) in chapter 4 and 5. Furthermore, another strong point of this work is that our studies' results are independent of the common comorbidity ADHD, a disorder known to considerably affect neural characteristics (Castellanos-Ryan et al., 2014; Castellanos et al., 2002; Rubia et al., 2008). For example, chapter 4 controlled for ADHD symptoms in twofold. First, girls with ADHD comorbidities were initially included for the primary analysis and then excluded from a secondary analysis; a comparison of both outcomes indicated no significant influence of ADHD comorbidity on our results. Second, a post-hoc multiple regression analysis was performed to measure the variance in white matter that is explained by ADHD symptoms, as was done in earlier studies (Fairchild et al., 2011; Pape et al., 2015; Passamonti et al., 2012). A more stringent method is used for Chapter 3, here typically developing and non-aggressive youths free from ADHD and other psychiatric disorders were included: in this manner any possible comorbidity is excluded from affecting the data.

Another important factor that needs mentioning are sex differences, which recently became a more crucial criterion within the research field of antisocial behavior (Moffitt & Caspi, 2001; Silverthorn & Frick, 1999; Vloet et al., 2014). Nevertheless, the vast majority of empirical research on antisocial behavior has been conducted with male participants. Even though, sex differences are commonly observed in the adolescent brain (De Bellis et al., 2001; Giedd et al., 1999; Lenroot & Giedd, 2010; Lenroot et al., 2007). Multiple behavioral studies have suggested sex-dependent developmental trajectories for antisocial behavior (Cohen et al., 1993; Eley et al., 1999; Fairchild et al., 2014; Lahey et al., 2006; McCabe et al., 2004; Odgers et al., 2008; Silverthorn & Frick, 1999;

Veenstra et al., 2006), however, only few neuroimaging studies have investigated sex differences in youths with antisocial behavior on a neural level (Fairchild et al., 2013a; Zhang et al., 2014a). The reason for this low number of female studies is probably the lower prevalence-rate of girls with antisocial behavior (Moffitt et al., 2001; Vloet et al., 2014). Therefore, the investigation of possible sex effects was a relevant theme in this dissertation, and was successfully explored by including and analyzing both sexes independently (chapter 3 and 5) or including solely female participants (chapter 4). Unfortunately, all of the above mentioned criteria for homogenous grouping could not be implemented in our meta-analysis (chapter 2), since the study inclusion was limited by the scarceness of neuroimaging studies investigating young samples with antisocial behavior. To overcome this limitation, we implemented other stringent inclusion criteria (e.g. specific fMRI paradigms and analysis methods) to improve the analytical accuracy of our meta-analyses examining the robustness of previously found neural correlates in youths with antisocial behavior.

Despite the above mentioned strength of this dissertation one limitation within three of our studies (chapter 2, 4 and 5) has to be addressed: the discrimination based on the age of onset –childhood-onset or adolescent-onset– of the antisocial behavior was not taken into account for our patient populations. Time-of-onset group distinction was proposed by empirical research decades ago (Aguilar et al., 2000; Moffitt, 1993; Moffitt et al., 1996; Odgers et al., 2007; Odgers et al., 2008), and is nowadays incorporated into the DSM-V (APA, 2013). Not only are individuals with childhood-onset (i.e. symptoms prior to age of 10 years) more likely to persist their antisocial behavior into adulthood, they also differ in structural and functional neural patterns from individuals with adolescent-onset antisocial behavior (Fairchild et al., 2011; Huebner et al., 2008; Hyatt et al., 2012; Passamonti et al., 2010; Stadler et al., 2007). Age-of-onset could therefore be an important criterion to take into account, however, it should be noted that girls have more often an adolescent-onset diagnosis than boys, indicating again the importance of sex differences in antisocial behavior (McCabe et al., 2004). In this dissertation, dividing our participants based on onset-type lead to extreme unbalanced groups, and excluding either the child-onset or adolescent-onset group would have decreased the analytical power to such an undesirable level that we have decided to combine both onset-types (chapter 4 & 5). Investigating boys and girls with antisocial behavior separately and divided according to onset-type should be the aim for future research studies in the neuroscience field. Furthermore, longitudinal studies –from childhood to adulthood– are necessary to gain more insight into the developmental trajectories of antisocial behavior. Another potential limitation is alcohol/substance abuse (chapter 4 and 5), a factor known to affect the brain (Bellis et al., 2005) and frequently associated with antisocial behavior (Crowley et al., 2001; Fergusson, Horwood, & Ridder, 2007). Even though, a minority of our patient population

had an alcohol/substance-use comorbidity, measured through the diagnostically interview (K-SADS-PL; Delmo et al., 2000), we cannot exclude potential effects on our results.

7.4. Future prospects

The present work furthers the knowledge about the neurobiological basis of antisocial behavior in youths using several neuroimaging techniques to measure different brain characteristics, such as gray matter, white matter tracts, and brain activity. A better understanding of the developmental trajectory of antisocial behavior could not only improve individualized diagnostics and facilitate early detection of children at risk, but could also stimulate the improvement of effective treatments and intervention programs. Early neural markers may help, since a timely start of intervention program precedes success (Pardini & Frick, 2013). Thus, increased knowledge allows health care institutions and juvenile systems to provide better personalized care for children and adolescents with antisocial behavior.

Several recommendations can be made for future studies to advance the understanding of antisocial behavior in youths. Future neuroimaging studies should take sex differences into account when investigating antisocial behavior in youths, for example, by means of avoiding mixed-gender groups or adding sex as a factor within statistical analysis. Considering the lower prevalence rate of girls with antisocial behavior, more effort should be made to recruit and investigate girls with antisocial behavior, a good example is the multi-disciplinary study FemNAT-CD that will recruit and investigate the neurobiology of 400 girls (and 400 boys) with conduct disorder across Europe (https://www.femnat-cd.eu/), chapter 3 contains data from this consortium.

Future studies implementing longitudinal designs may enable us to shed more light on the developmental pathway of antisocial behavior. This line of research also enables us to identify possible predictors or markers (e.g. brain correlates, behavior) for antisocial behavior; such predictors are beneficial for the improvement of prevention and treatment programs. Longitudinal designs will further allow the investigation of the bidirectional influence of neurobiological, psychobiological, and environmental influences on developing antisocial behavior. Furthermore, based on chapter 3 we suggest more studies need to examine the relationship between callous-unemotional traits and brain structure, not only in typically-developing individuals, strictly at-risk children, or those with antisocial behavior, but across the whole spectrum.

In chapter 5 we introduced preliminary results of eye gaze and neuronal activation during emotional face processing compared between youths with and without antisocial behavior. So far,

no fMRI study has investigated emotion processing and eye-tracking simultaneously. The effectiveness of our online eye-tracking neuroimaging paradigm is validated and we aim to finalize this project in the near future. We recommend future studies to combine biological measurements (e.g. heart rate, hormonal levels, genes) with neuroimaging data to improve the understanding of the complex neurobiological background of antisocial behavior in youths.

Additionally, we want to highlight the importance of fellow researchers translating their noteworthy scientific results to the public in order to raise general awareness of the investigated topic and its importance to society. Scientific publications are written using scientific language and a multitude of field-specific jargon. Therefore, scientists are encouraged to write their discoveries in an accessible language, in this way the general population is invited to read and further their knowledge about various scientific topics in a comfortable and leisurely manner (for example, see chapter 6). The topic of this dissertation may interest a broad audience since it concerns a generally known ("popular") child- and adolescent disorder. This increases the likelihood that parents, teachers, care givers, and even youths are interested in reading articles about the neurobiology of antisocial behavior. Additionally, public awareness is also beneficial for the researcher self, since enhanced public awareness of the topic could facilitate the recruitment of participants and funding for future or continuing study projects (e.g. longitudinal designs).

7.5. Conclusion

The results presented in this dissertation expand our current knowledge on the structural and functional neural correlates in children and adolescents with antisocial behavior in several ways. The results of this dissertation investigated the robustness of past study results in youths with antisocial behavior and provide future research a helpful informative background of the consistently altered brain regions in youths with antisocial behavior. Prior research has already demonstrated that callous-unemotional traits –a marker for severe antisocial behavior– affect the gray matter volume in several brain areas of youths with antisocial behavior (De Brito et al., 2009; Fairchild et al., 2013a; Wallace et al., 2014). However, this relationship has not been investigated – to our knowledge– independently of antisocial behavior and its comorbidities such as ADHD, depression, and anxiety. This thesis has observed gender-specific effects of callous-unemotional traits on gray matter volume in a large international population of typically developing youths, independent of psychiatric disorders. Thus providing original knowledge to this topic and new evidence for the importance of callous-unemotional traits and gender effects in antisocial behavior. In contrast to gray matter, the characteristics of white matter are less extensively investigated within antisocial behavior; this is especially true for girls. This work has expanded the current literature with novel findings of integrity alterations in white-matter structures of girls with conduct

disorder (i.e. the more severe variant of antisocial behavior); this work found no correlation between these observed white matter alterations and ADHD comorbidity or callous-unemotional traits.

An overall conclusion that emerged from our studies is that children and adolescents with antisocial behavior have robust gray and white matter alterations but also altered neural-activation patterns compared to their typically developing peers. Comparable brain alterations exist in adults with antisocial behavior (Bertsch et al., 2013; Birbaumer et al., 2005; Contreras-Rodriguez et al., 2014; de Oliveira-Souza et al., 2008; Ly et al., 2012; Muller et al., 2008). These similar-affected brain areas could serve as possible (predictive) markers for antisocial behavior in adulthood and throughout life; however, longitudinal studies –from child to adult– are needed to examine the possibility of such neurobiological markers and to inform research about the development trajectory of antisocial behavior. Furthermore, the results presented in this dissertation also point to a substantial impact of callous-unemotional traits on the young brain (i.e. insula) independent of the presence of clinical antisocial behavior, however, sex-dependent differences were observed. Future studies are necessary to further investigate callous-unemotional traits and gender differences within children and adolescents with antisocial behavior. Furthermore, due to the heterogeneity within groups of youths with antisocial behavior, it is a necessity to define homogenous cohorts based on sub diagnoses, comorbidities, age, gender, and substance abuse. We also recommend to investigate antisocial behavior in combination with previously identified biological and environmental risk factors (e.g. genetics, hormones, or childhood maltreatment). The findings within this dissertation encourage future studies to further investigate the developmental trajectories and potential neural markers of antisocial behavior in order to enhance early detection and improve intervention programs, which could ultimately reduce antisocial behavior and delinquency in our society.

References

Abe, O., Takao, H., Gonoi, W., Sasaki, H., Murakami, M., Kabasawa, H., . . . Yamasue, H. (2010). Voxel-based analysis of the diffusion tensor. *Neuroradiology, 52*(8), 699-710

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature, 433*(7021), 68-72

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *Journal of Neuroscience, 15*(9), 5879-5891

Aguilar, B., Sroufe, L. A., Egeland, B., & Carlson, E. (2000). Distinguishing the early-onset/persistent and adolescence-onset antisocial behavior types: From birth to 16 years. *Dev Psychopathol, 12*(2), 109-132

Albein-Urios, N., Verdejo-Roman, J., Soriano-Mas, C., Asensio, S., Martinez-Gonzalez, J. M., & Verdejo-Garcia, A. (2013). Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity in the emotional regulation networks during negative emotion maintenance and reappraisal. *Eur Neuropsychopharmacol, 23*(12), 1698-1707

Alegria, A. A., Radua, J., & Rubia, K. (2016). Meta-analysis of fMRI studies of disruptive behavior disorders. *American Journal of Psychiatry, 173*(11), 1119-1130

Alink, L. R., van Ijzendoorn, M. H., Bakermans-Kranenburg, M. J., Mesman, J., Juffer, F., & Koot, H. M. (2008). Cortisol and externalizing behavior in children and adolescents: mixed meta-analytic evidence for the inverse relation of basal cortisol and cortisol reactivity with externalizing behavior. *Developmental Psychobiology, 50*(5), 427-450

Anderson, N. E., Steele, V. R., Maurer, J. M., Rao, V., Koenigs, M. R., Decety, J., . . . Kiehl, K. A. (2017). Differentiating emotional processing and attention in psychopathy with functional neuroimaging. *Cognitive, Affective, & Behavioral Neuroscience*, 1-25

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature neuroscience, 2*(11), 1032-1037

Andersson, J. L., Jenkinson, M., & Smith, S. (2007). Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. *FMRIB Analysis Group of the University of Oxford, 2*

Aoki, Y., Cortese, S., & Tansella, M. (2015). Neural bases of atypical emotional face processing in autism: a meta-analysis of fMRI studies. *The World Journal of Biological Psychiatry, 16*(5), 291-300

APA. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM–5)*. Arlington, VA: American Psychiatric Association.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *Neuroimage, 11*(6), 805-821

Baker, R. H., Clanton, R. L., Rogers, J. C., & De Brito, S. A. (2015). Neuroimaging findings in disruptive behavior disorders. *CNS Spectr, 20*(4), 369-381

Bardone, A. M., Moffitt, T. E., Caspi, A., Dickson, N., Stanton, W. R., & Silva, P. A. (1998). Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*(6), 594-601

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., & Williams, S. C. (1999). Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci, 11*(6), 1891-1898

Basser, P. J., Mattiello, J., & LeBihan, D. (1994a). Estimation of the effective self-diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance, Series B, 103*(3), 247-254

Basser, P. J., Mattiello, J., & LeBihan, D. (1994b). MR diffusion tensor spectroscopy and imaging. *Biophys J, 66*(1), 259-267

Basser, P. J., & Pajevic, S. (2000). Statistical artifacts in diffusion tensor MRI (DT-MRI) caused by background noise. *Magnetic resonance in medicine, 44*(1), 41-50

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR in Biomedicine, 15*(7-8), 435-455

Bellis, M. D., Narasimhan, A., Thatcher, D. L., Keshavan, M. S., Soloff, P., & Clark, D. B. (2005). Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcoholism: Clinical and Experimental Research, 29*(9), 1590-1600

Bertsch, K., Grothe, M., Prehn, K., Vohs, K., Berger, C., Hauenstein, K., . . . Herpertz, S. C. (2013). Brain volumes differ between diagnostic groups of violent criminal offenders. *Eur Arch Psychiatry Clin Neurosci, 263*(7), 593-606

Beyer, F., Munte, T. F., Gottlich, M., & Kramer, U. M. (2014). Orbitofrontal Cortex Reactivity to Angry Facial Expression in a Social Interaction Correlates with Aggressive Behavior. *Cereb Cortex*

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., & Flor, H. (2005). Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Arch Gen Psychiatry, 62*(7), 799-805

Blair, K., Morton, J., Leonard, A., & Blair, R. (2006). Impaired decision-making on the basis of both reward and punishment information in individuals with psychopathy. *Personality and Individual Differences, 41*(1), 155-165

Blair, R. (2013). The neurobiology of psychopathic traits in youths. *Nature Reviews Neuroscience, 14*(11), 786-799

Blair, R. J. (2003). Neurobiological basis of psychopathy. *The British Journal of Psychiatry, 182*, 5-7

Blair, R. J. (2004). The roles of orbital frontal cortex in the modulation of antisocial behavior. *Brain and Cognition, 55*(1), 198-208

Blair, R. J. (2007a). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends Cogn Sci, 11*(9), 387-392

Blair, R. J. (2007b). Dysfunctions of medial and lateral orbitofrontal cortex in psychopathy. *Ann N Y Acad Sci, 1121*, 461-479

Blair, R. J. (2008a). The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. *Philosophical Transactions of the Royal Society of London, 363*(1503), 2557-2565

Blair, R. J. (2008b). Fine cuts of empathy and the amygdala: dissociable deficits in psychopathy and autism. *The Quarterly Journal of Experimental Psychology (Colchester), 61*(1), 157-170

Blair, R. J., Budhani, S., Colledge, E., & Scott, S. (2005). Deafness to fear in boys with psychopathic tendencies. *J Child Psychol Psychiatry, 46*(3), 327-336

Blair, R. J., Colledge, E., Murray, L., & Mitchell, D. G. (2001). A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *J Abnorm Child Psychol, 29*(6), 491-498

Blair, R. J., & Lee, T. M. (2013). The social cognitive neuroscience of aggression, violence, and psychopathy. *Soc Neurosci, 8*(2), 108-111

Boccardi, M., Frisoni, G. B., Hare, R. D., Cavedo, E., Najt, P., Pievani, M., . . . Tiihonen, J. (2011). Cortex and amygdala morphology in psychopathy. *Psychiatry Res, 193*(2), 85-92

Botvinick, M. M. (2007). Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci, 7*(4), 356-366

Breeden, A. L., Cardinale, E. M., Lozier, L. M., VanMeter, J. W., & Marsh, A. A. (2015). Callous-unemotional traits drive reduced white-matter integrity in youths with conduct problems. *Psychol Med, 45*(14), 3033-3046

Bubenzer-Busch, S., Herpertz-Dahlmann, B., Kuzmanovic, B., Gaber, T., Helmbold, K., Ullisch, M. G., . . . Zepf, F. (2015). Neural correlates of reactive aggression in children with attention-deficit/hyperactivity disorder and comorbid disruptive behaviour disorders. *Acta Psychiatrica Scandinavica*

Byrd, A. L., Loeber, R., & Pardini, D. A. (2014). Antisocial behavior, psychopathic features and abnormalities in reward and punishment processing in youth. *Clin Child Fam Psychol Rev, 17*(2), 125-156

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A, 100*(9), 5497-5502

Carre, J. M., Hyde, L. W., Neumann, C. S., Viding, E., & Hariri, A. R. (2013). The neural signatures of distinct psychopathic traits. *Soc Neurosci, 8*(2), 122-135

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., . . . Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851-854

Castellanos-Ryan, N., Struve, M., Whelan, R., Banaschewski, T., Barker, G. J., Bokde, A. L., . . . Conrod, P. J. (2014). Neural and cognitive correlates of the common and specific variance across externalizing problems in young adolescence. *Am J Psychiatry, 171*(12), 1310-1319

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., . . . Walter, J. M. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA, 288*(14), 1740-1748

Centifanti, L. C. M., & Modecki, K. (2013). Throwing caution to the wind: Callous-unemotional traits and risk taking in adolescents. *Journal of Clinical Child & Adolescent Psychology, 42*(1), 106-119

Chabrol, H., Valls, M., van Leeuwen, N., & Bui, E. (2012). Callous-unemotional and borderline traits in nonclinical adolescents: Personality profiles and relations to antisocial behaviors. *Personality and Individual Differences, 53*(8), 969-973

Chanraud, S., Zahr, N., Sullivan, E. V., & Pfefferbaum, A. (2010). MR diffusion tensor imaging: a window into white matter integrity of the working brain. *Neuropsychol Rev, 20*(2), 209-225

Chenevert, T. L., Brunberg, J. A., & Pipe, J. G. (1990). Anisotropic diffusion in human white matter: demonstration with MR techniques in vivo. *Radiology, 177*(2), 401-405

Cloninger, C. R., & Svrakic, D. M. (1997). Integrative psychobiological approach to psychiatric assessment and treatment. *Psychiatry, 60*(2), 120-141

Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., . . . Streuning, E. (1993). An epidemiological study of disorders in late childhood and adolescence—I. Age-and gender-specific prevalence. *Journal of Child Psychology and Psychiatry, 34*(6), 851-867

Cohn, M., Popma, A., Van Den Brink, W., Pape, L., Kindt, M., Van Domburgh, L., . . . Veltman, D. (2013). Fear conditioning, persistence of disruptive behavior and psychopathic traits: an fMRI study. *Transl Psychiatry, 3*(10), e319

Cohn, M. D., Viding, E., McCrory, E., Pape, L., van den Brink, W., Doreleijers, T. A., . . . Popma, A. (2016). Regional grey matter volume and concentration in at-risk adolescents: Untangling associations with callous-unemotional traits and conduct disorder symptoms. *Psychiatry Res, 254*, 180-187

Contreras-Rodriguez, O., Pujol, J., Batalla, I., Harrison, B. J., Bosque, J., Ibern-Regas, I., . . . Cardoner, N. (2014). Disrupted neural processing of emotional faces in psychopathy. *Soc Cogn Affect Neurosci, 9*(4), 505-512

Cope, L. M., Ermer, E., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2014). Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits. *J Abnorm Child Psychol, 42*(4), 659-668

Cope, L. M., Shane, M. S., Segall, J. M., Nyalakanti, P. K., Stevens, M. C., Pearlson, G. D., . . . Kiehl, K. A. (2012). Examining the effect of psychopathic traits on gray matter volume in a community substance abuse sample. *Psychiatry Res, 204*(2-3), 91-100

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70

Craig, M. C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., . . . Murphy, D. G. (2009). Altered connections on the road to psychopathy. *Mol Psychiatry, 14*(10), 946-953, 907

Crowe, S. L., & Blair, R. J. (2008). The development of antisocial behavior: what can we learn from functional neuroimaging studies? *Dev Psychopathol, 20*(4), 1145-1159

Crowley, T. J., Dalwani, M. S., Mikulich-Gilbertson, S. K., Du, Y. P., Lejuez, C. W., Raymond, K. M., & Banich, M. T. (2010). Risky decisions and their consequences: neural processing by boys with Antisocial Substance Disorder. *PLoS One, 5*(9), e12835

Crowley, T. J., Mikulich, S. K., Ehlers, K. M., Whitmore, E. A., & MacDonald, M. J. (2001). Validity of structured clinical evaluations in adolescents with conduct and substance problems. *J Am Acad Child Adolesc Psychiatry, 40*(3), 265-273

D'Argembeau, A., Ruby, P., Collette, F., Degueldre, C., Balteau, E., Luxen, A., . . . Salmon, E. (2007). Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective taking. *J Cogn Neurosci, 19*(6), 935-944

Dadds, M. R., Allen, J. L., McGregor, K., Woolgar, M., Viding, E., & Scott, S. (2014). Callous-unemotional traits in children and mechanisms of impaired eye contact during expressions of love: a treatment target? *J Child Psychol Psychiatry, 55*(7), 771-780

Dadds, M. R., El Masry, Y., Wimalaweera, S., & Guastella, A. J. (2008). Reduced eye gaze explains "fear blindness" in childhood psychopathic traits. *J Am Acad Child Adolesc Psychiatry, 47*(4), 455-463

Dadds, M. R., Jambrak, J., Pasalich, D., Hawes, D. J., & Brennan, J. (2011). Impaired attention to the eyes of attachment figures and the developmental origins of psychopathy. *Journal of Child Psychology and Psychiatry, 52*(3), 238-245

Dadds, M. R., Perry, Y., Hawes, D. J., Merz, S., Riddell, A. C., Haines, D. J., . . . Abeygunawardane, A. I. (2006). Attention to the eyes and fear-recognition deficits in child psychopathy. *Br J Psychiatry, 189*, 280-281

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179-194

Dalwani, M., Sakai, J. T., Mikulich-Gilbertson, S. K., Tanabe, J., Raymond, K., McWilliams, S. K., . . . Crowley, T. J. (2011). Reduced cortical gray matter volume in male adolescents with substance and conduct problems. *Drug Alcohol Depend, 118*(2-3), 295-305

Dalwani, M. S., McMahon, M. A., Mikulich-Gilbertson, S. K., Young, S. E., Regner, M. F., Raymond, K. M., . . . Sakai, J. T. (2015). Female adolescents with severe substance and conduct problems have substantially less brain gray matter volume. *PLoS One, 10*(5), e0126368

Davidson, R. J., Putnam, K. M., & Larson, C. L. (2000). Dysfunction in the neural circuitry of emotion regulation - A possible prelude to violence. *Science, 289*(5479), 591-594

De Bellis, M. D., Keshavan, M. S., Beers, S. R., Hall, J., Frustaci, K., Masalehdan, A., . . . Boring, A. M. (2001). Sex differences in brain maturation during childhood and adolescence. *Cerebral cortex, 11*(6), 552-557

De Brito, S. A., McCrory, E. J., Mechelli, A., Wilke, M., Jones, A. P., Hodgins, S., & Viding, E. (2011). Small, but not perfectly formed: decreased white matter concentration in boys with psychopathic tendencies. *Mol Psychiatry, 16*(5), 476-477

De Brito, S. A., Mechelli, A., Wilke, M., Laurens, K. R., Jones, A. P., Barker, G. J., . . . Viding, E. (2009). Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain, 132*(Pt 4), 843-852

De Oliveira-Souza, R., Hare, R. D., Bramati, I. E., Garrido, G. J., Azevedo Ignacio, F., Tovar-Moll, F., & Moll, J. (2008). Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *Neuroimage, 40*(3), 1202-1213

Decety, J., Michalska, K. J., Akitsuki, Y., & Lahey, B. B. (2009). Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. *Biol Psychol, 80*(2), 203-211

Decety, J., Skelly, L. R., & Kiehl, K. A. (2013). Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. *JAMA Psychiatry, 70*(6), 638-645

Decety, J., Yoder, K. J., & Lahey, B. B. (2015). Sex differences in abnormal white matter development associated with conduct disorder in children. *Psychiatry Res, 233*(2), 269-277

Delmo, C., Weiffenbach, O., Gabriel, M., & Poustka, F. (2000). *Kiddie-SADS - Present and Lifetime Version (K-SADS-PL)*. Frankfurt: Universität Frankfurt.

Derbyshire, S. W. (2000). Exploring the pain "neuromatrix". *Curr Rev Pain, 4*(6), 467-477

Dolan, M. C., & Fullam, R. S. (2009). Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. *Biol Psychiatry, 66*(6), 570-577

Dotterer, H. L., Hyde, L. W., Swartz, J. R., Hariri, A. R., & Williamson, D. E. (2017). Amygdala reactivity predicts adolescent antisocial behavior but not callous-unemotional traits. *Dev Cogn Neurosci, 24*, 84-92

Douek, P., Turner, R., Pekar, J., Patronas, N., & Le Bihan, D. (1991). MR color mapping of myelin fiber orientation. *J Comput Assist Tomogr, 15*(6), 923-929

Dupont, S., Bouilleret, V., Hasboun, D., Semah, F., & Baulac, M. (2003). Functional anatomy of the insula: new insights from imaging. *Surg Radiol Anat, 25*(2), 113-119

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp, 30*(9), 2907-2926

Eley, T. C., Lichtenstein, P., & Stevenson, J. (1999). Sex differences in the etiology of aggressive and nonaggressive antisocial behavior: Results from two twin studies. *Child Dev, 70*(1), 155-168

Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *J Abnorm Psychol, 121*(3), 649-658

Ermer, E., Cope, L. M., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2013). Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits. *J Am Acad Child Adolesc Psychiatry, 52*(1), 94-103 e103

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron, 51*(6), 871-882

Euston, D. R., Gruber, A. J., & McNaughton, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron, 76*(6), 1057-1070

Eysenck, H. J., Milton, T., & Simonsen, E. (1998). Personality and crime. *Psychopathy: Antisocial, criminal, and violent behavior*, 40-49

Fahim, C., He, Y., Yoon, U., Chen, J., Evans, A., & Perusse, D. (2011). Neuroanatomy of childhood disruptive behavior disorders. *Aggress Behav, 37*(4), 326-337

Fairchild, G., Hagan, C. C., Passamonti, L., Walsh, N. D., Goodyer, I. M., & Calder, A. J. (2014). Atypical neural responses during face processing in female adolescents with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 53*(6), 677-687 e675

Fairchild, G., Hagan, C. C., Walsh, N. D., Passamonti, L., Calder, A. J., & Goodyer, I. M. (2013a). Brain structure abnormalities in adolescent girls with conduct disorder. *J Child Psychol Psychiatry, 54*(1), 86-95

Fairchild, G., Passamonti, L., Hurford, G., Hagan, C. C., von dem Hagen, E. A., van Goozen, S. H., . . . Calder, A. J. (2011). Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. *Am J Psychiatry, 168*(6), 624-633

Fairchild, G., Stobbe, Y., van Goozen, S. H., Calder, A. J., & Goodyer, I. M. (2010). Facial expression recognition, fear conditioning, and startle modulation in female subjects with conduct disorder. *Biol Psychiatry, 68*(3), 272-279

Fairchild, G., van Goozen, S. H., Calder, A. J., & Goodyer, I. M. (2013b). Research Review: Evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. *Journal of Child Psychology and Psychiatry, 54*(9), 924-940

Fairchild, G., Van Goozen, S. H., Calder, A. J., Stollery, S. J., & Goodyer, I. M. (2009a). Deficits in facial expression recognition in male adolescents with early-onset or adolescence-onset conduct disorder. *Journal of Child Psychology and Psychiatry, 50*(5), 627-636

Fairchild, G., van Goozen, S. H., Stollery, S. J., Aitken, M. R., Savage, J., Moore, S. C., & Goodyer, I. M. (2009b). Decision making and executive function in male adolescents with early-onset or adolescence-onset conduct disorder and control subjects. *Biol Psychiatry, 66*(2), 162-168

Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neurosci Biobehav Rev, 35*(3), 903-911

Fanti, K. A. (2016). Understanding heterogeneity in conduct disorder: A review of psychophysiological studies. *Neuroscience & Biobehavioral Reviews*

Ferguson, C. J. (2010). Genetic contributions to antisocial personality and behavior: A meta-analytic review from an evolutionary perspective. *The Journal of Social Psychology, 150*(2), 160-180

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. *Drug Alcohol Depend, 88 Suppl 1*, S14-26

Ficks, C. A., & Waldman, I. D. (2014). Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR. *Behavior Genetics, 44*(5), 427-444

Finger, E. C., Marsh, A., Blair, K. S., Majestic, C., Evangelou, I., Gupta, K., . . . Blair, R. J. (2012). Impaired functional but preserved structural connectivity in limbic white matter tracts in youth with conduct disorder or oppositional defiant disorder plus psychopathic traits. *Psychiatry Res, 202*(3), 239-244

Finger, E. C., Marsh, A. A., Blair, K. S., Reid, M. E., Sims, C., Ng, P., . . . Blair, R. J. (2011). Disrupted reinforcement signaling in the orbitofrontal cortex and caudate in youths with conduct disorder or oppositional defiant disorder and a high level of psychopathic traits. *Am J Psychiatry, 168*(2), 152-162

Finger, E. C., Marsh, A. A., Mitchell, D. G., Reid, M. E., Sims, C., Budhani, S., . . . Blair, J. R. (2008). Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Arch Gen Psychiatry, 65*(5), 586-594

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences, 97*(20), 11050-11055

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., . . . Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*(3), 341-355

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. *Neuroimage, 9*(2), 195-207

Frick, P. J. (2009). Extending the construct of psychopathy to youth: implications for understanding, diagnosing, and treating antisocial children and adolescents. *The Canadian Journal of Psychiatry, 54*(12), 803-812

Frick, P. J., Cornell, A. H., Barry, C. T., Bodin, S. D., & Dane, H. E. (2003). Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and self-report of delinquency. *J Abnorm Child Psychol, 31*(4), 457-470

Frick, P. J., & Marsee, M. A. (2006). *Psychophathy and developmental pathways to antisocial behavior in youth*. New York: Guilford.

Frick, P. J., O'Brien, B. S., Wootton, J. M., & McBurnett, K. (1994). Psychopathy and conduct problems in children. *Journal of abnormal psychology, 103*(4), 700-707

Frick, P. J., & White, S. F. (2008). Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior. *J Child Psychol Psychiatry, 49*(4), 359-375

Friston, K. J., Holmes, A. P., Poline, J., Grasby, P., Williams, S., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI time-series revisited. *Neuroimage, 2*(1), 45-53

Gao, Y., Glenn, A. L., Schug, R. A., Yang, Y., & Raine, A. (2009). The neurobiology of psychopathy: a neurodevelopmental perspective. *Can J Psychiatry, 54*(12), 813-823

Garavan, H., Pendergrass, J. C., Ross, T. J., Stein, E. A., & Risinger, R. C. (2001). Amygdala response to both positively and negatively valenced stimuli. *Neuroreport, 12*(12), 2779-2783

Gatzke-Kopp, L. M., Beauchaine, T. P., Shannon, K. E., Chipman, J., Fleming, A. P., Crowell, S. E., . . . Aylward, E. (2009). Neurological correlates of reward responding in adolescents with and without externalizing behavior disorders. *Journal of abnormal psychology, 118*(1), 203

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., . . . Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature neuroscience, 2*(10), 861-863

Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron, 67*(5), 728-734

Glenn, A. L., & Raine, A. (2008). The neurobiology of psychopathy. *Psychiatr Clin North Am, 31*(3), 463-475, vii

Glenn, A. L., & Raine, A. (2014). Neurocriminology: implications for the punishment, prediction and prevention of criminal behaviour. *Nature Reviews Neuroscience, 15*(1), 54-63

Glenn, A. L., Raine, A., & Schug, R. A. (2009). The neural correlates of moral decision-making in psychopathy. *Mol Psychiatry, 14*(1), 5-6

Gray, J. A., & McNaughton, N. (1982). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system.* New York: Oxford University Press.

Gregory, S., Simmons, A., Kumari, V., Howard, M., Hodgins, S., & Blackwood, N. (2012). The antisocial brain: psychopathy matters: a structural MRI investigation of antisocial male violent offenders. *Arch Gen Psychiatry, 69*(9), 962-972

Han, T., Alders, G. L., Greening, S. G., Neufeld, R. W., & Mitchell, D. G. (2011). Do fearful eyes activate empathy-related brain regions in individuals with callous traits? *Soc Cogn Affect Neurosci*

Haney-Caron, E., Caprihan, A., & Stevens, M. C. (2014). DTI-measured white matter abnormalities in adolescents with Conduct Disorder. *J Psychiatr Res, 48*(1), 111-120

Harenski, C. L., Harenski, K. A., & Kiehl, K. A. (2014). Neural processing of moral violations among incarcerated adolescents with psychopathic traits. *Dev Cogn Neurosci, 10*, 181-189

Harenski, C. L., Harenski, K. A., Shane, M. S., & Kiehl, K. A. (2010). Aberrant neural processing of moral violations in criminal psychopaths. *Journal of abnormal psychology, 119*(4), 863-874

Hawes, D. J., Brennan, J., & Dadds, M. R. (2009). Cortisol, callous-unemotional traits, and pathways to antisocial behavior. *Current Opinion in Psychiatry, 22*(4), 357-362

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in cognitive sciences, 4*(6), 223-233

Herpertz, S. C., Huebner, T., Marx, I., Vloet, T. D., Fink, G. R., Stoecker, T., . . . Herpertz-Dahlmann, B. (2008). Emotional processing in male adolescents with childhood-onset conduct disorder. *J Child Psychol Psychiatry, 49*(7), 781-791

Holmes, A. P., Blair, R., Watson, J., & Ford, I. (1996). Nonparametric analysis of statistic images from functional mapping experiments. *Journal of Cerebral Blood Flow & Metabolism, 16*(1), 7-22

Huebner, T., Vloet, T. D., Marx, I., Konrad, K., Fink, G. R., Herpertz, S. C., & Herpertz-Dahlmann, B. (2008). Morphometric brain abnormalities in boys with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 47*(5), 540-547

Hummer, T. A., Wang, Y., Kronenberger, W. G., Dunn, D. W., & Mathews, V. P. (2015). The relationship of brain structure to age and executive functioning in adolescent disruptive behavior disorder. *Psychiatry Res, 231*(3), 210-217

Hwang, S., Nolan, Z., White, S., Williams, W., Sinclair, S., & Blair, R. (2016). Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. *Psychol Med, 46*(07), 1485-1496

Hyatt, C. J., Haney-Caron, E., & Stevens, M. C. (2012). Cortical thickness and folding deficits in conduct-disordered adolescents. *Biol Psychiatry, 72*(3), 207-214

Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., & Turski, P. A. (1996). Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport, 7*(11), 1765-1769

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage, 62*(2), 782-790

Jones, A. P., Happe, F. G., Gilbert, F., Burnett, S., & Viding, E. (2010). Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. *J Child Psychol Psychiatry, 51*

Jones, A. P., Laurens, K. R., Herba, C. M., Barker, G. J., & Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *Am J Psychiatry, 166*(1), 95-102

Jones, D., Horsfield, M., & Simmons, A. (1999). Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magn Reson Med, 42*

Jones, D. K. (2008). Studying connections in the living human brain with diffusion MRI. *Cortex, 44*(8), 936-952

Kiehl, K. A., Smith, A. M., Hare, R. D., Mendrek, A., Forster, B. B., Brink, J., & Liddle, P. F. (2001). Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry, 50*(9), 677-684

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. *Mol Psychiatry, 11*(10), 903-913

Kimonis, E. R., Frick, P. J., Munoz, L. C., & Aucoin, K. J. (2008). Callous-unemotional traits and the emotional processing of distress cues in detained boys: testing the moderating role of aggression, exposure to community violence, and histories of abuse. *Dev Psychopathol, 20*(2), 569-589

Klahr, A. M., & Burt, S. (2014). Practitioner review: Evaluation of the known behavioral heterogeneity in conduct disorder to improve its assessment and treatment. *Journal of Child Psychology and Psychiatry, 55*(12), 1300-1310

Klapwijk, E. T., Aghajani, M., Colins, O. F., Marijnissen, G. M., Popma, A., Lang, N. D., . . . Vermeiren, R. R. (2015). Different brain responses during empathy in autism spectrum disorders versus conduct disorder and callous-unemotional traits. *Journal of Child Psychology and Psychiatry*

Klapwijk, E. T., Lelieveld, G.-J., Aghajani, M., Boon, A. E., van der Wee, N. J., Popma, A., . . . Colins, O. F. (2016). Fairness decisions in response to emotions: a functional MRI study among criminal justice-involved boys with conduct disorder. *Soc Cogn Affect Neurosci, 11*(4), 674-682

Kruesi, M. J., Casanova, M. F., Mannheim, G., & Johnson-Bilder, A. (2004). Reduced temporal lobe volume in early onset conduct disorder. *Psychiatry Research: Neuroimaging, 132*(1), 1-11

Lagopoulos, J. (2007). Voxel-based morphometry made simple. *Acta Neuropsychiatrica, 19*(3), 213-214

Lahey, B. B., Loeber, R., Burke, J. D., & Applegate, B. (2005). Predicting future antisocial personality disorder in males from a clinical assessment in childhood. *Journal of Consulting and Clinical Psychology, 73*(3), 389-399

Lahey, B. B., Van Hulle, C. A., Waldman, I. D., Rodgers, J. L., D'Onofrio, B. M., Pedlow, S., . . . Keenan, K. (2006). Testing descriptive hypotheses regarding sex differences in the development of conduct problems and delinquency. *J Abnorm Child Psychol, 34*(5), 730-748

Lahey, B. B., Waldman, I. D., & McBurnett, K. (1999). Annotation: the development of antisocial behavior: an integrative causal model. *J Child Psychol Psychiatry, 40*(5), 669-682

Lansford, J. E., Criss, M. M., Pettit, G. S., Dodge, K. A., & Bates, J. E. (2003). Friendship quality, peer group affiliation, and peer antisocial behavior as moderators of the link between negative parenting and adolescent externalizing behavior. *Journal of Research on Adolescence, 13*(2), 161-184

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of magnetic resonance imaging, 13*(4), 534-546

Ledoux, J., & Schiller, D. (2009). The human amygdala *The human amygdala*: Guilford Press.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184

Lee, J. H., Durand, R., Gradinaru, V., Zhang, F., Goshen, I., Kim, D.-S., . . . Deisseroth, K. (2010). Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. *Nature, 465*(7299), 788-792

Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain and Cognition, 72*(1), 46-55

Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., . . . Giedd, J. N. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage, 36*(4), 1065-1073

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

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: a meta-analytic review. *Behav Brain Sci, 35*(3), 121-143

Liu, H., Liao, J., Jiang, W., & Wang, W. (2014). Changes in low-frequency fluctuations in patients with antisocial personality disorder revealed by resting-state functional MRI. *PLoS One, 9*(3), e89790

Lockwood, P. L., Sebastian, C. L., McCrory, E. J., Hyde, Z. H., Gu, X. S., De Brito, S. A., & Viding, E. (2013). Association of Callous Traits with Reduced Neural Response to Others' Pain in Children with Conduct Problems. *Current Biology, 23*(10), 901-905

Loeber, R., Burke, J. D., Lahey, B. B., Winters, A., & Zera, M. (2000). Oppositional defiant and conduct disorder: a review of the past 10 years, part I. *J Am Acad Child Adolesc Psychiatry, 39*(12), 1468-1484

Logothetis, N. K., & Pfeuffer, J. (2004). On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging, 22*(10), 1517-1531

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annu. Rev. Physiol., 66*, 735-769

Lozier, L. M., Cardinale, E. M., VanMeter, J. W., & Marsh, A. A. (2014). Mediation of the relationship between callous-unemotional traits and proactive aggression by amygdala response to fear among children with conduct problems. *JAMA Psychiatry, 71*(6), 627-636

Luo, Q., Nakic, M., Wheatley, T., Richell, R., Martin, A., & Blair, R. J. (2006). The neural basis of implicit moral attitude--an IAT study using event-related fMRI. *Neuroimage, 30*(4), 1449-1457

Ly, M., Motzkin, J. C., Philippi, C. L., Kirk, G. R., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2012). Cortical thinning in psychopathy. *Am J Psychiatry, 169*(7), 743-749

Marsh, A. A., & Blair, R. (2008a). Deficits in facial affect recognition among antisocial populations: a meta-analysis. *Neuroscience & Biobehavioral Reviews, 32*(3), 454-465

Marsh, A. A., & Blair, R. J. (2008b). Deficits in facial affect recognition among antisocial populations: a meta-analysis. *Neurosci Biobehav Rev, 32*(3), 454-465

Marsh, A. A., Finger, E. C., Fowler, K. A., Adalio, C. J., Jurkowitz, I. T., Schechter, J. C., . . . Blair, R. (2013a). Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. *Journal of Child Psychology and Psychiatry, 54*(8), 900-910

Marsh, A. A., Finger, E. C., Fowler, K. A., Adalio, C. J., Jurkowitz, I. T., Schechter, J. C., . . . Blair, R. J. (2013b). Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. *J Child Psychol Psychiatry, 54*(8), 900-910

Marsh, A. A., Finger, E. C., Fowler, K. A., Jurkowitz, I. T., Schechter, J. C., Yu, H. H., . . . Blair, R. J. (2011a). Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. *Psychiatry Res, 194*(3), 279-286

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., . . . Blair, R. J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry, 165*(6), 712-720

Marsh, A. A., Finger, E. C., Schechter, J. C., Jurkowitz, I. T., Reid, M. E., & Blair, R. J. (2011b). Adolescents with psychopathic traits report reductions in physiological responses to fear. *J Child Psychol Psychiatry, 52*(8), 834-841

McCabe, K. M., Rodgers, C., Yeh, M., & Hough, R. (2004). Gender differences in childhood onset conduct disorder. *Dev Psychopathol, 16*(1), 179-192

McColgan, E. B., Rest, J. R., & Pruitt, D. B. (1983). Moral judgment and antisocial behavior in early adolescence. *Journal of Applied Developmental Psychology, 4*(2), 189-199

Michalska, K. J., Decety, J., Zeffiro, T. A., & Lahey, B. B. (2015). Association of regional gray matter volumes in the brain with disruptive behavior disorders in male and female children. *Neuroimage Clin, 7*, 252-257

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci, 24*(1), 167-202

Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychological Review, 100*(4), 674-701

Moffitt, T. E., Arseneault, L., Jaffee, S. R., Kim-Cohen, J., Koenen, K. C., Odgers, C. L., . . . Viding, E. (2008). Research review: DSM-V conduct disorder: research needs for an evidence base. *J Child Psychol Psychiatry, 49*(1), 3-33

Moffitt, T. E., & Caspi, A. (2001). Childhood predictors differentiate life-course persistent and adolescence-limited antisocial pathways among males and females. *Dev Psychopathol, 13*(2), 355-375

Moffitt, T. E., Caspi, A., Dickson, N., Silva, P., & Stanton, W. (1996). Childhood-onset versus adolescent-onset antisocial conduct problems in males: Natural history from ages 3 to 18 years. *Dev Psychopathol, 8*(2), 399-424

Moffitt, T. E., Caspi, A., Rutter, M., & Silva, P. A. (2001). *Sex differences in antisocial behavior: Conduct disorder, delinquency, and violence in the Dunedin Longitudinal Study*. New York: Cambridge University Press.

Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., & Grafman, J. (2005). The neural basis of human moral cognition. *Nature Reviews Neuroscience, 6*(10), 799-809

Mori, S., Crain, B. J., Chacko, V., & Van Zijl, P. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology, 45*(2), 265-269

Mori, S., Kaufmann, W. E., Davatzikos, C., Stieltjes, B., Amodei, L., Fredericksen, K., . . . Raymond, G. V. (2002). Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. *Magnetic resonance in medicine, 47*(2), 215-223

Moseley, M. E., Cohen, Y., Kucharczyk, J., Mintorovitch, J., Asgari, H., Wendland, M., . . . Norman, D. (1990). Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology, 176*(2), 439-445

Motzkin, J. C., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2011). Reduced prefrontal connectivity in psychopathy. *J Neurosci, 31*(48), 17348-17357

Muller, J. L., Ganssbauer, S., Sommer, M., Dohnel, K., Weber, T., Schmidt-Wilcke, T., & Hajak, G. (2008). Gray matter changes in right superior temporal gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Res, 163*(3), 213-222

Nilsson, K. W., Sjöberg, R. L., Wargelius, H. L., Leppert, J., Lindström, L., & Oreland, L. (2007). The monoamine oxidase A (MAO-A) gene, family function and maltreatment as predictors of destructive behaviour during male adolescent alcohol consumption. *Addiction, 102*(3), 389-398

Nock, M. K., Kazdin, A. E., Hiripi, E., & Kessler, R. C. (2006). Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol Med, 36*(5), 699-710

Odgers, C. L., Caspi, A., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., . . . Moffitt, T. E. (2007). Prediction of differential adult health burden by conduct problem subtypes in males. *Arch Gen Psychiatry, 64*(4), 476-484

Odgers, C. L., Moffitt, T. E., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2008). Female and male antisocial trajectories: from childhood origins to adult outcomes. *Dev Psychopathol, 20*(2), 673-716

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872

Oguz, I., Farzinfar, M., Matsui, J., Budin, F., Liu, Z., Gerig, G., . . . Styner, M. (2014). DTIPrep: quality control of diffusion-weighted images. *Front Neuroinform, 8*, 4

Ortiz, J., & Raine, A. (2004). Heart rate level and antisocial behavior in children and adolescents: a meta-analysis. *Journal*

of the American Academy of Child & Adolescent Psychiatry, 43(2), 154-162
Osumi, T., Nakao, T., Kasuya, Y., Shinoda, J., Yamada, J., & Ohira, H. (2012). Amygdala dysfunction attenuates frustration-induced aggression in psychopathic individuals in a non-criminal population. *J Affect Disord, 142*(1-3), 331-338
Pape, L. E., Cohn, M. D., Caan, M. W., van Wingen, G., van den Brink, W., Veltman, D. J., & Popma, A. (2015). Psychopathic traits in adolescents are associated with higher structural connectivity. *Psychiatry Res, 233*(3), 474-480
Pardini, D., & Frick, P. J. (2013). Multiple developmental pathways to conduct disorder: current conceptualizations and clinical implications. *J Can Acad Child Adolesc Psychiatry, 22*(1), 20-25
Pardini, D. A., & Byrd, A. L. (2012). Perceptions of aggressive conflicts and others' distress in children with callous-unemotional traits: 'I'll show you who's boss, even if you suffer and I get in trouble'. *J Child Psychol Psychiatry, 53*(3), 283-291
Pardini, D. A., Frick, P. J., & Moffitt, T. E. (2010). Building an evidence base for DSM–5 conceptualizations of oppositional defiant disorder and conduct disorder: Introduction to the special section. *J Abnorm Child Psychol, 119*(4), 683
Pardini, D. A., Lochman, J. E., & Frick, P. J. (2003). Callous/unemotional traits and social-cognitive processes in adjudicated youths. *J Am Acad Child Adolesc Psychiatry, 42*(3), 364-371
Pardini, D. A., Lochman, J. E., & Powell, N. (2007). The development of callous-unemotional traits and antisocial behavior in children: Are there shared and/or unique predictors? *Journal of Clinical Child and Adolescent Psychology, 36*(3), 319-333
Pardini, D. A., Raine, A., Erickson, K., & Loeber, R. (2014). Lower amygdala volume in men is associated with childhood aggression, early psychopathic traits, and future violence. *Biol Psychiatry, 75*(1), 73-80
Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I. M., Nimmo-Smith, I., Hagan, C. C., & Calder, A. J. (2012). Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. *PLoS One, 7*(11), e48789
Passamonti, L., Fairchild, G., Goodyer, I. M., Hurford, G., Hagan, C. C., Rowe, J. B., & Calder, A. J. (2010). Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry, 67*(7), 729-738
Pedersen, W., & Mastekaasa, A. (2011). Conduct disorder symptoms and subsequent pregnancy, child-birth and abortion: a population-based longitudinal study of adolescents. *Journal of Adolescence, 34*(5), 1025-1033
Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348
Phan, K. L., Wager, T. D., Taylor, S. F., & Liberzon, I. (2004). Functional neuroimaging studies of human emotions. *CNS Spectr, 9*(4), 258-266
Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., . . . David, A. S. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature, 389*(6650), 495-498
Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic resonance in medicine, 36*(6), 893-906
Poldrack, R. A., Fletcher, P. C., Henson, R. N., Worsley, K. J., Brett, M., & Nichols, T. E. (2008). Guidelines for reporting an fMRI study. *Neuroimage, 40*(2), 409-414
Potegal, M. (2012). Temporal and frontal lobe initiation and regulation of the top-down escalation of anger and aggression. *Behav Brain Res, 231*(2), 386-395
Pujara, M., Motzkin, J. C., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2014). Neural correlates of reward and loss sensitivity in psychopathy. *Soc Cogn Affect Neurosci, 9*(6), 794-801
Quay, H. C. (1993). The psychobiology of undersocialized aggressive conduct disorder: A theoretical perspective. *Dev Psychopathol, 5*(1-2), 165-180
Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry, 57*(2), 119-127; discussion 128-129
Raine, A., Lencz, T., Taylor, K., Hellige, J. B., Bihrle, S., Lacasse, L., . . . Colletti, P. (2003). Corpus callosum abnormalities in psychopathic antisocial individuals. *Arch Gen Psychiatry, 60*(11), 1134-1142
Raine, A., Venables, P. H., & Mednick, S. A. (1997). Low resting heart rate at age 3 years predisposes to aggression at age 11 years: evidence from the Mauritius Child Health Project. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(10), 1457-1464
Raine, A., & Yang, Y. (2006). Neural foundations to moral reasoning and antisocial behavior. *Soc Cogn Affect Neurosci, 1*(3), 203-213
Rajmohan, V., & Mohandas, E. (2007). The limbic system. *Indian Journal of Psychiatry, 49*(2), 132
Raybaud, C. (2010). The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. *Neuroradiology, 52*(6), 447-477
Retz, W., Retz-Junginger, P., Supprian, T., Thome, J., & Rosler, M. (2004). Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. *Behav Sci Law, 22*(3), 415-425
Rhee, S. H., & Waldman, I. D. (2002). Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull, 128*(3), 490-529
Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443-447
Rogers, J. C., & De Brito, S. A. (2016). Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. *JAMA Psychiatry, 73*(1), 64-72
Rubia, K., Halari, R., Smith, A. B., Mohammed, M., Scott, S., Giampietro, V., . . . Brammer, M. J. (2008). Dissociated functional brain abnormalities of inhibition in boys with pure conduct disorder and in boys with pure attention deficit hyperactivity disorder. *Am J Psychiatry, 165*(7), 889-897
Rubia, K., Smith, A. B., Halari, R., Matsukura, F., Mohammad, M., Taylor, E., & Brammer, M. J. (2009). Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. *Am J Psychiatry, 166*(1), 83-94
Sakai, J. T., Dalwani, M. S., Mikulich-Gilbertson, S. K., Raymond, K., McWilliams, S., Tanabe, J., . . . Crowley, T. J. (2017). Imaging Decision about Whether to, or Not to, Benefit Self by Harming Others: Adolescents with Conduct and Substance Problems, with or without Callous-Unemotionality, or Developing Typically. *Psychiatry Research: Neuroimaging*
Sarkar, S., Craig, M. C., Catani, M., Dell'acqua, F., Fahy, T., Deeley, Q., & Murphy, D. G. (2013). Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. *Psychol Med, 43*(2), 401-411
Sauder, C. L., Beauchaine, T. P., Gatzke-Kopp, L. M., Shannon, K. E., & Aylward, E. (2012). Neuroanatomical correlates of heterotypic comorbidity in externalizing male adolescents. *J Clin Child Adolesc Psychol, 41*(3), 346-352
Schaffer, M., Clark, S., & Jeglic, E. L. (2009). The role of empathy and parenting style in the development of antisocial behaviors. *Crime & Delinquency, 55*(4), 586-599
Schiffer, B., Müller, B. W., Scherbaum, N., Hodgins, S., Forsting, M., Wiltfang, J., . . . Leygraf, N. (2011). Disentangling structural brain alterations associated with violent behavior from those associated with substance use disorders. *Arch Gen Psychiatry, 68*(10), 1039-1049
Schmeck, K., & Poustka, F. (2001). Temperament and disruptive behavior disorders. *Psychopathology, 34*(3), 159-163
Schwartz, D., Dodge, K. A., Pettit, G. S., Bates, J. E., & US, T. C. P. P. R. G. (2000). Friendship as a moderating factor in the pathway between early harsh home environment and later victimization in the peer group. *Dev Psychol, 36*(5), 646-662
Scott, S., Knapp, M., Henderson, J., & Maughan, B. (2001). Financial cost of social exclusion: follow up study of antisocial children into adulthood. *BMJ, 323*(7306), 191

Sebastian, C. L., De Brito, S. A., McCrory, E. J., Hyde, Z. H., Lockwood, P. L., Cecil, C. A., & Viding, E. (2016). Grey matter volumes in children with conduct problems and varying levels of callous-unemotional traits. *J Abnorm Child Psychol, 44*(4), 639-649

Sebastian, C. L., McCrory, E. J., Cecil, C. A., Lockwood, P. L., De Brito, S. A., Fontaine, N. M., & Viding, E. (2012). Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. *Arch Gen Psychiatry, 69*(8), 814-822

Sebastian, C. L., McCrory, E. J., Dadds, M. R., Cecil, C. A., Lockwood, P. L., Hyde, Z. H., . . . Viding, E. (2014). Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits. *Psychol Med, 44*(1), 99-109

Sharp, C., Burton, P. C., & Ha, C. (2011). "Better the devil you know": a preliminary study of the differential modulating effects of reputation on reward processing for boys with and without externalizing behavior problems. *Eur Child Adolesc Psychiatry, 20*(11-12), 581-592

Silverthorn, P., & Frick, P. J. (1999). Developmental pathways to antisocial behavior: The delayed-onset pathway in girls. *Dev Psychopathol, 11*(01), 101-126

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Matthews, P. M. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505

Soares, J., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience, 7*, 31

Sobhani, M., Baker, L., Martins, B., Tuvblad, C., & Aziz-Zadeh, L. (2015). Psychopathic traits modulate microstructural integrity of right uncinate fasciculus in a community population. *Neuroimage Clin, 8*, 32-38

Stadler, C., Poustka, F., & Sterzer, P. (2010). The heterogeneity of disruptive behavior disorders–implications for neurobiological research and treatment. *Front Psychiatry, 1*, 21

Stadler, C., Sterzer, P., Schmeck, K., Krebs, A., Kleinschmidt, A., & Poustka, F. (2007). Reduced anterior cingulate activation in aggressive children and adolescents during affective stimulation: association with temperament traits. *J Psychiatr Res, 41*(5), 410-417

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., & Poustka, F. (2005). Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biol Psychiatry, 57*(1), 7-15

Sterzer, P., Stadler, C., Poustka, F., & Kleinschmidt, A. (2007). A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage, 37*(1), 335-342

Stevens, M. C., & Haney-Caron, E. (2012). Comparison of brain volume abnormalities between ADHD and conduct disorder in adolescence. *J Psychiatry Neurosci, 37*(6), 389-398

Storm-Mathisen, A., & Vaglum, P. (1994). Conduct disorder patients 20 years later: a personal follow-up study. *Acta Psychiatrica Scandinavica, 89*(6), 416-420

Sundermann, B., & Pfleiderer, B. (2012). Functional connectivity profile of the human inferior frontal junction: involvement in a cognitive control network. *BMC Neurosci, 13*, 119

Sundram, F., Deeley, Q., Sarkar, S., Daly, E., Latham, R., Craig, M., . . . Murphy, D. G. (2012). White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex, 48*(2), 216-229

Thapar, A., Langley, K., Fowler, T., Rice, F., Turic, D., Whittinger, N., . . . O'Donovan, M. (2005). Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry, 62*(11), 1275-1278

Tolan, P. H., & Leventhal, B. (2013). *Disruptive behavior disorders*: Springer.

Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage, 16*(3), 765-780

Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Hum Brain Mapp, 33*(1), 1-13

van den Bos, W., Vahl, P., Güroğlu, B., van Nunspeet, F., Colins, O., Markus, M., . . . Crone, E. A. (2014). Neural correlates of social decision-making in severely antisocial adolescents. *Soc Cogn Affect Neurosci*, nsu003

Van der Velden, F., Brugman, D., Boom, J., & Koops, W. (2010). Moral cognitive processes explaining antisocial behavior in young adolescents. *International Journal of Behavioral Development, 34*(4), 292-301

van Goozen, S. H., Fairchild, G., Snoek, H., & Harold, G. T. (2007). The evidence for a neurobiological model of childhood antisocial behavior. *Psychol Bull, 133*(1), 149-182

van Honk, J., Harmon-Jones, E., Morgan, B. E., & Schutter, D. J. (2010). Socially explosive minds: The triple imbalance hypothesis of reactive aggression. *Journal of Personality, 78*(1), 67-94

Veenstra, R., Lindenberg, S., Oldehinkel, A. J., De Winter, A. F., & Ormel, J. (2006). Temperament, environment, and antisocial behavior in a population sample of preadolescent boys and girls. *International Journal of Behavioral Development, 30*(5), 422-432

Viding, E., Fontaine, N. M., & McCrory, E. J. (2012a). Antisocial behaviour in children with and without callous-unemotional traits. *Journal of the Royal Society of Medicine, 105*(5), 195-200

Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A., De Brito, S. A., & McCrory, E. J. (2012b). Amygdala response to preattentive masked fear in children with conduct problems: the role of callous-unemotional traits. *Am J Psychiatry, 169*(10), 1109-1116

Vilanova, A., Zhang, S., Kindlmann, G., & Laidlaw, D. (2006). An introduction to visualization of diffusion tensor imaging and its applications *Visualization and Processing of Tensor Fields* (pp. 121-153): Springer.

Vitaro, F., Brendgen, M., & Tremblay, R. E. (2000). Influence of deviant friends on delinquency: Searching for moderator variables. *J Abnorm Child Psychol, 28*(4), 313-325

Vloet, T. D., Großheinrich, N., Konrad, K., Freitag, C. M., & Herpertz-Dahlmann, B. (2014). Mädchen mit Störungen des Sozialverhaltens. *Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie, 42*(2), 95-108

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci, 6*(7), 533-544

Wallace, G. L., White, S. F., Robustelli, B., Sinclair, S., Hwang, S., Martin, A., & Blair, R. J. (2014). Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. *J Am Acad Child Adolesc Psychiatry, 53*(4), 456-465

Waller, R., Dotterer, H. L., Murray, L., Maxwell, A. M., & Hyde, L. W. (2017). White-matter tract abnormalities and antisocial behavior: A systematic review of diffusion tensor imaging studies across development. *NeuroImage: Clinical*

Weber, S., Habel, U., Amunts, K., & Schneider, F. (2008). Structural brain abnormalities in psychopaths-a review. *Behav Sci Law, 26*(1), 7-28

Wedeen, V. J., Rosene, D. L., Wang, R., Dai, G., Mortazavi, F., Hagmann, P., . . . Tseng, W.-Y. I. (2012). The geometric structure of the brain fiber pathways. *Science, 335*(6076), 1628-1634

White, S. F., Marsh, A. A., Fowler, K. A., Schechter, J. C., Adalio, C., Pope, K., . . . Blair, R. J. (2012). Reduced amygdala response in youths with disruptive behavior disorders and psychopathic traits: decreased emotional response versus increased top-down attention to nonemotional features. *Am J Psychiatry, 169*(7), 750-758

White, S. F., Tyler, P. M., Erway, A. K., Botkin, M. L., Kolli, V., Meffert, H., . . . Blair, J. R. (2016). Dysfunctional representation of expected value is associated with reinforcement-based decision-making deficits in adolescents with conduct problems. *J Child Psychol Psychiatry, 57*(8), 938-946

Woolfenden, S. R., Williams, K., & Peat, J. (2002). Family and parenting interventions for conduct disorder and delinquency: a meta-analysis of randomised controlled trials. *Archives of disease in childhood, 86*(4), 251-256

Wright, I., McGuire, P., Poline, J.-B., Travere, J., Murray, R., Frith, C., . . . Friston, K. (1995). A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage, 2*(4), 244-252

Yang, Y., & Raine, A. (2009). Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Res Neuroimaging, 174*(2), 81-88

Yang, Y., Raine, A., Colletti, P., Toga, A. W., & Narr, K. L. (2009a). Abnormal temporal and prefrontal cortical gray matter thinning in psychopaths. *Mol Psychiatry, 14*(6), 561-562, 555

Yang, Y., Raine, A., Narr, K. L., Colletti, P., & Toga, A. W. (2009b). Localization of deformations within the amygdala in individuals with psychopathy. *Arch Gen Psychiatry, 66*(9), 986-994

Yoder, K. J., Lahey, B. B., & Decety, J. (2016). Callous traits in children with and without conduct problems predict reduced connectivity when viewing harm to others. *Sci Rep, 6*, 20216

Zhang, J., Gao, J., Shi, H., Huang, B., Wang, X., Situ, W., . . . Yao, S. (2014a). Sex differences of uncinate fasciculus structural connectivity in individuals with conduct disorder. *Biomed Res Int, 2014*, 673165

Zhang, J., Zhu, X., Wang, X., Gao, J., Shi, H., Huang, B., . . . Yao, S. (2014b). Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. *J Am Acad Child Adolesc Psychiatry, 53*(4), 466-475 e461

Acknowledgements

I would like to thank everyone who has supported me during my PhD studies. First, I would like to express my sincere gratitude for the guidance, advice, and mentorship of my supervisors Prof. Dr. Dr. Christina Stadler and Dr. Nora Raschle. I thank Christina for the support and freedom she has given me during my PhD, especially during the difficult times when I needed to fly back to the Netherlands. I would like to thank Nora for her expertise, creativity, and enthusiasm for neuroscience, this has been a constant source of inspiration.

I am deeply grateful to my family and friends, who have always supported me and my ambitions, even when it meant letting me immigrate to Switzerland. I dedicate this thesis to my close friend Barbera. Barbera's perseverance, humor, and caring for others made her one of the most wonderful people that I have ever met in my life. Thanks to her, I not only have a positive view on life but I also find the strength and persistence to pursue the things I find important in life. I want to thank my parents, my sister, and my brother for always being there for me when I needed them. I want to especially thank my close friend Maartje for her immeasurable support and care; you especially helped me through one of the saddest periods in my life. Then I would also like to thank Anna and Evelien for their support during the last couple of years, our skype-calls and city trips have always been a great source of strength. I am very grateful for the new friends I made in Basel, especially Silvia, who could always make me laugh during stressful times.

Furthermore, my appreciation goes to all my dear colleagues from the Stadler group, Janine and Olga for all the shared moments of joy, laughter, sorrow, and excitement. I want to thank all the people at Schanzenstrasse for making the office such a nice and friendly place to be. Special thanks go to Claudia for her advice during the DTI analysis and Reto's support during our (often late night) analyzing sessions. Furthermore, I am grateful for everyone from the Universitätsspital Basel who helped me in any way during the course of my research. I would like to thank all our previous and current master students, research assistants, and ZIWI's for supporting our studies, without their continuous help we would not be so successful with our research projects.

Last but not least, I thank all the children, adolescents, and their families that contributed their time and effort in participating in our two research projects.

Nederlandse Samenvatting

Antisociaal gedrag wordt wereldwijd veelvuldig waargenomen bij jongeren en volwassenen. Mede door de enorme belasting op deze individuen, maar ook door de noemenswaardige economische last op de samenleving is het een aanzienlijk probleem voor de volksgezondheid. Meer kennis en dus een beter inzicht in de onderliggende neurobiologische mechanismen van antisociaal gedrag kan de huidige diagnostiek (bijvoorbeeld het eerder herkennen van kinderen die verhoogd risico lopen), preventieprogramma's en behandelingsmethoden verbeteren. Tot op heden hebben verscheidene neuro-imaging onderzoeken verschillen in de hersenen aangetoond bij jongeren die antisociaal gedrag vertonen, ten opzichte van jongeren met een gezonde/normale hersenontwikkeling. Desondanks bestaan er discrepanties tussen deze onderzoeksresultaten met betrekking tot de hersengebieden die als afwijkend worden beschouwd, maar ook in de mate van verandering (zoals meer of minder hersenactiviteit). Deze tegenstrijdige bevindingen worden hoogstwaarschijnlijk veroorzaakt door de heterogeniteit binnen de groepen jongeren met antisociaal gedrag die in deze studies onderzocht zijn, vooral lettend op sekse, klinische diagnosis en de aanwezigheid van psychopathische trekken zoals kenmerken van ongevoeligheid en emotieloosheid (ookwel "callous-unemotional traits" genoemd).

Het hoofddoel van dit proefschrift was het bijdragen van nieuwe neurobiologische kennis over antisociaal gedrag bij kinderen en adolescenten door de structuur en activiteit van de hersenen nader te bestuderen, waarbij extra rekening gehouden is met mogelijke seksverschillen en psychopathische kernmerken. Allereerst hebben wij de huidige neuro-imaging literatuur geanalyseerd met behulp van drie meta-analyses. Zo kon eerdergenoemde heterogeniteit in antisociaal gedrag overbrugd worden, om vervolgens een overlappend patroon van structurele en functionele neurale correlaten in jongeren met antisociaal gedrag te ontdekken. Ten tweede heeft dit onderzoek ook de relatie tussen psychopathische trekken en hersenstructuur afzonderlijk voor jongens en meisjes onderzocht en onafhankelijk van psychiatrische comorbiditeiten. Ten derde hebben wij in dit proefschrift onderzocht of de witte stof (de uitlopers van de hersencellen) in de hersenen verschilt tussen meisjes met en zonder een antisociale gedragsstoornis ("conduct disorder"), de zwaardere variant van antisociaal gedrag.

Dit proefschrift breidt op verschillende manieren onze huidige kennis uit op gebied van structurele en functionele neurale correlaten in kinderen en adolescenten met antisociaal gedrag. Allereerst, de resultaten uit onze meta-analyses (**hoofdstuk 2**) wijzen op een consistent patroon van verminderde grijze hersenstof en hypoactivatie in verschillende hersengebieden die zich bevinden in de prefrontale en limbische cortex. Deze bevindingen komen overeen met een recent voorgesteld neurobiologisch model dat veranderingen in zulke hersengebieden verbindt met de kenmerken van antisociaal gedrag, zoals disfunctionele empathie en emotioneel leervermogen. Ten tweede hebben we een positieve relatie gevonden (**hoofdstuk 3**) tussen psychopathische kenmerken en het bilaterale insula volume in

een grote internationale groep van normaal ontwikkelende jongens, onafhankelijk van psychiatrische aandoeningen. Deze relatie was afwezig voor meisjes. Dit resultaat doet vermoeden dat bepaalde psychopathische kenmerken (d.w.z. ongevoeligheid en emotieloosheid) een seksespecifieke neurobiologische basis hebben die zelfs in een normatieve populatie gevonden kunnen worden. Ten derde presenteert dit proefschrift (**hoofdstuk 4)** nieuwe bevindingen wat betreft veranderingen in de witte stof van het corpus callosum ("hersenbalk", die de twee hersenhelften met elkaar verbindt) van meisjes met antisociaal gedrag. Dit suggereert een verminderde interhemisferische communicatie en daardoor het verminderde vermogen om emoties te verwerken, een veel gezien symptoom bij personen die antisociaal gedrag vertonen.

Kortom, dit proefschrift biedt nieuwe bevindingen met betrekking tot de neurobiologie van antisociaal gedrag in jongeren en benadrukt het belang van sekseverschillen en kenmerken van ongevoeligheid en emotieloosheid. Onze resultaten moedigen toekomstige onderzoeken aan om de ontwikkelingstrajecten en potentiele hersenindicatoren/markers van antisociaal gedrag verder te onderzoeken. Op deze manier kunnende preventie- en behandelingsprogramma's worden verbeterd, met het uiteindelijke doel antisociaal gedrag en criminaliteit in onze samenleving te reduceren.

Baseldütschi Zämmefassig

Antisoziales Verhalte isch in dr Bevölkerig bi Kinder und Erwachsene wit verbreitet und s‘stellt e grosses Gsundheitsproblem dar wege dr grosse belaschtig für d‘einzelni Person und d‘Wirtschaft. E besseres Verständnis vo de z‘grundliegende neurobiologische Mechanisme von antisozialem Verhalte garantiert e verbesserig in dr aktuelle Diagnostik (z.B.: fruehi Erkennig vo gfördete Kinder) und effektivi Präventiv- und Behandligsprogramm. Bis jetzt hend bildgäbendi Studie neurologische Unregelmässigkeite in Jugendliche mit antisozialem Verhalte gfunde; einewäg, d‘Stelläne vo denen Unregelmässigkeite unterscheide sich vo Studie zu Studie. D Unterschied kömme wohrschinlich vo dr verschiedeheit vo de untersuechte Judengliche mit antisozialem Verhalte, bsunders bezüglich Gschlecht, klinischer Diagnose und em vorhande sii vo gfühllos-unemotionale (Persönlichkeits)Eigeschafte.

S‘zentrale Ziel vo dere Dissertation isch gse s neurowisseschaftliche Wisse vo antisozialem Verhalte bi Kinder und Erwachsene zvertiefe indem d‘zgrundliegendi Struktur und d‘neurobiologischi Funktionswies untersuecht wärde, mit em Fokus uf megligi Unterschied bim Gschlecht und de gfühllos-unemotionale (Persönlichkeits)Eigeschafte. Zerscht hend mir die aktuelli bildgäbendi Literatur mithilf vo Metaanalysene untersuecht. Das mit em Ziel d‘Diversität vo antisozialem Verhalte z‘überwinde und es allgemeins „überlappendes“ Muschter von strukturelle und funktionelle Unterschied bi Jugendliche mit antisozialem Verhalte z‘biko. Zweitens isch s‘Verhältnis zwische gfühllos-unemotional (Persönlichkeits)Eigeschafte und dr Gehirnstruktur unabhängig vom Gschlecht und psychiatrische Komorbidäte untersuecht worde. Drittens isch d’Integrität von dr wisse Substanz in ere homogene gruppe vo Maidle mit Verhaltensstörig – dr stärkere Veriante vo antisozialem Verhalte –im Verglich zu normal entwickelnde Gliechaltrige untersuecht worde.

Die Arbet erwieteret unsers aktuelle Wisse vo strukturelle und funktionale neuronale Zämmehang bi Kinder und Erwachsene mit antisozialem Verhalte uf verschideni Arte. Erstens hend unseri metaanalytische Resultat uf e konsistänts Muschter vo dr Reduktion vo dr graue Substanz und Hypoaktivierige in Gehirnregione im präfrontale und limbische Kortex higwiese. Die Resultat passe zumene kürzlich vorgstellte neurobiologische Model, dass Veränderige in ähliche Hirnregione mit de Verhaltensänderige vo antisozialem Verhalte (z.B. dysfunktion in dr Empathie, emotionales Lerne und dr Entscheidigsfindig) verbindet. Zweitens hend mir e positivi Beziehig zwische gfühllos-unemotional (Persönlichkeits)Eigeschafte und em Volume vo dr bilaterale insula inere grosse internationale Gruppe vo sich normal entwickelnde Bube, abr nit Maidli, unabhängig vo psychiatrische Störige beobachtet. Das zeigt, dass gfühllos-unemotional (Persönlichkeits)Eigeschafte e gschlechterspezifischi neurobiologischi Grundlag zuesätzlich zu psychiatrische Probene hend. Drittens präsentiert die Arbet neuartigi Fund vo Änderige in dr Integrität vo dr wisse Substanz im Gehirnbalke vo Maidli mit anitisozialem Verhalte. Das dütet uf e megligs reduzierts interhemisphärisches arbeite hi und dorus folgend e reduzierti Fähigkeit zur emotionale Verarbeitig.

Zsämmegfasst tuet d Disseration neui Fund bezüglich dr Neurobiologie vo antisozialem Verhalte in Judengliche liefere und sie hebt d'Wichtigkeit vo gfühllos-unemotional (Persönlichkeits)Eigeschafte und Gschlechtunterschied hervor. Unseri Resultat ermuetige wieteri Studie dr Entwickligsverlauf und potenzielli neuronali Marker von antisozialem Verhalte wieter z'untersueche. Das um d'Frieherkennig und Interventionsprogram z'verbessere, was letztendlig antisoziales Verhalte und Kriminalität in unserer Gsellschaft reduziere könnti.

Translated by Samuel Martin

Declaration by Candidate and Publication List

I declare that this dissertation is prepared independently, the three research articles have been published or submitted to peer-reviewed journals and were written in collaboration with the listed co-authors. All citations are specified and only the mentioned sources were used in this dissertation.

The following articles are included:

Article 1

Menks, W. M., Furger, R., Lenz, C., Fehlbaum, L. V., Stadler, C., & Raschle, N. M. (**2017**). Microstructural White Matter Alterations in the Corpus Callosum of Girls with Conduct Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(3), 258-265.
Data acquisition, data analysis, interpretation of the data, drafting and writing the article.

Article 2

Raschle, N. M., Menks, W. M., Fehlbaum, L. V., Tshomba, E., & Stadler, C. (**2015**). Structural and Functional Alterations in Right Dorsomedial Prefrontal and Left Insular Cortex Co-Localize in Adolescents with Aggressive Behaviour: an ALE Meta-Analysis. *PloS one*, *10*(9), e0136553.
Data acquisition, data analysis, interpretation of the data, drafting, formatting and critically revising the article.

Article 3

Raschle, N. M., Menks, W. M., Fehlbaum, L. V., Steppan, M., Smaragdi, A., Gonzalez, K., Rogers, J., Clanton, R., Kohls, G., Martinelli, A., Bernhard, A., Fairchild, G., de Brito, S., Konrad, K., Herpertz-Dahlmann, B., Freitag, C. M., & Stadler, C. (**under review**). Callous-Unemotional Traits and Brain Structure: Gender-Specific Effects in Typically-Developing Youths.
Data acquisition, data analysis, interpretation of the data, formatting and critical revision of the article.

Extra Article

Raschle, N. M., Tshomba, E., Menks, W. M., Fehlbaum, L. V., & Stadler, C. (**2016**) Emotions and the Brain–Or How to Master "The Force". Front Young Minds. 4:16. doi: 10.3389/frym.2016.00016
Illustration design and critical revision of the article.

"If we knew what it was we were doing, it would not be called research, would it?"

attributed to Einstein