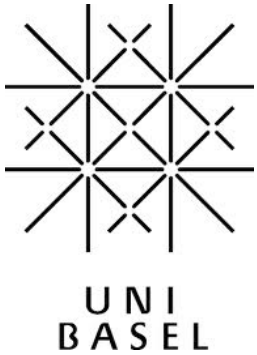

Neuronal basis of emotion processing and regulation in conduct disorder

A cumulative dissertation

Submitted to the Faculty of Psychology, University of Basel,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

by

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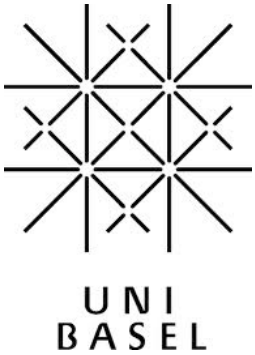

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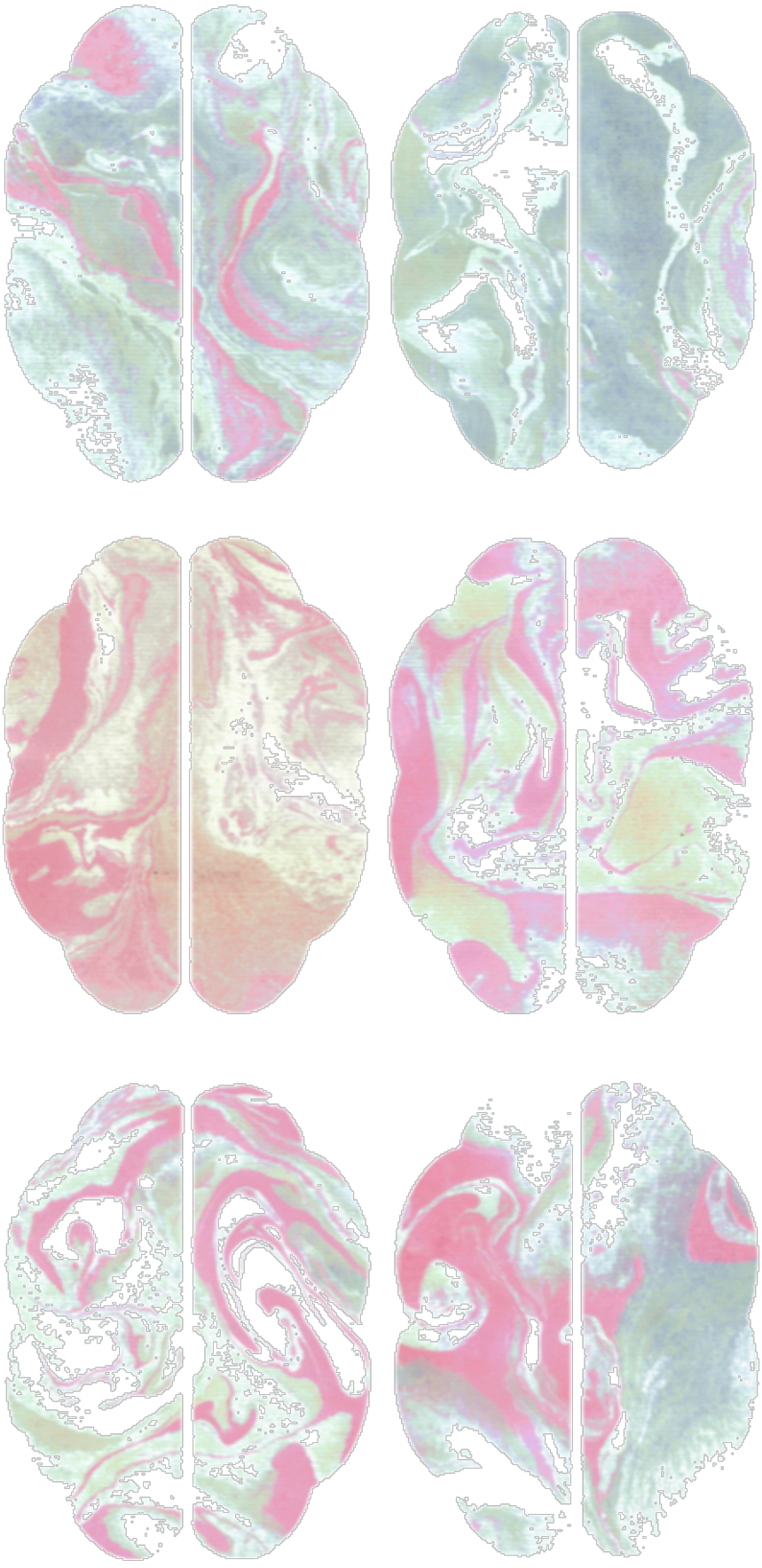


Content

Abstract

Emotion regulation, a key component of healthy development, has been shown to be deficient in several psychiatric conditions, including conduct disorder. Conduct disorder is a neuropsychiatric disorder of childhood and adolescence characterized by severe aggressive behavior and violation of societal norms. It is highly prevalent and results in substantial economic costs and negative social consequences. Neuroimaging evidence has revealed brain activity alterations in several regions, including prefrontal, temporal, and limbic cortex (amygdala, insula, and cingulate gyrus). While the neuronal basis of emotion processing in conduct disorder has been intensely investigated, the brain correlates of implicit and explicit emotion regulation remain unclear.

The main aim of this dissertation was to extend current knowledge by investigating the neuronal mechanisms of emotion regulation in children and adolescents with conduct disorder. First, we conducted a meta-analysis in order to identify the neuronal correlates of emotion processing in adolescents with aggressive behavior. We then developed an affective Stroop task designed to investigate the interplay between emotion and cognition in a paediatric population, and validated it in healthy young adults. We then employed the task to study the neuronal characteristics of implicit emotion-cognition interaction in children and adolescents with conduct disorder. Finally, we investigated explicit emotion regulation by cognitive reappraisal (i.e., reinterpretation of the meaning of an emotional stimulus) in conduct disorder.

We here present findings on altered brain function during tasks assessing implicit and explicit emotion regulation in adolescents with conduct disorder that are in agreement with behaviorally observed deficits. Our meta-analysis on emotion processing in conduct disorder summarized previous literature indicating prefrontal and limbic brain structure and function alterations. The results from our study employing the affective Stroop task in healthy adults validated the usefulness of our task design and replicated previous findings suggesting that emotion significantly impacts cognition on a behavioral and neuronal level. Using the affective Stroop and cognitive reappraisal tasks in adolescents with conduct disorder revealed neuronal alterations within prefrontal and limbic regions, brain areas implicated in both emotion and cognition. Overall, the results of this dissertation provide novel evidence on the neuronal basis of emotion regulation deficits in conduct disorder. Future studies shall further investigate emotion regulation in specific subgroups of conduct disorder, for example those with psychopathic traits or high levels of anxiety with the ultimate goal of influencing the child's immediate environment and society as a whole.

1 Introduction

1.1 Conduct disorder

During early development and throughout childhood and adolescence, individuals adapt to environmental demands while continuously developing their personality and individuality, and improving their emotional and cognitive abilities. Developmental changes include, amongst others, advances in social competence, emotion management, and neurobiological changes, and are often dependent on environmental factors such as positive family and peer relationships (Dodge et al., 2003; Park, 2004). All of these factors enhance positive feelings and are crucial for a successful coping with stressful life events and challenges during the development of an independent self. Adolescence has been suggested to be a particularly sensitive period for healthy and maladaptive development patterns (Blakemore & Mills, 2014; Steinberg, 2005, 2014). Unfavorable dispositions during this sensitive period can lead to a set of difficulties in managing the challenges of daily life and have been related to mental health problems characterized by poor social abilities, depressive symptoms, and aggressive behavior (Gowers, 2005; Silk, Steinberg, & Morris, 2003).

Children's ability to self-regulate their emotions already starts developing early in life and is viewed as a key component for adaptive functioning (Eisenberg, Spinrad, & Eggum, 2010). Deficits in emotion regulation can result in atypical developmental outcomes: Especially when negative affect is involved, individuals may show inappropriate reactions resulting in impulsive and aggressive behavior towards others (Eiden, Edwards, & Leonard, 2007; Frick & Morris, 2004; McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011). Such aggressive behavior and emotion regulation difficulties constitute an integral part of the symptomatology of externalizing mental disorders. Individuals with persistent antisocial behavior may be diagnosed with conduct disorder (CD), one of the most frequent psychiatric disorders of childhood and adolescence. The lifetime prevalence of CD ranges between 2-16%, differs greatly for males (12%) and females (7.1%), and is amongst the most common reasons for referrals to psychiatric institutions in the United States (Kazdin, 1995; Nock, Kazdin, Hiripi, & Kessler, 2006). The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association (2013)) defines CD as a "repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated" (p. 469). Symptoms are further classified according to four main clusters, including *aggression to people and animals*, *destruction of*

property, *deceitfulness or theft*, and *serious violations of rules* (American Psychiatric Association, 2013).

Within DSM-5, CD is classified as *mild*, when few symptoms are present and cause mild harm only, *moderate*, when the number of symptoms and harm caused are intermediate, or *severe*, when patients present with many symptoms and cause considerable harm. A minority of adolescents with CD additionally displays elevated callous-unemotional (CU) traits. In the new DSM-5 this was recognized by implementing a specifier named *with limited prosocial emotions* including behavioral characteristics such as lack of guilt and empathy, cold and uncaring behavior towards others, lack of concern about the consequences of one's own behavior, as well as shallow/superficial affect (American Psychiatric Association, 2013; Kimonis et al., 2015; Stadler, Poustka, & Sterzer, 2010). Evidence indicates that adolescents with CD and with high CU traits are at specific risk for lifetime persistent aggressive and antisocial behavior (Frick & Dickens, 2006).

CD is a highly heterogeneous disorder, which is reflected in the distinction between childhood-onset and adolescent-onset CD, subtypes of aggressive behavior, as well as a variety of risk factors, symptom profiles, and comorbidities. In an attempt to take interpersonal variability into account, the DSM-5 distinguishes between childhood-onset (emerging prior to age 10) and adolescent-onset (emerging after age 10) subtypes of CD. The childhood-onset subtype has been attributed a more persistent and genetically driven course of development than the adolescent-onset type (Loeber, Burke, Lahey, Winters, & Zera, 2000; Moore, Silberg, Roberson-Nay, & Mezuk, 2017), but has been blamed to represent an oversimplifying approach with limited predictive value (Fairchild, Goozen, Calder, & Goodyer, 2013; Loeber et al., 2000).

Classification approaches have further distinguished between reactive (hot, impulsive, affective) and proactive (cold, instrumental) aggression (Kempes, Matthys, De Vries, & Van Engeland, 2005; Stadler et al., 2010; Vitaro, Brendgen, & Barker, 2006). Reactive aggression is typically preceded by negative emotions and triggers anger – aggression is immediate and impulsive. It is not goal-directed and responds to negative reinforcement. Proactive aggression, in contrast, is goal-oriented, driven by anticipated rewards, and includes physiological arousal. While reactive aggression has been linked to physical abuse, impulsive behavior, and peer rejection, proactive aggression has been related to the presence of elevated CU traits, delinquent behavior, and is thought to be specific for CD.

Ample evidence moreover indicates an involvement of several risk factors for the development of CD. Psychosocial risk factors include inconsistent parenting, early maltreatment, parental psychopathology, and low socio-economic status. However, also genetic, physiological, and temperamental influences have been discussed (for a review see Stadler et al. (2010)). In addition, adolescents with CD are at increased risk for comorbid mental disorders such as anxiety disorders, substance use disorders, attention deficit/hyperactivity disorder (ADHD), or oppositional defiant disorder (ODD) (Nock et al., 2006).

Together with ODD, CD has been categorized as a disruptive behavior disorder (DBD) (American Psychiatric Association, 2013). While ODD is characterized by a milder form of aggressive and antisocial behavior, a CD diagnosis is linked with more severe aggressive behavior and societal consequences. In the literature, ODD and CD have been placed along a continuum of antisocial behavior, rather than representing two separate disorders. As such, a subgroup of children with ODD will develop CD later in life. More specifically, children with an early onset and higher severity of conduct problems are at higher risk for developing CD (Nock, 2006, Moffit et al., 2008). Moreover, CD can continue as antisocial personality disorder (ASPD) in adulthood.

If left untreated, conduct problems in childhood will often persist and increase in severity over time (Bunte, Schoemaker, Hessen, van der Heijden, & Matthys, 2014), resulting in substantial consequences and costs for society and public health. These may include higher rates of delinquency, poor academic performance, teenage pregnancies, negative relationships, and mental disorders in adulthood, all together leading to additional public health costs per child of above $70’000 (Biederman et al., 2008; Capaldi, Crosby, & Stoolmiller, 1996; Erskine et al., 2016; Fergusson, John Horwood, & Ridder, 2005; Foster & Jones, 2005; Lahey, Loeber, Burke, & Applegate, 2005; Swanson, 1994). Therefore, adequate treatment and prevention are of particular importance. Interventions focusing on the improvement of skills for solving emotional, social, and cognitive problems of children and parents, such as cognitive/dialectical behavioral therapy, parent management training, and multisystemic therapy, have proven effective and are under constant development and improvement (Blair, Leibenluft, & Pine, 2014; Kazdin, 1997; Stadler et al., 2010). In order to improve current programs, a deeper understanding of the behavioral and neuronal basis of CD is needed. Investigations aiming at the characterization of children and adolescents with DBD are therefore of utmost importance.

1.2 Functional neuroimaging evidence

Modern neuroimaging techniques allow researchers to capture the intricate nature of neuronal mechanisms in humans. With the use of functional magnetic resonance imaging (fMRI) neuronal activity in response to task performance can be observed, providing a more comprehensive picture of behavioral impairments in individuals with psychiatric disorders.

Functional MRI uses the properties of the magnetic field and radiofrequency pulses to detect local changes in the oxygenation of blood, which indirectly reflect brain activity. When an individual performs a cognitive task, the body sends out an increased amount of blood to the responsible brain regions. In fact, more blood is sent to the brain regions than is needed in order to refill the oxygen used by the neurons, resulting in an excess of oxygenated blood. The blood oxygen level dependent (BOLD) signal measured by the MRI reflects this change in blood oxygenation. With the use of statistical computations and visualization techniques, brain activity increases in response to a particular task can be monitored with a good spatial resolution (Poldrack, Mumford, & Nichols, 2011).

In order to produce statistical maps displaying the neuronal response of brain regions responsible for one particular mental activity, many steps are needed. In general, this procedure consists of data preprocessing (including slice timing correction, realignment, coregistration, segmentation, normalization to a standard brain template, and smoothing), model specification, and statistical analysis. Adequate preprocessing of fMRI data ensures that confounding sources are accounted for. As such, different steps are conducted in order to correct for inconsistent acquisition times of different brain slices (slice timing correction), head motion (realignment), or scanner inhomogeneity (distortion correction), and the images acquired are mapped to the individual's structural images (coregistration), segmented into gray matter, white matter, and cerebrospinal fluid (segmentation), aligned with a standardized brain template (e.g., normalization to the Montreal Neurological Institute template MNI), and blurred to improve the signal-to-noise ratio (i.e., smoothing) (Chen & Glover, 2015; Poldrack et al., 2011). Next, the general linear model to predict the neuronal response is defined and parametric or nonparametric statistical analyses with correction for multiple comparisons are computed. Moreover, repeated rigorous quality controls throughout data acquisition, preprocessing, and analysis pipeline warrant the quality of data and correct interpretation of results.

In the past years, researchers have meticulously studied the neuronal correlates of CD and linked brain activity to behavioral characteristics. In line with the behaviorally observed

impairments in emotion processing and regulation, neuroimaging evidence has overall indicated altered brain function in several areas in DBD. As such, brain alterations in orbitofrontal, dorsolateral, and dorsomedial prefrontal cortices, temporal lobe, and limbic regions (amygdala, insula, and cingulate gyrus) were detected during different tasks engaging the emotion processing network of the brain, for example emotional Theory of Mind, empathy for pain, or face processing tasks (Baker, Clanton, Rogers, & De Brito, 2015; Fairchild et al., 2014; Passamonti et al., 2010). However, research has produced mixed findings regarding the direction of the neuronal response of these regions. While some report hypoactivations, others report hyperactivations in adolescents with disruptive behavior. This is likely due to symptom heterogeneity, variation in tasks employed, differences in the clinical sample chosen, age and sex of the participants, or the presence of CU traits. For example, studies have reported both increased (Herpertz et al., 2008; Sebastian et al., 2014; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005; Viding et al., 2012) and decreased (Jones, Laurens, Herba, Barker, & Viding, 2009; Marsh et al., 2008; Sebastian et al., 2012) amygdala activity in response to emotional face processing or emotional Theory of Mind tasks related to variations in CU traits (Baker et al., 2015; Blair, 2010a). Increased amygdala activity has been reported for individuals with low levels of CU traits, whereas decreased amygdala activation has been detected in individuals with elevated CU traits.

Based on the impulsive patterns of behavior observed in adolescents with CD, research has moreover investigated response inhibition in CD. While some studies have reported impaired response inhibition performance in CD (Castellanos-Ryan, Rubia, & Conrod, 2011; van der Meer & van der Meere, 2004), other investigations have not detected such differences (Banich et al., 2007; Rubia et al., 2010; Rubia et al., 2008). Evidence in adults with psychopathic or CU traits, in contrast, has consistently reported an improved performance during response inhibition (Blair et al., 2006; Hiatt, Schmitt, & Newman, 2004; Schiffer et al., 2014; Sommer, Hajak, Döhnel, Meinhardt, & Müller, 2008), potentially indicating a developmental effect or effects of antisocial symptom severity. Neuroimaging studies in adolescents with CD or conduct problems have revealed alterations in a wide network of brain regions. More specifically, they have detected neuronal increases (Banich et al., 2007) and decreases (Rubia et al., 2010; Rubia et al., 2009; Rubia et al., 2008) in the medial prefrontal cortex, temporoparietal, occipital, subcortical, and limbic regions during visuo-spatial response inhibition tasks (Banich et al., 2007; Rubia et al., 2010; Rubia et al., 2009; Rubia et al., 2008).

In the upcoming section we will more extensively review previous behavioral and neuroimaging findings of emotion regulation in healthy individuals and adolescents with CD.

1.3 Emotion regulation

Experiencing emotional states and adapting one's own behavior in order to respond appropriately to environmental cues involves the use of emotion regulation skills, a broad term that subsumes at least two cognitive processes: implicit and explicit emotion regulation (Gyurak, Gross, & Etkin, 2011). Implicit emotion regulation is automatic and not monitored by the individual, whereas explicit emotion regulation is conscious, actively monitored (Gyurak et al., 2011), and involves strategies including reinterpretation of the meaning of an emotional stimulus with the explicit goal to influence its emotional impact (i.e., *cognitive reappraisal*, Gross (1998)). The following sections will focus on evidence on a form of implicit emotion regulation, namely emotion-cognition interaction, and explicit emotion regulation by cognitive reappraisal in healthy individuals and those with DBD.

1.3.1 Emotion-cognition interaction

Successfully integrating emotionally salient information and cognitive processes that serve goal-directed behavior is a prerequisite for healthy functioning (Blair, 2002; Okon-Singer, Hendler, Pessoa, & Shackman, 2014; Tugade, Fredrickson, & Feldman Barrett, 2004), a skill which has been repeatedly reported to be deficient in neuropsychiatric disorders, such as anxiety disorders (Blair et al., 2012; Hasler, Mondillo, Drevets, & Blair, 2009), post-traumatic stress syndrome (Mueller-Pfeiffer et al., 2010; Roy, Costanzo, Blair, & Rizzo, 2014; Vythilingam et al., 2007; White, Costanzo, Blair, & Roy, 2015), and ADHD (Hwang et al., 2015), and has further been suggested to be impacted in CD (Hwang et al., 2016). However, in order to understand the impairments observed in neuropsychiatric disorders, it is crucial to examine healthy functioning in a first step.

Behavioral studies investigating implicit emotion-cognition interaction in healthy adults have provided insights into the successful integration of these processes. Past investigations have reported both improvements as well as impairments due to emotion stimulation prior to tasks demanding cognitive resources, and have resulted in a broad understanding among researchers on different factors that influence emotion-cognition interaction. Stimulus and task characteristics, cognitive load, individual differences, and level of threat are all factors that have been shown to substantially impact the nature of emotion-cognition interaction (Cohen & Henik, 2012; Gupta, Hur, & Lavie, 2016; Hartikainen, Ogawa, & Knight, 2000; Okon-Singer, Lichtenstein-Vidne, & Cohen, 2013). As a result, experiencing emotions may differently impact consequent cognitive behavior. Visual or auditory emotional stimulus presentation has shown to improve cognitive performance (i.e., shorter reaction times and/or

higher accuracy) during conflict processing, visual attention, or decision making (Kanske & Kotz, 2011; Schupp et al., 2007; Zinchenko, Kanske, Obermeier, Schroger, & Kotz, 2015). In contrast, impaired cognitive performance (i.e., longer reaction times and/or lower accuracy) after emotion presentation was detected during a variety of tasks including working memory (Dolcos & McCarthy, 2006; Uher, Brooks, Bartholdy, Tchanturia, & Campbell, 2014), perceptual (Gupta & Deák, 2015), and response inhibition tasks (Blair et al., 2007; Hart, Green, Casp, & Belger, 2010; Hwang, White, Nolan, Sinclair, & Blair, 2014; Sommer et al., 2008).

Functional MRI studies have reported an implication of parietal, prefrontal, and limbic regions such as the amygdala, insula, and anterior cingulate during implicit emotion-cognition interaction using tasks integrating emotional stimuli with different cognitive stimuli (e.g., working memory (Gray, Braver, & Raichle, 2002; Kellermann et al., 2011), arithmetic (Van Dillen, Heslenfeld, & Koole, 2009), or response inhibition tasks (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Gu, Liu, Van Dam, Hof, & Fan, 2013; Melcher, Born, & Gruber, 2011; Rahm, Liberg, Wiberg-Kristoffersen, Aspelin, & Msghina, 2013; Sommer et al., 2008); for a review see Cromheeke and Mueller (2014) or Song et al. (2017)).

The affective Stroop task is a paradigm that has proven to be a valid measure for implicit emotion-cognition interaction and has successfully been implemented by several authors (Blair et al., 2007; Hart et al., 2010; Hwang et al., 2016; Hwang et al., 2014). It involves both stimuli with strong emotional valence and a Stroop task with variations in cognitive load, which is achieved through trials of varying difficulty. More specifically, the Stroop task measures response inhibition and consists of congruent trials reflecting a low cognitive load (easy task), and incongruent trials reflecting a high cognitive load (difficult task). The Stroop effect (Stroop, 1935) represents increased reaction times and lower accuracy for trials with high cognitive load compared to trials with low cognitive load (Blair et al., 2007; Hart et al., 2010; Hwang et al., 2014). Studies using affective Stroop tasks in healthy adults have revealed an implication of the amygdala and orbitofrontal cortex in response to emotional images, and frontal and cingulate regions in response to Stroop task trials (Blair et al., 2007; Hart et al., 2010). Results on the interaction between emotional images and Stroop task trials are more complex to interpret. Blair and colleagues (2007) reported significantly decreased activity in areas responsible for emotion processing (bilateral amygdala and ventrolateral prefrontal cortex) during task performance after emotion processing, especially during high cognitive load trials. In line with the model by Desimone and Duncan (1995), the authors concluded that activity in the amygdala is reduced due to competing mechanisms of top-down

attentional selection evoked by simultaneous emotion and cognitive processing. Hart and colleagues (2010), in contrast, detected decreased neuronal activity after emotion stimulation in regions such as the insula, superior frontal cortex, and temporal cortex during low cognitive load trials, but no decreases during high cognitive load trials. This finding led the authors to conclude that increased cognitive load can override decreased activation in insula and prefrontal cortex observed during low cognitive load trials. Overall, both studies reported decreases in performance and changes in prefrontal and limbic cortex in order to meet cognitive demands of high complexity. The observed differences between the two investigations (Blair et al., 2007; Hart et al., 2010) may arise from task design variations such as the duration and timing of the stimulus presentation, or from sample size differences and the specific characteristics of each study.

Behavioral and neuroimaging evidence has suggested that both emotion and cognitive processing are impaired in adolescents with disruptive behavior and even represent risk factors for a continuation of antisocial behavior later in life (Campbell, Shaw, & Gilliom, 2000; Davidson, Putnam, & Larson, 2000; Wang, Chassin, Lee, Haller, & King, 2017; Young et al., 2009). Behaviorally, previous studies have revealed impaired performance (longer reaction times/higher error rates) during implicit emotion-cognition interaction in adolescents with DBD (Euler, Sterzer, & Stadler, 2014; Hwang et al., 2016; Prateeksha, Roopesh, & Vijayasagar, 2014).

To date, one investigation has aimed at revealing the neuronal correlates of implicit emotion-cognition interaction in DBD (Hwang et al., 2016). The authors reported reduced emotion-related amygdala and ventromedial prefrontal cortex activity, and reduced cognition-related insula activity during an affective Stroop task in DBD. While amygdala and prefrontal cortex activity was inversely correlated with CU traits level, insula activity was inversely related to ADHD symptomatology. This study provides the only evidence so far indicating neuronal dysfunctions during implicit emotion regulation through emotion-cognition interaction in adolescents with DBD.

1.3.2 Cognitive reappraisal

Cognitive reappraisal is an explicit emotion regulation strategy, which is used to cognitively change an emotional experience. More specifically, the meaning of a stimulus and the personal connection to it are reinterpreted in order to modify (mostly downregulate) the emotional reaction (Gross, 1998; Ochsner, Silvers, & Buhle, 2012). It decreases the negative emotion experience by targeting the early stage of emotion generation (Goldin, McRae,

Ramel, & Gross, 2008; Szasz, Szentagotai, & Hofmann, 2011; Wolgast, Lundh, & Viborg, 2011) and can have long-lasting effects (Kross & Ayduk, 2008).

Cognitive reappraisal has been shown to evoke increased neuronal activation in a wide network of cognition-related prefrontal brain regions (dorsomedial, dorsolateral, ventrolateral prefrontal cortex), cingulate cortex, and temporoparietal regions. Dorsolateral and posterior prefrontal areas are recruited to monitor reappraisal goals, dorsal anterior cingulate cortex to monitor if the emotions are reinterpreted in the intended way, ventrolateral prefrontal areas to select goal-directed responses, and dorsomedial prefrontal cortex to interpret the own emotional state (Kohn et al., 2014; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; Kevin N Ochsner et al., 2004; Ochsner et al., 2012). Activity in the amygdala, which was elicited by the emotions evoked in the first place, is reduced by cognitive reappraisal, in line with the behaviorally observed decreases in negative affect (Buhle et al., 2014; Goldin et al., 2008; McRae et al., 2010).

Deficient emotion regulation represents a core impairment across different neuropsychiatric disorders, such as anxiety disorders (Mennin, McLaughlin, & Flanagan, 2009), ADHD (Shaw, Stringaris, Nigg, & Leibenluft, 2014), or DBD (Teisl & Cicchetti, 2008). Even though emotion regulation has been hypothesized to play a substantial role in the development and maintenance of CD (Teisl & Cicchetti, 2008), no behavioral or neuronal studies investigating explicit emotion regulation by cognitive reappraisal in disruptive behavior exist to date.

1.4 Gaps in knowledge

During the last decades, our knowledge on the neuronal mechanisms of typically developing individuals and adolescents with CD has increased significantly thanks to numerous studies devoted to further characterize this group. Despite the considerable progress within this research field, limitations of past studies restrict the conclusions than can be drawn from the findings.

One major limitation of past investigations concerns the small sample sizes most results are based on. Potential reasons for this limitation are the high costs implicated in using expensive neuroimaging techniques such as MRI, but most importantly challenges in recruitment and testing of young neuropsychiatric populations, resulting in a lack of statistical power and low reproducibility (Button et al., 2013). Therefore, the findings of past studies are often inconsistent, indicating both hyper- and hypoactivations in relevant brain regions. This is possibly due to different inclusion criteria with regards to the age range, sex, IQ, and the

methods and experimental designs used. Meta-analyses are a valid method to combine the results from earlier studies in order to draw an overall conclusion based on statistical computations. Coordinate-based meta-analyses such as activation likelihood estimation (ALE) meta-analyses as performed via GingerALE (Eickhoff et al., 2009) allow researchers to identify brain regions with a consistent neuronal response during performance of a particular task or structural alterations by converging the coordinates of MRI findings across studies. As such, **aim 1** of the present dissertation was to combine the results from previous studies investigating the neuronal basis of aggressive behavior with GingerALE in order to detect peak coordinate clusters of gray matter volume alterations and neuronal activation changes in those adolescents, as well as a potential overlap of structural and functional peaks (**study 1**).

Past research has investigated not only the way individuals process emotions and perform cognitive tasks, but also the interaction thereof, i.e., tasks that demand both emotion and cognitive processing (e.g., implicit emotion regulation with the use of an affective Stroop task). However, earlier investigations have provided ambiguous results. Moreover, studies have often focused on providing novel task designs and findings with increased chances of publication. While this may be of great relevance in order to deepen our knowledge, the need to replicate previously reported findings has often been neglected. However, only by replicating studies, results can be re-evaluated and, ideally, generalized. In line with this idea, journals have increasingly acknowledged the value of replication studies within recent years (Fletcher & Grafton, 2013). Therefore, **aim 2** of this dissertation was to investigate the neuronal basis of implicit emotion regulation using an affective Stroop task in healthy young adults (**study 2**). The motivation for this study was twofold: First, replicating results on the neuronal mechanisms of healthy emotion-cognition interaction with a child-friendly task design based on a previous study by Hart et al. (2010). Second, evaluating the task design for further application in adolescents with CD (see aim 3).

While many studies have provided evidence for altered brain activity in response to emotion processing in adolescents with DBD, only one study so far has investigated the neuronal basis of implicit emotion-cognition interaction in adolescents with this diagnosis. Moreover, it remains unclear whether the observed impairments persist if only including adolescents with a strict diagnosis of CD. Therefore, **aim 3** of this dissertation was to investigate the neuronal basis of implicit emotion regulation using an affective Stroop task in adolescents with CD (**study 3**).

Furthermore, the neuronal characteristics of deficient explicit emotion regulation as measured by cognitive reappraisal (K. N. Ochsner et al., 2004) have not yet been investigated in CD. Within **aim 4** of this dissertation, we were therefore targeting at characterizing the neuronal basis of cognitive reappraisal in adolescents with CD (**study 4**) as part of a European consortium project (FemNAT-CD, https://www.femnat-cd.eu).

In addition to the four main aims, three subaims are part of this dissertation. **Subaim 5.1** originated from the need to translate and disseminate scientific findings to the general public, and in particular to children and adolescents (**study 5**). In order to make research accessible to a non-expert public and fostering the interest of individuals of all ages in scientific findings it is crucial to find an appropriate language. Subaim 5.1 aimed at translating the findings of our meta-analysis to the non-scientific community and the youngest members of our society by providing them with an understanding of the concept of aggressive behavior, neuroimaging methods, and scientific procedure. **Subaim 5.2** focused on white matter alterations in female antisocial behavior (**study 6**). Past investigations have focused on investigating white matter tracts in males with DBD, but did not yet account for possible sex differences. As such, subaim 5.2 aimed at characterizing white matter in females with antisocial behavior with the use of diffusion tensor imaging (DTI). **Subaim 5.3** involved the investigation of CU traits in relation to brain structure in typically developing adolescents (**study 7**). Alterations in brain structure in relation to CU traits have previously been demonstrated in clinical samples. However, it is unclear whether CU traits are related to changes in brain structure beyond a psychiatric diagnosis. Here, our goal was to shed light on the neuronal correlates of CU traits in the absence of antisocial behavior.

1.5 Aims

Aim 1/study 1: Investigate structural and functional alterations in adolescents with aggressive behavior with an ALE meta-analysis

- Conduct a systematic literature review on structural and functional correlates of aggressive behavior
- Perform two separate meta-analyses with the use of the GingerALE software in order to identify clusters of structural (gray matter volume) and functional (neuronal activity during emotion processing) alterations in adolescents with aggressive behavior
- Run a conjunction analysis to detect overlaps between structural and functional alterations in adolescents with aggressive behavior

Aim 2/study 2: Investigate the neuronal basis of implicit emotion regulation using an affective Stroop task in healthy young adults

Aim 3/study 3: Investigate the neuronal basis of implicit emotion regulation using an affective Stroop task in adolescents with CD

Aim 4/study 4: Investigate the neuronal basis of explicit emotion regulation by cognitive reappraisal in adolescents with CD

Subaims:

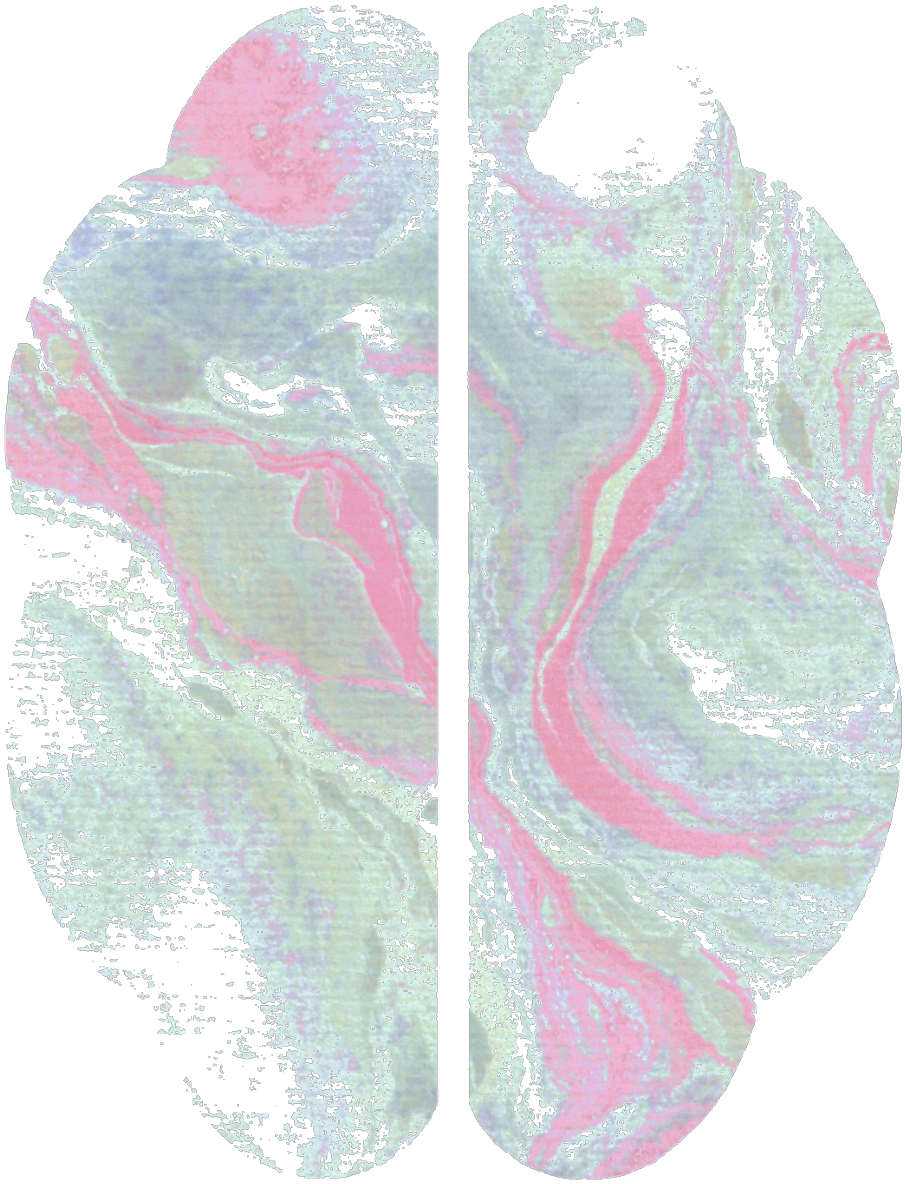
Subaim 5.1/study 5: Translate and disseminate the concept and methods of neuroscience to the general public, in particular children and adolescents

Subaim 5.2/study 6: Investigate white matter alterations in the corpus callosum of females with CD

Subaim 5.3/study 7: Investigate CU traits in relation to brain structure in typically developing adolescents

2 Study 1

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



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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 behaviour 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 behavioural observations, suggesting that the presence of early brain alterations in individuals with aggressive behaviour 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 behaviour* (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 (M. S. 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.

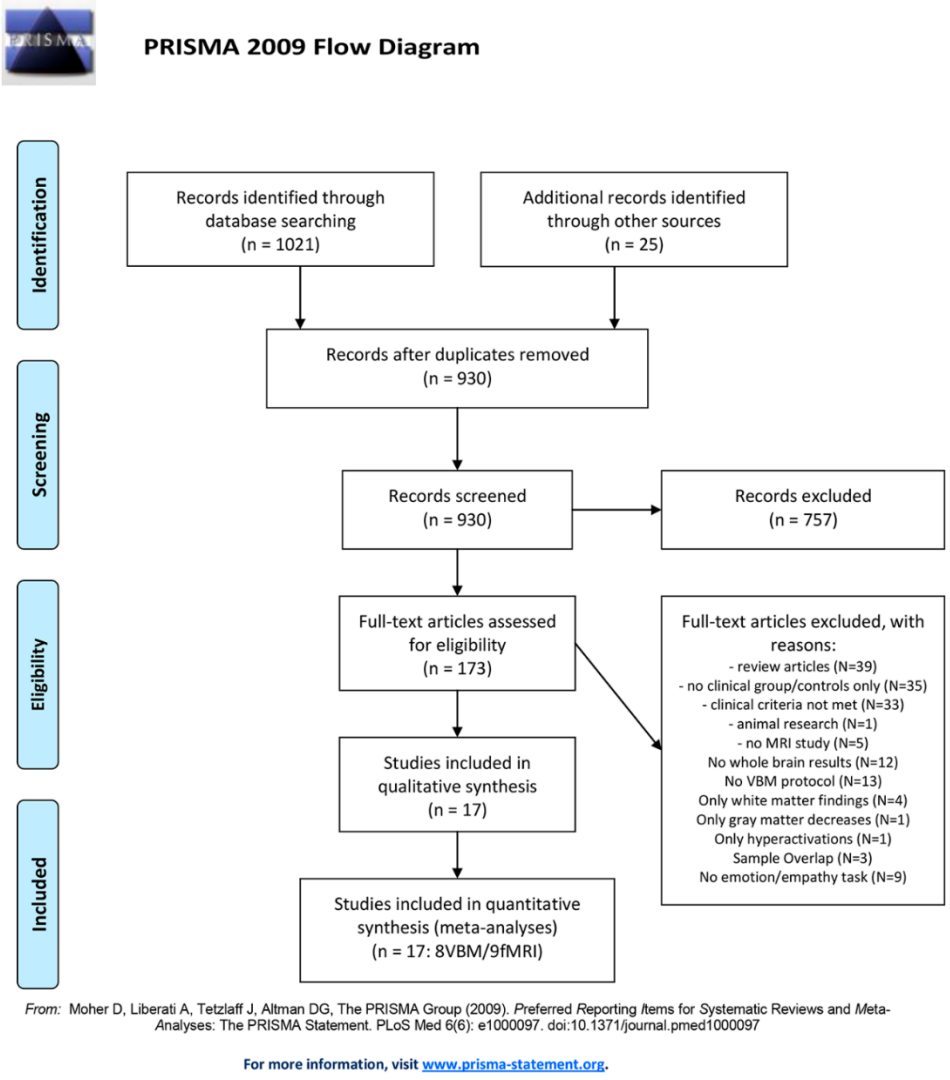

Figure 1. Systematic literature research. Literature research according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality Of Reporting Of Meta-analyses (QUOROM) statement (59) resulting in 17 neuroimaging studies included in the current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

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, 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,** (M. Dalwani et al., 2011; M. S. Dalwani et al., 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 (M. S. 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 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.

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.

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.

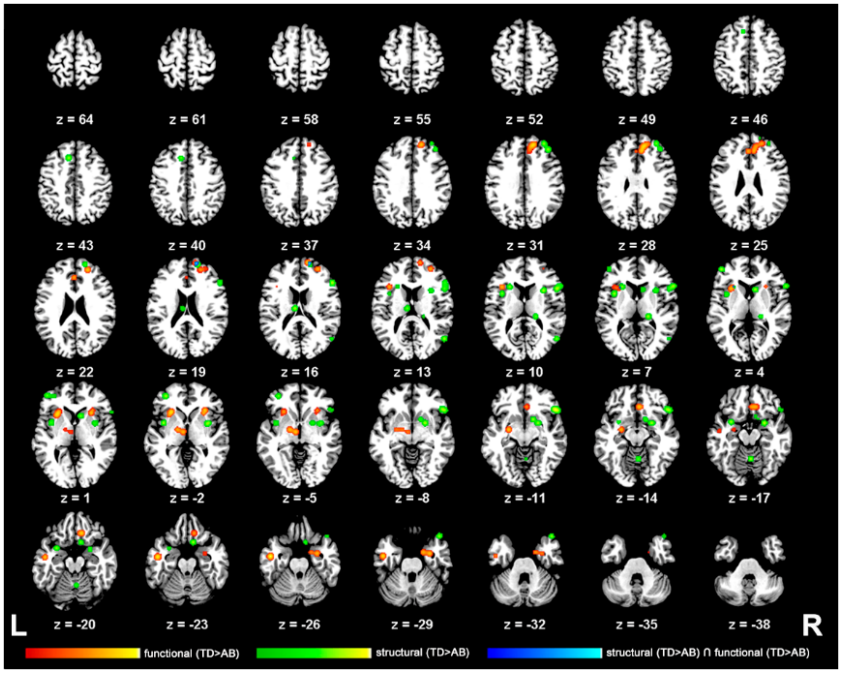

Figure 2. Neuronal alterations in adolescents with aggressive behavior (TD>AB): Results from an ALE meta-analysis. 2-D axial slices displaying the thresholded and binarized ALE maps of significant overlap (p<0.05, FDR-corrected) in studies of structural (green) and functional (red) alterations in adolescent 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,	13,	R	1952	54	16	10
	insula	44 , 45			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,	8, 9,	R/L	3728	14	44	30
		10, 32			8	36	28
	anterior cingulate gyrus						
					22	48	22
					32	50	14
					0	36	24
2	thalamus, lentiform nucleus,		L	1944	-6	-12	-4
	putamen, medial globus pallidus				-26	-8	-12
	amygdala				-16	-8	-4
3	claustrum, insula	13	L	1896	-28	20	0
					-38	20	12
4	middle frontal gyrus,	11, 24	R	1328	12	30	-20
	anterior cingulate				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.

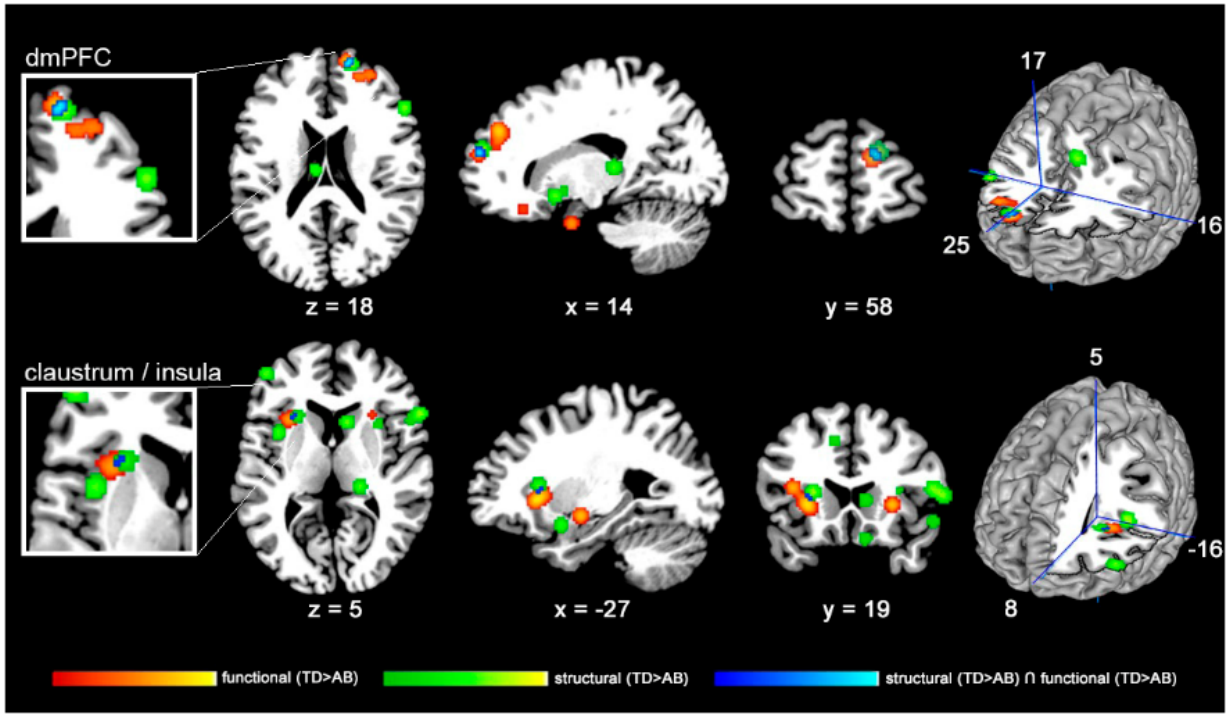

Figure 3. Structural and functional neuroimaging findings in youths with AB co-localize in right dorsomedial prefrontal cortex (dmPFC) and left insular cortex. 2-D slices displaying the thresholded and binarized ALE maps of significant overlap (p<0.05, FDR-corrected) in studies of structural (green) 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 (M. 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 criteria 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 (M. S. 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. (M. 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 (M. 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.

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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

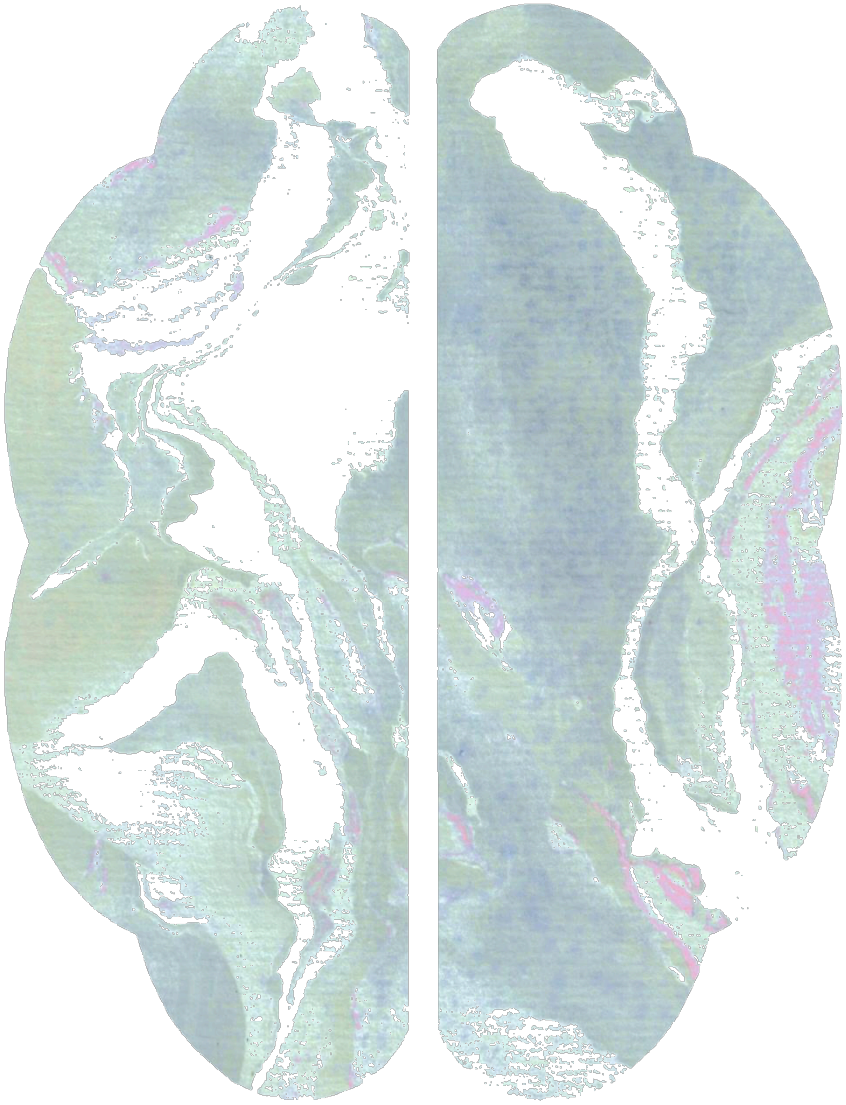
Zhang, J., Gao, J., Shi, H., Huang, B., Wang, X., Situ, W., . . . Yao, S. (2014). Sex differences of uncinate fasciculus structural connectivity in individuals with conduct disorder. *Biomed Res Int, 2014*, 673165. doi: 10.1155/2014/673165

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

Supplementary material is available in Appendix A.

3 Study 2

Investigating the neural correlates of emotion-cognition interaction using an affective Stroop task



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Abstract

The human brain has the capacity to integrate various sources of information and continuously adapts our behavior according to situational needs in order to allow a healthy functioning. Emotion-cognition interactions are a key example for such integrative processing. However, the neuronal correlates investigating the effects of emotion on cognition remain to be explored and replication studies are needed. Previous neuroimaging studies have indicated an involvement of emotion and cognition-related brain structures including parietal and prefrontal cortices and limbic brain regions. Here we employed whole brain event-related functional magnetic resonance imaging during an affective number Stroop task and aimed at replicating previous findings using an adaptation of an existing task design in 30 healthy young adults. The Stroop task is an indicator of cognitive control and enables the quantification of interference in relation to variations in cognitive load. By the use of emotional primes (negative/neutral) prior to Stroop task performance, an emotional variation is added as well. Behavioral in-scanner data showed that negative primes delayed and disrupted cognitive processing. Trials with high cognitive demand furthermore negatively influenced cognitive control mechanisms. Neuronally, the emotional primes consistently activated emotion-related brain regions (e.g., amygdala, insula, and prefrontal brain regions) while Stroop task performance lead to activations in cognition networks of the brain (prefrontal cortices, superior temporal lobe, and insula). When assessing the effect of emotion on cognition, increased cognitive demand led to decreases in neural activation in response to emotional stimuli (negative>neutral) within prefrontal cortex, amygdala, and insular cortex. Overall, these results suggest that emotional primes significantly impact cognitive performance and increasing cognitive demand leads to reduced neuronal activation in emotion-related brain regions, and therefore support previous findings investigating emotion-cognition interaction in healthy adults. Moreover, emotion and cognition seem to be tightly related to each other, as indicated by shared neural networks involved in both of these processes. Emotion processing, cognitive control, and their interaction are crucial for healthy functioning and a lack thereof is related to psychiatric disorders such as disruptive behavior disorders. Future studies may investigate the neural characteristics of children and adolescents with disruptive behavior disorders.

Introduction

An adequate handling of emotional information is a key factor for healthy functioning within our everyday life. How a person processes and regulates emotions impacts their cognition, behavior, and well-being (Dolan, 2002; Gross, 2002; John and Gross, 2004). Thereby, emotion processing not only influences cognitive control, but cognitive control may likewise affect emotions. Research has indicated that a fine balance of the emotion and cognition networks ultimately allows appropriate functioning (Hart et al., 2010). A failure to successfully process or regulate emotions is characteristic for different mental health disorders, including disruptive behavior disorders (Sterzer et al., 2005), attention-deficit/hyperactivity disorder (ADHD) (Walcott and Landau, 2004), or psychosis (Livingstone et al., 2009). Therefore, an improved understanding of the mechanism supporting successful emotion regulation skills is of utmost personal, clinical, and societal relevance (Gross, 2002).

Behavioral research studies have demonstrated that emotional stimuli can positively or negatively impact cognitive processing. For example, the presentation of emotional stimuli has shown to disrupt working memory performance (Dolcos and McCarthy, 2006) and impact reaction times during a perceptual task (Gupta and Deak, 2015). Similarly, it was demonstrated that the presence of an emotional stimulus can reduce task accuracy and reaction times during Stroop task performance, which reflects cognitive control mechanisms (Blair et al., 2007; Hart et al., 2010; Uher et al., 2014). Visually presented and/or auditory-induced emotions can also positively influence cognition, resulting in improved accuracy or shorter reaction times during tasks including conflict processing, visual attention, or decision making (Schupp et al., 2007; Kanske and Kotz, 2011; Zinchenko et al., 2015). Factors that are known to influence the interaction of cognitive and emotional processes include cognitive load, level of threat, physical stimulus properties, position of emotional distractors (left or right hemifield), individual differences, and the availability of conflict-resolving brain resources (Arnsten and Goldman-Rakic, 1998; Hartikainen et al., 2000; Pessoa, 2009; Thompson et al., 2010; Cohen and Henik, 2012; Gupta and Raymond, 2012; Kanske, 2012; Okon-Singer et al., 2013; Gupta et al., 2016). By transiently enhancing or diminishing cognitive functioning, emotional states may thus impact the control of thoughts and behavior in order to meet situational demands (Gray et al., 2002).

Neuroimaging methods, such as functional magnetic resonance imaging (fMRI), can investigate the neural networks underlying emotional and cognitive processes as well as their interaction. Brain regions responsible for simple emotion-processing tasks are the amygdala, right insula, as well as the medial and ventrolateral prefrontal cortex (Phan et al., 2002; Dolcos and McCarthy, 2006; Van Dillen et al., 2009). Thereby, the engagement of individual brain regions depends on the quality of the emotion being processed. For example fear is particularly known to elicit amygdala activation, sadness is commonly represented by subcallosal cingulate activity, and emotion processing tasks with an additional cognitive component (e.g., emotional recall) also target the insular and anterior cingulate cortex (for a review see Phan et al. (2002)). Brain regions associated with simple cognitive control (e.g. during working memory, conflict resolution, inhibition, or emotion regulation tasks) include the ventromedial, right (dorso-)lateral and orbital prefrontal cortex, lateral and right superior parietal cortex, and anterior cingulate cortex (Phan et al., 2002; Ochsner et al., 2004; Ochsner and Gross, 2005; Dolcos and McCarthy, 2006; Van Dillen et al., 2009; Pitskel et al., 2011).

To date, several fMRI studies have aimed at targeting the more complex interaction between cognition and emotion. The most commonly identified neural correlates of emotion-cognition interaction sites include parietal and prefrontal cortices, as well as limbic brain regions (i.e., cingulate, amygdala, and insula; (Gray et al., 2002; Etkin et al., 2006; Blair et al., 2007; Van Dillen et al., 2009; Hart et al., 2010; Melcher et al., 2011; Kellermann et al., 2012; Gu et al., 2013; Cromheeke and Mueller, 2014)). For example, Etkin and colleagues (2006) used an emotional conflict task and found that neural activation within the amygdala, dorsomedial-, and dorsolateral prefrontal cortex represents the level of emotional conflict, while the rostral anterior cingulate may reflect emotional conflict per se (Etkin et al., 2006). Likewise, Gu and colleagues (2013) identified shared and distinct brain regions responsible for cognitive and emotion processing or the interaction of both (Gu et al., 2013). In particular, an interaction effect was observed within in bilateral anterior insula, somatosensory cortices, and frontoparietal regions. Using an emotional working memory task, Gray and colleagues (2002) pinpointed left and right lateral prefrontal cortex as the site of emotion-cognition interaction. And finally, Blair et al. (2007) as well as Hart and colleagues (2007) combined emotional stimuli and Stroop task performance within their designs in order to elicit areas that are dynamically modulated either by increased emotional or enhanced cognitive demands. Again, bilateral amygdala, inferior frontal/ventrolateral prefrontal, and the cingulate cortex were

identified as areas of neural changes dependent on cognitive and/or emotional load (Blair et al., 2007; Hart et al., 2010).

For the present study we adapted and re-evaluated the affective number Stroop task as implemented by Hart and colleagues (2010). Our goal was the investigation of dynamic changes in either the emotion or cognition network elicited by both variations in emotional content (through the use of negative as opposed to neutral images), and changes in cognitive demand (using different conditions of a number Stroop task). A further motivation for this study was the characterization of the neural correlates representing the effect of emotions on cognition in young adults as a basis for future studies in children and adolescents with social disorders (e.g., disruptive behavior disorders). This is of particular interest since behavioral studies have already demonstrated altered emotion-cognition interactions in disruptive behavior disorders (Euler et al., 2014). Nevertheless, the neural correlates in these clinical populations are still unknown. Therefore, our aims were to: (I) elicit activation in emotion-related brain regions in response to the affective primes implemented within our task (e.g., amygdala, insula, and prefrontal cortex (Phan et al., 2002)); (II) demonstrate activation in cognitive brain regions in response to the Stroop task (e.g., prefrontal cortex, lateral and right superior parietal cortex, anterior cingulate cortex; (Laird et al., 2005)); (III) investigate previously identified brain regions that are significant in relation to the emotion-cognition interaction (e.g. amygdala, prefrontal cortex and anterior insula (Gray et al., 2002; Etkin et al., 2006; Blair et al., 2007; Hart et al., 2010; Gu et al., 2013)) and assess their involvement within the task described here. Based on strong prior behavioral evidence (Homack and Riccio, 2004), we hypothesized to observe delayed reaction times and reduced task accuracy for trials with increased cognitive load (i.e., from congruent to stars to incongruent Stroop trials), and for trials following affective (negative) primes compared to neutral primes. Neurally, we expected to replicate the above mentioned findings of changes in neural activation patterns within the emotion and/or cognition network in dependence to cognitive load (Gray et al., 2002; Etkin et al., 2006; Blair et al., 2007; Van Dillen et al., 2009; Hart et al., 2010; Melcher et al., 2011; Kellermann et al., 2012; Gu et al., 2013; Cromheeke and Mueller, 2014).

Material and Methods

Participants. Thirty healthy, German-speaking volunteers (mean age: 21.74 years; range 19-24 years; 15 males) with no prior psychological or neurological history were included in the current study. Participants took part in one testing session that included psychometric testing, one functional neuroimaging task and a T1-weighted structural image acquisition. Two participants were excluded from analysis since one of them had completely missing and the other person very low in-scanner performance (e.g., more than 20% misses in each run). All participants were further right-handed, had normal or corrected-to-normal vision, and provided written informed consent as approved by the local ethics committee (Ethikkommission der Nordwest- und Zentralschweiz).

Psychometrics. Participants included in this study completed a battery of standardized tests comprising verbal and non-verbal-IQ (German version of the Vocabulary and Matrix reasoning subtests of the WAIS-IV (Petermann, 2012), present mood (EWL (Janke, 1978)), behavioral and emotional functioning (YSR (Achenbach, 1991)), psychopathic traits (YPI (Andershed H, 2007)), and handedness (EDI (Caplan and Mendoza, 2011)). The YPI, YSR, and EWL were missing for one person. The resulting behavioral group characteristics are provided in **Table 1**.

Table 1. Behavioral group characteristics.

		mean ± SD
Age (in years)		21.73 ± 1.53
IQ (WAIS-IV)	Vocabulary	12.63 ± 3.15
	Matrix reasoning	10.83 ± 1.37
YPI	Dishonest charm	9.31 ± 2.88
	Grandiosity	8.55 ± 2.95
	Lying	7.10 ± 1.40
	Manipulation	7.76 ± 2.20
	Remorselessness	7.45 ± 2.25
	Unemotionality	10.52 ± 3.19
	Callousness	12.28 ± 1.65
	Thrill-seeking	12.31 ± 2.65
	Impulsiveness	11.14 ± 2.77
	Irresponsibility	8.28 ± 2.63
	Grandiose manipulative dimension	8.18 ± 1.84
	Callous unemotional dimension	10.08 ± 1.51
	Impulsive irresponsible dimension	10.57 ± 2.04
	Total score	9.56 ± 1.41

YSR	Withdrawn	56.66 ± 7.34
	Somatic complaints	54.55 ± 5.23
	Anxiety/depression	54.86 ± 5.15
	Social problems	53.34 ± 4.41
	Thought problems	52.76 ± 4.94
	Attention problems	55.28 ± 5.94
	Delinquent behavior	54.03 ± 5.74
	Aggressive behavior	52.14 ± 3.98
	Total score internalizing behavior	53.52 ± 8.03
	Total score externalizing behavior	50.03 ± 6.90
	Total score problem scale	52.69 ± 7.95

For WAIS-IV, standard scores are reported; for YPI, mean scores are reported; and for YSR, *t*-values are reported.

fMRI - Task procedure. The neuroimaging session included event-related functional neuroimaging during the performance of an emotional number Stroop task. Additionally, T1-weighted structural images were acquired for each participant. The emotional number Stroop task was adapted and modified based on a design described by Hart and colleagues ((2010); see trial design in **Figure 1**). We decided to use a number Stroop task as it has particularly been developed for use in the MR environment and has previously successfully been implemented in neuroimaging research studies (e.g., (Blair et al., 2007; Hart et al., 2010)). Each trial started with an emotional prime of either neutral or negative valence, presented for 150ms. Negative (Neg) or neutral (Neu) primes were first followed by an item of the number Stroop task presented for 1500ms, before a short relaxation period of 350ms ended the trial. During the number Stroop task, participants were presented with an array of 1, 2, 3, or 4 digits and were asked to indicate through button press the number of items presented. The number of items was either congruent (C) in relation to the printed digits (e.g., the digit 4 in an array of 4) or incongruent (IC) with the printed digits (e.g., digit 4 in an array of 3). Star shaped stimuli (S) were used as a control condition (no interference of digit and item number) and null trials (trials with a black screen instead of the Stroop trial) were added during the randomization process. Emotional stimuli were adapted from the Developmental Affective Photo System (DAPS; a child-appropriate picture system (Cordon et al., 2013)), which uses part of the IAPS (International Affective Picture System (Lang, 2008)) commonly used in adults. We implemented DAPS images because this task was designed to ultimately be employed in children and adolescents with psychiatric disorders. However, given that all images remained part of the IAPS system, the chosen stimuli were considered suitable for

both adult and adolescent populations. A list of the images used is provided in **Supplemental Information 1**. In combination with the negative or neutral primes, the following combinations of prime and trial condition were possible: negative-congruent (Neg_C), negative-stars (Neg_S), negative-incongruent (Neg_IC), and neutral-congruent (Neu_C), neutral-stars (Neu_S), neutral-incongruent (Neu_IC). Prior to study start, our task was behaviorally tested in adults. Pilot data assessment indicated a significant emotion by cognition interaction for reaction time and accuracy measurements (see **Supplemental Information 1.2**).

Prior to the start of the experiments, an optimal stochastic trial order allowing for a rapid event-related design was determined using optseq2, a tool for automatically scheduling events for rapid-presentation event-related fMRI experiments (for further information see http://surfer.nmr.mgh.harvard.edu/optseq/ or experiments using similar designs (Ferri et al., 2012; Kuhlmann et al., 2016)). We administered a total of 300 Stroop trials (100 for each C/S/IC) and 50 null trials. All 300 Stroop trials were preceded by either neutral or negative primes (50:50). Total scan time was about 11.5 minutes. The complete experiment was performed over the course of 2 runs. At the end of the neuroimaging session, participants were further asked to perform valence ratings of the images presented in the scanner using a Likert scale from -2 to 2 (with -2 representing very negative valence, 0 being neutral, and 2 indicating high attractiveness of the stimulus). For each participant the mean scores of the negative images affect rating were used as a covariate of no interest within the group analysis to account for differences in valence judgements between the young adults (see also **Supplemental Information 2.1 Emotional valence rating**).

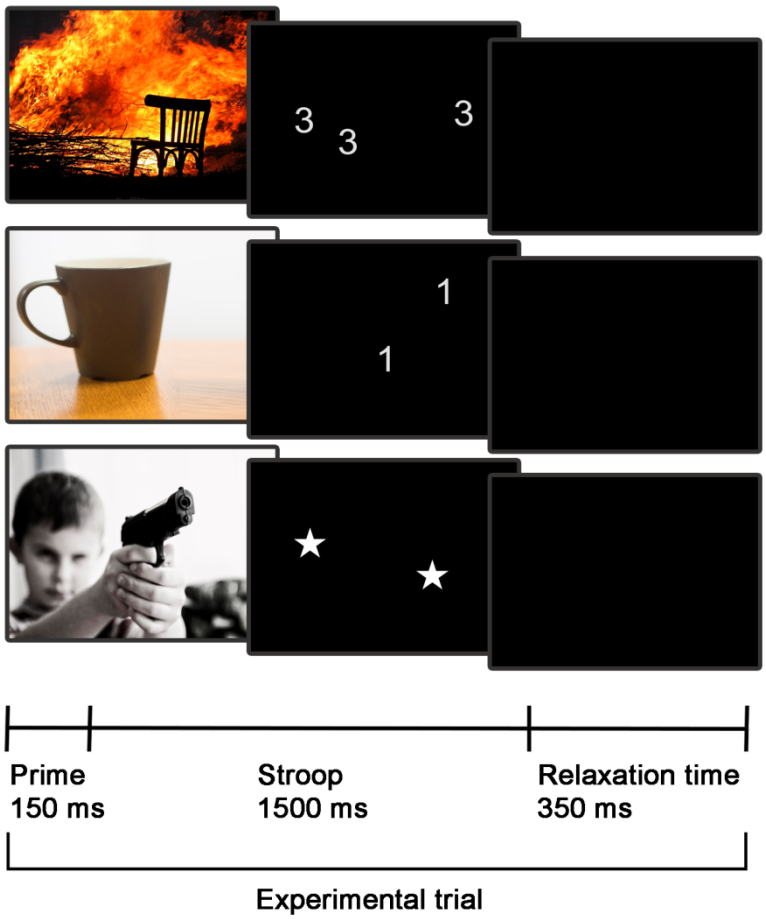

Figure 1. fMRI task design. Three exemplary emotional Stroop trials are displayed, depicting the following conditions (from top to bottom): Negative-congruent trial, neutral-incongruent trial and negative-stars trial.

fMRI - Image acquisition and analysis. Whole brain blood oxygen level-dependent (BOLD) fMRI data and T1-weighted mprage images were acquired on a Siemens 3T MR imaging system (Siemens Prisma, Erlangen, Germany) and a 20-channel phased-array radio frequency head coil. For the fMRI task a rapid event-related stochastic design with TR=2000 ms, TE=30.0 ms, FOV=192 mm; image matrix=64x 64 mm; voxel size=3 mm and number of slices=37 was used. We further acquired a high resolution T1-weighted structural image using the following specifications: TR=1900.0 ms; TE=3.42 ms; FOV=256; image matrix = 256x256; voxel size = 1 mm. T1-weighted mprage structural neuroimaging data was used for co-registration and to calculate the total intracranial volume (TIV). Men and women are known to differ in overall brain size (Leonard et al., 2008; Luders et al., 2009; Giedd et al., 2012). This was also true for the present sample where TIV significantly differed between males and females (males M=1529.52 ± 87.22 / females M=: 1360.72 ± 91.99; $t(28)=5.16$, $p<0.001$). Likewise, socioeconomic status, sex, and age all correlate with total intracranial

volume (Luders et al., 2009; Taki et al., 2011; Jednorog et al., 2012; Luders et al., 2014). This was accounted for by using a covariate of no interest in consequent random effects analyses. Therefore, TIV was extracted through the voxel-based morphometry toolbox (VBM8; http://dbm.neuro.uni-jena.de/vbm) as implemented in SPM8 and executed in MATLAB (Mathworks, Natick, MA).

All functional MRI data was analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included slice timing correction, realignment, co-registration to the structural images, segmentation of the structural image, normalization to the Montreal Neurologic Institute (MNI) standard brain, and smoothing using an 8mm full-width at half maximum Gaussian kernel. During single subject analysis, the following regressors were built: Neg_C, Neg_S, Neg_IC, Neu_C, Neu_S, Neu_IC. Contrast images were created to investigate (1) the main effect of emotion (Neg>Neu trials), (2) the main effect of cognition (IC>C or IC>S trials), and (3) the influence of emotion on cognition along with increasing cognitive demand as based on two-sample t-tests comparing Neg_C vs. Neu_C, Neg_S vs. Neu_S, and Neg_IC vs. Neu_IC trials.

Due to the challenges in capturing the intricate nature of emotion-cognition interactions, the majority of publications in this field have based their interpretation on a priori based regions of interests only. Here we present both small volume peak-level FWE-corrected findings at $p<0.05$ for the main regions of interest (i.e. amygdala, insula, and /inferior frontal junction/precentral gyrus according to previous literature (Gray et al., 2002; Etkin et al., 2006; Blair et al., 2007; Hart et al., 2010; Gu et al., 2013); defined anatomically using the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002)) and uncorrected, exploratory, whole brain findings ($p<0.001$).

Region of interest analyses. In order to further characterize the effects of cognitive load on the neural basis of emotion-cognition interactions, we further extracted mean peak activation scores as based on FWE-corrected findings from the two main contrasts targeting the emotion (Neg>Neu trials) and cognition (IC>S trials) networks of the brain. More specifically the signal change at the local peak activation scores for bilateral amygdala, right insula, and bilateral precentral gyrus were extracted using the marsbar toolbox (Matthew Brett, 2002) and further assessed using paired-samples *t*-tests.

In-scanner performance. In-scanner performance was assessed by computing the mean accuracy and reaction time in response to Neg_C, Neg_S, Neg_IC, Neu_C, Neu_S, and Neu_IC Stroop trials. For both accuracy and reaction times two separate 2 (emotion: Neg, Neu) by 3 (task: C, S, IC) repeated measures ANOVAs were performed in order to investigate the main effect of task, main effect of emotion, and the influence of emotion on task.

3. Results

In-scanner performance. The 2 (emotion: Neg, Neu) by 3 (task: C, S, IC) ANOVA on *task accuracy* (i.e., correctly answered Stroop trials) indicated a significant main effect of emotion ($F(1,29)=7.34$, $p=.011$) and a main effect of cognition ($F(2,28)=12.38$, $p<.0001$). Bonferroni corrected post hoc tests indicated that the main effect on emotion was constituted by lower accuracy following negative primes (compared to neutral primes) during Stroop task. Furthermore, significant differences in accuracy derived from the incongruent condition compared to the congruent ($p<.0001$) and stars condition ($p=.002$). However, the difference between congruent and stars conditions did not reach significance ($p=1.00$). Finally, the emotion by cognition interaction did not reach significance ($F(2,28)=.33$, $p=.722$).

The 2x3 ANOVA implementing *reaction time* revealed a main effect of emotion ($F(1,29)= 11.93$, $p=.002$) and a main effect of cognition ($F(2,28)= 80.27$, $p<.001$). Bonferroni corrected post hoc tests revealed significant reaction time differences for incongruent compared to congruent ($p<.0001$), congruent compared to stars ($p=.019$), and incongruent compared to stars ($p<.0001$) conditions. The emotion by cognition interaction did not reach significance ($F(2,28)= .54$, $p=.590$). An overview of the in-scanner performance as based on the mean accuracy and reaction time for the whole group is given in **Table 2**.

Table 2. In-scanner performance (accuracy, reaction times).

		Congruent [±SD]	**Stars [±SD]**	**Incongruent [±SD]**
Accuracy [raw scores]	Negative prime	49.2 [1.5]	49.3 [1.0]	47.7 [3.1]
	Neutral prime	49.7 [1.1]	49.6 [0.9]	48.3 [2.4]
Reaction Times [ms]	Negative prime	720.5 [72.6]	731.0 [84.3]	800.0 [88.9]
	Neutral prime	704.5 [66.0]	718.6 [73.4]	791.9 [90.3]

***fMRI results*.** The fMRI result part is organized in line with our a priori listed main aims: (**1**) testing the activation of the emotion network by use of the negative prime (Neg>Neu trials); (**2**) assessing the activation of the cognition network by comparing an incongruent to a neutral Stroop condition (IC>S); (**3**) evaluating the emotion-cognition interaction dependent on increased cognitive load (Neg_C vs. Neu_C, Neg_S vs. Neu_S, and Neg_IC vs. Neu_IC trials). First, testing the (**1**) emotion processing network revealed that trials with a preceding negative prime compared to those with a preceding neutral prime led to significant increases in activation in known emotion processing areas of the brain (Phan et al., 2002), including insula, amygdala, and prefrontal cortices (for an overview of activated areas see **Table 3, Figure 2**). Secondly, testing the (**2**) cognition network by use of the Stroop task (IC>S) revealed activations in areas including left precentral gyrus (FWE-corrected) and uncorrected within further areas including the superior frontal brain regions, temporal cortex, and insula (**Table 3, Figure 2**).

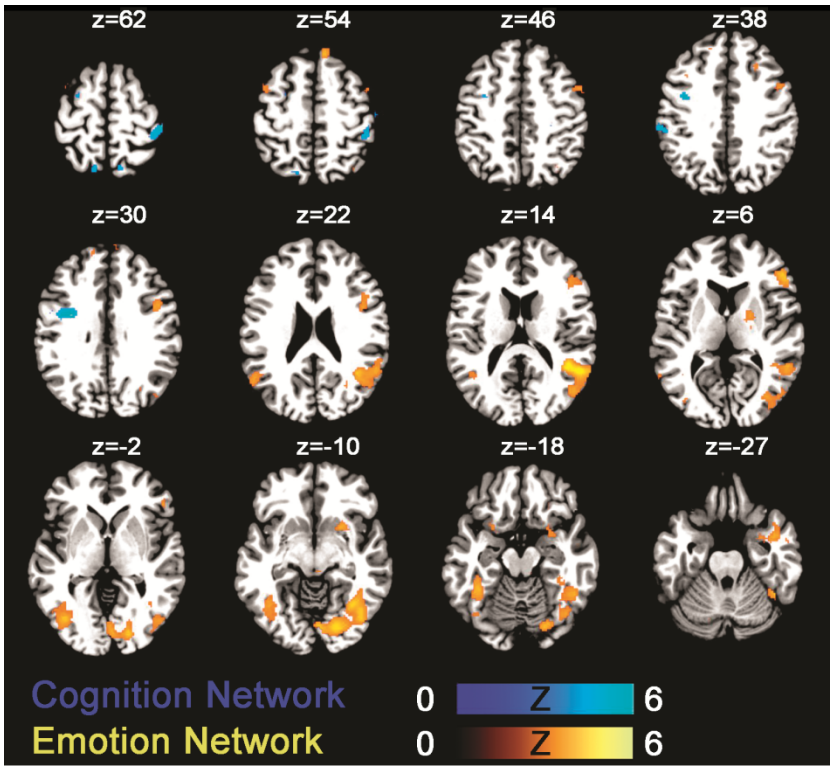

Figure 2. Statistical parametric maps showing brain activation linked to the emotion network (green-blue; negative>neutral trials) and the cognition network (gold-yellow; incongruent>congruent). Results are displayed at a $p<0.001$, uncorrected threshold and neurologically displayed on axial slices using the Multi-image Analysis GUI as available at http://ric.uthscsa.edu/mango/mango.html.

Table 3. MNI coordinates, cluster size and Z-scores for significant FWE small-volume corrected results and uncorrected ($p<0.001$; indicated with an asterix*) whole brain findings representing the emotion processing network (negative trials > neutral trials) and the cognition network (incongruent > stars trials) elicited by the given task.

Brain Region	**Hem**	**k**	**Z_0**	**MNI coordinates [mm]**		
				x	**y**	**z**
Emotion Network (Neg>NeuTrials)						
precentral	**R**	**187**	**3.84**	**46**	**6**	**30**
insula	**R**	**29**	**4.67**	**26**	**8**	**-14**
amygdala	**R**	**19**	**3.65**	**30**	**0**	**-26**
amygdala	**L**	**1**	**3.16**	**-22**	**6**	**-18**
*occipital, temporal lobe, including calcarine, fusiform, lingual, angular gyrus	R/L	3241	5.04	44	-48	12
*inferior/middle temporal/occipital lobe, including fusiform gyrus	L	793	4.35	-38	-46	-16
*inferior orbitofrontal lobe, including precentral gyrus	R	662	4.59	52	32	4

*cerebellum	L	249	4.05	-12	-80	-40
*middle temporal, superior marginal, angular gyrus	L	186	3.8	-52	-60	20
*superior frontal lobe	R	73	4.15	10	38	54
*cerebellum	L	72	3.93	-10	-50	-48
*putamen, pallidum	R	68	3.89	20	-4	8
*middle frontal lobe, precentral gyrus	L	58	3.55	-44	6	56
*angular gyrus, superior parietal lobe	R	58	3.33	34	-64	50
*middle temporal lobe	R	39	3.63	58	-2	-24
*superior temporal pole, insula, olfactory, inferior/superior orbitofrontal	L	29	3.46	-24	10	-18
*middle/superior occipital lobe	R	28	3.48	28	-66	24
*superior medial frontal lobe	R	18	3.25	8	60	30
*middle frontal gyrus	R	15	3.57	26	26	40
*inferior/middle temporal lobe	L	13	3.28	-44	-8	-22
*inferior frontal, pars opercularis, middle frontal lobe	L	12	3.61	-36	18	36
*superior frontal lobe	L	10	3.32	-12	54	30
*superior frontal lobe	L	9	3.38	-16	42	36
*middle temporal gyrus	L	9	3.21	-60	-56	6
*cerebellum	R	7	3.31	10	-32	-22
*middle occipital lobe	R	7	3.18	42	-74	32
*superior medial frontal, superior motor area	L	5	3.32	-4	28	66
*caudate	L	3	3.14	-8	10	8
*middle temporal pole	L	2	3.16	-40	16	-34
*middle temporal pole	L	1	3.25	-38	14	-30
*middle occipital lobe	L	1	3.14	-36	-66	16
*superior temporal pole	L	1	3.12	-36	12	-28
*thalamus	R	1	3.11	10	-6	0
Cognition Network (IC>S)						
precentral	**L**	**87**	**4.03**	**-36**	**-2**	**34**
*caudate	R	120	3.89	-4	10	16
*paracentral lobule, supplementary motor area	R/L	96	3.7	-6	-30	64
*superior temporal lobe	R	79	3.86	56	-30	14
*superior temporal lobe, heschl's gyrus, insula, rolandic operculum	R	48	3.98	46	-18	6
*superior temporal lobe	L	27	3.41	-58	-16	4
*postcentral gyrus	R	20	3.58	52	-20	60
*insula, rolandic operculum	L	15	3.8	-42	-10	18
*putamen	L	15	3.51	-24	-6	18
*superior frontal lobe	R	4	3.31	14	42	30

*thalamus	L	2	3.2	-16	-22	16
*superior temporal lobe	R	1	3.19	52	-26	10

Results reported at small-volume FWE correction of $p<0.05$
* additional uncorrected whole brain clusters at $p<0.001$
Hem=Hemisphere; k= cluster size; Neg= negative; Neu=neutral; C=congruent condition; IC=incongruent condition; S=stars condition

Both control conditions (IC>S and IC>S) were contrasted with the IC condition. However, we decided to focus on IC>S trials for definition of the cognition network since more prefrontal activation was evoked, potentially due to different effects of the primes on congruent as opposed to stars trials. This procedure is in line with similar previous fMRI Stroop publications (for a review see (Laird et al., 2005)). Finally, (**3**) the influence of emotion on cognitive control was measured by contrasting Stroop trials with a prior negative prime to those Stroop trials following a neutral trial. Two-sample t-tests for negative vs. neutral trials were calculated for Stroop trials with increasing cognitive load (from congruent, to stars, and incongruent condition) and revealed differential activations for each of the three contrasts reflecting the influence of emotion on cognitive task performance as modulated by differential cognitive load. More specifically, for the contrast 'Neg>Neu trials' during the congruent Stroop task condition, significant increases in activations were identified in bilateral amygdala, right insula, and right precentral gyrus (FWE-corrected) and on a whole-brain uncorrected level within further regions of the occipital, temporal, and inferior/middle frontal gyrus. For the opposite contrast 'Neg<Neu trials' during the congruent Stroop trial, FWE-corrected activation within left precentral gyrus was observed. For the contrast 'Neg>Neu trials' during the stars Stroop task condition, significant FWE-corrected findings were identified in right amygdala, while further cluster of activations were located within bilateral inferior occipital cortex (uncorrected whole brain approach). For the opposite contrast 'Neg<Neu trials' significant activation was located within right precentral gyrus (FWE-corrected) and using a whole brain approach further clusters were located within occipital and superior frontal brain regions, left precuneus of the superior parietal lobe. Finally, for the contrast 'Neg>Neu trials' during the incongruent Stroop task condition significant clusters of activations were based in inferior frontal and middle frontal brain regions (uncorrected findings only), while the opposite contrast of 'Neg<Neu trials' during the incongruent Stroop task condition led to activity within left insula (FWE-corrected) as well as in further occipital

brain regions, left pre- and postcentral gyrus, when using an uncorrected whole-brain approach (**Table 4, Figure 3**).

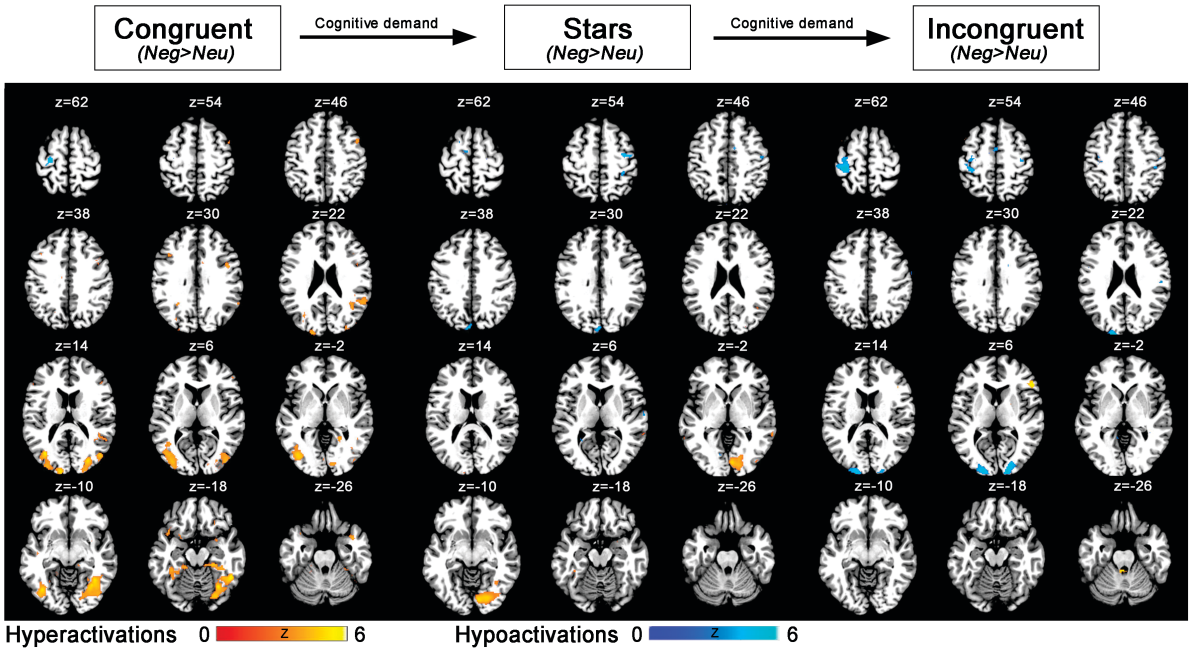

Figure 3. Statistical parametric maps showing emotion-cognition interaction related brain activation (blue: hypoactivations; red: hyperactivations) for negative>neutral emotional primes and the conditions congruent, stars, incongruent (ordered by lowest to highest cognitive load). Results are displayed at a $p<0.001$, uncorrected threshold and neurologically displayed on axial slices using the Multi-image Analysis GUI as available at http://ric.uthscsa.edu/mango/mango.html.

Table 4. MNI coordinates, cluster size and Z-scores for significant FWE small-volume corrected results and uncorrected (p<0.001; indicated with an asterix*) whole-brain findings representing the influence of emotion on cognitive processes dependent on cognitive load (i.e. congruent, stars and incongruent trials).

Brain Region	**Hem**	**k**	**Z_0**	**MNI coordinates [mm]**		
				x	**y**	**z**
Congruent (NegC>NeuC)						
precentral	**R**	**64**	**3.79**	**46**	**0**	**32**
insula	**R**	**7**	**3.65**	**30**	**8**	**-16**
amygdala	**R**	**6**	**3.39**	**28**	**2**	**-16**
amygdala	**L**	**2**	**3.33**	**-22**	**6**	**-18**
*occipitotemporal including fusiform, calcarine, lingual gyrus, cuneus, cerebellum	R	2037	4.88	32	-66	-14
*temporal/occipital lobe, including fusiform gyrus, cuneus	L	1470	4.64	-34	-72	14
*middle/superior temporal lobe, angular gyrus	R	361	4.24	44	-42	18
*inferior temporal lobe, cerebellum, fusiform, parahippocampal gyrus	L	303	3.95	-34	-52	-14
*cerebellum, fusiform, lingual, parahippocampal gyrus	R	222	4.39	22	-34	-20
*inferior/middle frontal lobe, including pars triangularis and opercularis	L	54	3.57	-40	18	32
*superior temporal pole, inferior orbitofrontal lobe	L	51	3.77	-42	16	-16
*amygdala	R	47	4	30	6	-14
*lingual, parahippocampal gyrus	R	46	4.01	22	-50	-4
*cerebellum	L	44	3.75	-10	-54	-50
*superior temporal pole	R	30	3.82	40	6	-26
*lingual gyrus	L	28	3.43	-16	-52	-6
*inferior/superior orbitofrontal lobe	R	24	4.29	22	30	-16
*middle cingulum	R	19	3.64	10	6	34
*superior temporal pole, superior orbitofrontal lobe, insula	L	14	3.36	-26	12	-18
*inferior frontal lobe, including pars triangularis	R	14	3.26	46	30	16
*middle/superior temporal pole, inferior orbitofrontal lobe	L	12	3.53	-34	14	-24
*inferior frontal lobe, including pars triangularis	R	12	3.35	40	24	18
*middle temporal lobe	R	11	3.37	48	-50	0
*middle/superior occipital lobe	L	10	3.29	-24	-92	32

*cerebellum	R	9	3.32	32	-46	-44
*inferior frontal gyrus, including pars opercularis	L	5	3.44	-36	6	24
*middle/superior temporal lobe	L	5	3.27	-46	-16	-8
*inferior/superior parietal lobe	L	5	3.22	-28	-54	48
*inferior frontal lobe, including pars triangularis	R	5	3.19	54	38	6
*middle cingulum	L	4	3.35	-10	-14	40
*middle/superior occipital lobe	R	4	3.22	28	-72	36
*inferior frontal lobe, including pars triangularis	L	4	3.17	-52	30	16
*middle/superior occipital lobe	R	4	3.16	30	-72	26
*cerebelum	R	4	3.13	40	-58	-32
*supplementary motor area	R	2	3.3	10	8	72
*lingual gyrus	L	2	3.16	-2	-80	-2
*superior occipital lobe	L	1	3.14	-20	-66	38
*angular gyrus	R	1	3.09	30	-60	52
Congruent (NegC<NeuC)						
precentral	**L**	**100**	**4.21**	**-26**	**-20**	**60**
Stars (NegS>NeuS)						
amygdala	**R**	**1**	**3.66**	**26**	**2**	**-18**
*inferior occipitotemporal, including lingual, fusiform, calcarine, cerebellum	R/L	862	5.27	8	-84	-6
*inferior temporal lobe, including fusiform gyrus	L	52	3.56	-40	-42	-16
*middle temporal lobe	R	50	4.11	66	-42	2
*inferior temporal lobe, including fusiform gyrus	R	41	3.7	36	-58	-10
*middle temporal lobe	R	40	4.01	56	0	-22
*gyrus rectus, amygdala	R	19	3.65	20	10	-16
*cerebellum	L	14	3.38	-14	-70	-30
*inferior occipital lobe	R	8	3.3	42	-82	-4
*middle temporal, lobe including angular gyrus	R	8	3.21	44	-60	20
*middle/superior temporal pole	L	7	3.32	-38	12	-28
*middle temporal lobe	L	5	3.3	-64	-50	0
*superior occipital lobe	L	5	3.19	-12	-100	12
*cerebelum	R	4	3.24	34	-66	-50
*fusiform gyrus	R	3	3.24	42	-44	-14
*superior occipital lobe	R	3	3.14	26	-84	24
*angular gyrus	R	2	3.16	40	-72	50
*cerebellum	R	2	3.15	12	-32	-20

*putamen	R	1	3.2	26	14	-6
*inferior occipital lobe	L	1	3.16	-40	-72	-6
*angular gyrus	R	1	3.16	44	-70	50
*anterior cingulate	R	1	3.15	14	40	16
*inferior occipital lobe	L	1	3.12	-42	-68	-6
*middle orbitofrontal lobe	R	1	3.14	26	38	-12
*thalamus	L	1	3.1	-6	-14	2
*superior temporal pole	R	1	3.1	40	4	-24
Stars (NegS<NeuS)						
precentral	**R**	**53**	**4.12**	**34**	**-12**	**56**
*superior occipital lobe, including cuneus, precuneus	L	127	4.58	-6	-92	36
*inferior parietal lobe, postcentral gyrus	R	31	3.61	32	-42	52
*supplementary motor area	L	24	3.42	-10	-8	64
*precuneus	L	16	3.63	-26	-52	4
*middle cingulum, supplementary motor area	R	14	3.66	10	-2	44
*lingual gyrus	L	14	3.22	-10	-72	-4
*superior parietal lobe, postcentral gyrus	R	12	3.23	14	-54	66
*superior temporal lobe	R	11	3.33	66	-14	6
*superior parietal lobe	R	6	3.24	24	-54	64
*precentral gyrus	R	2	3.34	22	-18	62
*superior frontal lobe	L	2	3.16	-18	6	62
Incongruent (NegIC>NeuIC)						
*inferior frontal lobe, including pars triangularis	R	108	3.94	54	30	4
*cerebellum, vermis	R/L	32	3.72	-2	-40	-28
*middle frontal lobe	L	20	3.56	-40	10	60
*pallidum, putamen	R	5	3.4	24	0	4
*superior/medial frontal lobe	L	3	3.17	-6	36	58
*caudate	L	1	3.11	-6	8	12
*cerebellum	L	1	3.1	-10	-72	-36
Incongruent (NegIC<NeuIC)						
insula	**L**	**14**	**3.67**	**-36**	**-2**	**10**
*postcentral, precentral gyrus	L	614	4.35	-34	-32	62
*middle/superior occipital lobe, including cuneus	L	426	4.24	-18	-98	20
*middle/superior occipital lobe, including cuneus, calcarine gyrus	R	239	4.55	16	-100	8
*postcentral, precentral gyurs	R	25	3.56	38	-22	52
*supramarginal gyrus, postcentral	R	23	3.39	44	-30	48
*supplementary motor area	R/L	22	3.29	-2	-4	54

*postcentral, precentral gyrus	R	14	3.41	52	-18	42
*supramarginal gyrus, rolandic operculum	R	10	3.3	54	-22	22
*cerebellum, lingual gyrus	L	9	3.32	-10	-50	-2
*postcentral gyrus	R	9	3.24	64	-6	38
*precentral gyrus	L	9	3.18	-22	-14	72
*superior occipital lobe, including cuneus	L	6	3.45	-8	-88	42
*precentral gyrus	R	5	3.27	30	-16	70
*supplementary motor area	L	4	3.33	-12	-14	50
*precuneus	L	3	3.17	-12	-42	4
*precentral gyrus	L	2	3.28	-52	0	24
*postcentral gyrus	R	2	3.13	62	0	32
*precentral gyrus	R	1	3.13	26	-28	76
*precentral gyrus	R	1	3.12	64	2	28
*lingual gyrus	L	1	3.11	-6	-56	0
*postcentral gyrus	R	1	3.1	26	-46	64
*supplementary motor area	L	1	3.1	-10	-10	54

Results reported at small-volume FWE correction of $p<0.05$
* additional uncorrected whole brain clusters at $p<0.001$
Hem=Hemisphere; k= cluster size; Neg= negative; Neu=neutral; C=congruent condition; IC=incongruent condition; S=stars condition

Region of interest analyses

Results. Further investigations on the influence of emotion on cognition within peak regions of interests as based on FWE-corrected peak regions derived from the here identified emotion- (Neg>Neu trials) and cognition (IC>S) network revealed a significant trend within left amygdala, right insula and right precentral gyrus to show decreases of neural activation along for emotional primes with increasing cognitive demand. More specifically paired two samples t-tests indicated significant decreases of neural activation for (Neg>Neu) from congruent to incongruent condition within left amygdala, right insula and right precentral gyrus (all $p<0.05$). For the right insula the comparison between stars and incongruent condition likewise became significant (**see Figure 4**; additional graphics for the remaining regions that did not reach significance see **Supplemental Information 3**).

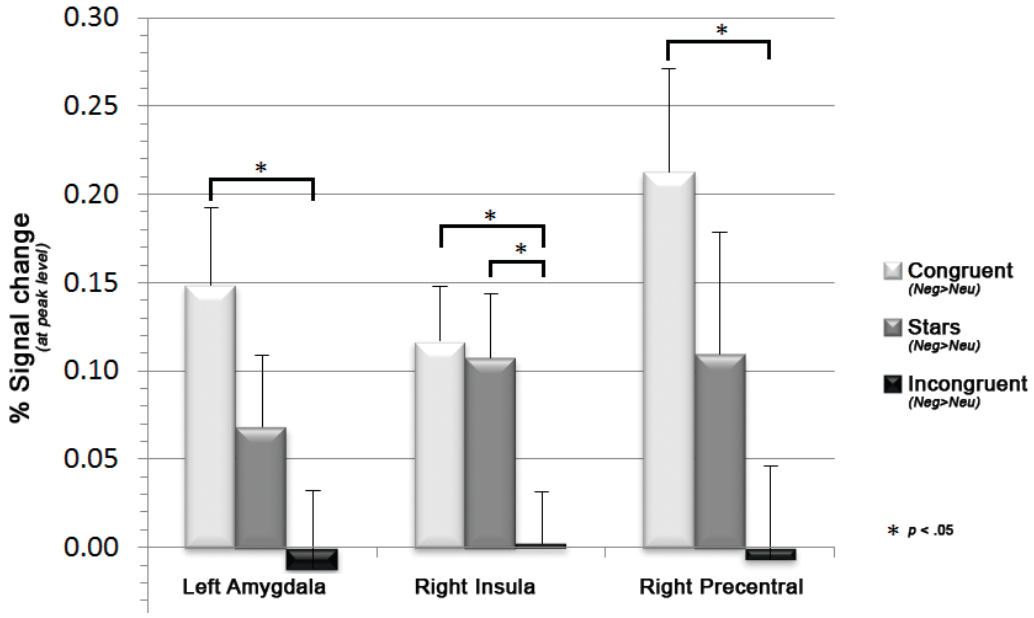

Figure 4. Bar graphs displaying decreases in the mean parameter estimates in left precentral gyrus and right amygdala along with increasing cognitive demand (i.e. for congruent, stars and incongruent Stroop trials), as well as the associated sagittal brain slices including the statistical parametric maps (blue: hypoactivations; red: hyperactivations). Results are displayed at a $p<0.001$, uncorrected threshold and neurologically displayed on axial slices using the Multi-image Analysis GUI as available at http://ric.uthscsa.edu/mango/mango.html.

4. Discussion

In this study we investigated the influence of emotions on cognition in each corresponding network through the use of negative or neutral primes prior to a number Stroop task with increasing levels of cognitive demand. Our main behavioral findings demonstrated increased reaction time and reduced Stroop-task accuracy following negative primes and/or increasing cognitive demand. Neurally, the emotional primes consistently activated emotion-related brain regions (including amygdala, insula, and prefrontal brain regions) while the Stroop effect was associated with activations in areas linked to cognitive processing (including left inferior frontal junction/precentral gyrus, inferior/superior parietal lobe, and insula). And finally, the neural correlates representing the influence of emotion on cognition implementing variations in cognitive demand lead to decreases in neural activation in response to emotional stimuli (negative>neutral) along with increased cognitive demand within prefrontal cortex, amygdala, and insular cortex. Additionally, in trials with no preceding emotional prime (neutral>negative), significant increases along with increasing cognitive demand where observed. Overall we conclude that neural activation during a number Stroop task

performance is increasingly disrupted by preceding negative images along with increasing cognitive demand.

Behavioral effects following emotional primes and Stroop trials with different cognitive load

In line with previous work, negative compared to neutral primes prior to a Stroop task affected task performance, which resulted in decreased task accuracy and increased reaction times (Blair et al., 2007, Mitchell et al., 2006, Gray et al., 2002, Padmala et al., 2011). Furthermore, more incorrect answers were given during incongruent trials compared to congruent (Etkin et al, 2006) or stars trials, while the latter two showed similar accuracy measurements. Participants were fastest in responding to congruent trials, followed by stars trials and eventually incongruent trials, which reflects the so-called Stroop effect (Stroop, J.R., 1935, Hart et al., 2010; Blair et al., 2007). We propose that in this study reading the number was a more automatized/faster process compared to counting the actual stimuli, thus resulting in shorter reaction times for congruent compared to stars trials. Interestingly, congruent and stars trials had equivalent numbers of correctly answered trials, although participants responded faster to congruent than to stars trials. We therefore conclude that the behavioral advantage of the congruent condition only affected reaction time (increased speed), but not accuracy. However, behavioral analysis failed to observe an interaction effect between emotional priming and task difficulty in accuracy and reaction times. In line with the dual competition model by Pessoa (2009) and supported by previous studies (Hart et al., 2010, Melcher et al., 2011, Padmala et al., 2011) the interference of negative primes on task performance was expected to augment with higher cognitive task load due to competing mechanisms. However, in line with previous evidence (e.g., Blair and colleagues (2007); van Dillen and colleagues (2009)), we did not observe a significant interaction effect in the present analysis.

Neural basis of emotion-cognition interaction

Here we demonstrate that the influence of emotion on cognition is neurally reflected within brain regions including prefrontal cortex, amygdala and insular cortex. Furthermore, activation in these brain regions shows an attenuating trend when increasing cognitive demand. Likewise, neural activation in the left inferior frontal junction/precentral gyrus, as indicative of cognitive control, is increased during neutral prime trials compared to trials following a negative prime. Prefrontal brain regions, amygdala, and insula have all

consistently been identified as relevant for emotion-cognition interactions or emotional conflict resolution (Gray et al., 2002; Beer et al., 2006; Etkin et al., 2006; Blair et al., 2007; Hart et al., 2010; Gu et al., 2013; Buhle et al., 2014). Likewise, similar areas are activated during tasks requiring cognitive reappraisal (an emotion regulation strategy in which the stimulus meaning is reinterpreted to downregulate the emotional valence; (Ochsner et al., 2002; Ochsner et al., 2004; Ochsner and Gross, 2005)). Thus, we suggest that the here presented emotional number Stroop task activates similar areas within the neural network that are required for deliberate cognitive reappraisal.

The prefrontal cortex can functionally and cytoarchitectonically be subdivided into distinct sub-regions, several of which are of relevance to affective processing, cognition, or both (Pessoa, 2008). Overall, prefrontal brain regions are commonly linked to attention, working memory, goal-directed behavior (e.g., cognitive control or decision making (Pessoa, 2008; Stokes et al., 2013; Leech and Sharp, 2014), and affective processing (Phan et al., 2002). From an evolutionary perspective, early research has suggested that the evolution of the human prefrontal cortex, particularly its expansion in volume, may reflect the development of more complex social behavior (Dunbar and Shultz, 2007). While such an interpretation may be too simplistic, still researchers commonly agree that the distinct parts of the prefrontal cortex are recruited by different high-level cognitive demands (Eickhoff et al., 2016). Based on animal and human studies, a functional and cytoarchitectonical subdivision of the medial prefrontal cortex may at least result in areas including the orbitofrontal cortex (BA11), ventral prefrontal cortex and prefrontal pole (BA10), and dorsomedial prefrontal cortex and frontal pole (BA9) (Eickhoff et al., 2016). All of these areas are strongly interconnected and associated with various other circuitries of the brain, including the limbic network (Reid et al., 2016). Finally, particularly the right inferior frontal gyrus has been suggested to be a crucial hub during inhibitory processing and may consequently be an area affected in response control disorders (Aron et al., 2014).

Emotion processing is generally assigned to medial prefrontal brain regions, whereas the amygdala, anterior cingulate cortex, or insula are thought to possess a more distinct function within emotional tasks (Phan et al., 2002). The amygdala is one of the most traditionally viewed emotion and motivation processing center. With its relatively small structure, the amygdala nevertheless comprises a multitude of anatomical connections allowing many intricate functionalities (Janak and Tye, 2015). While abundant research has linked the

amygdala to affective processing and particularly fear conditioning, strong evidence points towards a more integral role of the amygdala as a key node for valence processing during different aversive states, including fear, anxiety, or reward processing (Murray et al., 2014; Janak and Tye, 2015). Here we demonstrated that the amount of amygdala activation obtained during emotion-cognition interaction was highest during Stroop trials with lowest cognitive demand and decreases with increasing task difficulty. This finding is in line with Etkin (2006) as well as Blair and colleagues (2007) that found decreases in neural activation within the amygdala during concurrent task with increasing cognitive demand. In line with previous suggestions (Etkin et al., 2006), it could be concluded that amygdala activation mirrors the amount of emotional conflict, rather than the resolution of such. Importantly the amygdala is strongly interconnected with areas of the prefrontal/orbitofrontal cortex (Davidson et al., 2000). This bi-directional connection allows regulatory processes important for mental well-being. For example, early deprivation or life stress may lead to disruption in amygdala-prefrontal coupling and patients with symptoms including anxiety, posttraumatic stress disorder, or heightened aggression oftentimes show structural and functional impairments within these circuitries (Gee et al., 2013).

The present task closely resembles two prior fMRI study designs (Blair et al., 2007; Hart et al., 2010). With the exception of adaptations that account for the age of the participants being tested (i.e., use of only negative stimuli and age-appropriate images), it may be considered a replication study. The present manuscript used an adapted version of an affective number Stroop task as implemented by Hart and colleagues (2010) and resulted in comparable findings. Reproducibility of scientific studies is crucial in order to inform about the robustness of an observed phenomenon (Martin and Clarke, 2017). Comparing our findings more closely to these two prior studies confirm the following main findings: (1.) In line with both studies, negative primes slowed the participants' reaction time during the number Stroop task and are thus confirmed to interrupt goal-directed processing; (2.) In line with Blair and colleagues (2007) increasing cognitive demand led to decreases in emotion-related brain regions (e.g. amygdala, insula, prefrontal cortex). Hart and colleagues observed the same trend (2010), however, no neural decreases in dorsolateral prefrontal areas during incongruent trials. Therefore, the authors concluded that high cognitive demand may override the attenuation effect in the prefrontal cortex. In contrast to Hart et al. (2010), we only observed decreases in neural activation with increasing cognitive demand. It remains to be investigated whether such a difference may be due to the number and characteristics of participants tested (N=14;

5males in (Hart et al., 2010)/N=30; 15 males in the present study) or are potentially due to the difference in stimuli choice and/or slightly longer presentation (an additional 500ms) of the Stroop trial in our study. It is important to note that the slightly longer Stroop presentation rate was chosen due to the aim of consequently applying this task in younger participants.

The insula is a functionally heterogeneous brain region which is situated in the depth of the Sylvian fissure and may be divided into three sections: a dorsal anterior, a ventral anterior, and a posterior part (Nieuwenhuys, 2012; Uddin et al., 2014). The anterior insular cortex is, mostly bilaterally, connected to limbic and prefrontal brain regions (e.g. the amygdala), while the posterior part is more strongly interconnected with parietal, occipital and temporal parts of the brain (Kurth et al., 2010; Nieuwenhuys, 2012). The insula has shown to be activated during a wide range of functions, including auditory processing, vestibular and somatosensory functions, the perception of pain and temperature, viscerosensation, taste, olfactory processing, somatomotor control and motor plasticity, speech production, cognitive control, bodily awareness, as well as emotion processing (Nieuwenhuys, 2012). Importantly, according to research the anterior insula has a critical role during the regulation of social behavior, since its structure and function is altered in individuals with social disorders (including disruptive behavior disorder (Sterzer et al., 2007; Raschle et al., 2015)). Here our results are in line with findings assigning a critical role for the insula in emotion-cognition interactions (Hart et al., 2010; Shackman et al., 2011; Gu et al., 2013).

Emotion-cognition integration in psychiatric disorders

An intact integration and healthy balance of competing emotion-cognition processing is crucial for our everyday functioning and an imbalance, as for example observed in individuals with emotion processing deficits, is linked to different mental health disorders (Monk, 2008). For example, faulty integration or regulation of emotion-cognition processes may result in heightened violence and aggression (Davidson et al., 2000). Therefore it has been suggested that individuals with heightened aggression traits, as for example observed in children and adolescents with disruptive behavior disorders, may show impairments in these prefrontal circuitries responsible for successful emotion-cognition interaction and regulation. In fact, various structural and functional neuroimaging studies pinpoint areas of the limbic and prefrontal network to be disrupted in aggressive individuals (Raschle et al., 2015; Rogers and De Brito, 2016). Consequently, we conclude that future studies may implement the here

presented design in order to further characterize aggressive youths and potentially impact individualized classification and treatment approaches in health and disease.

Limitations

A potential caveat in the design of this study concerns the valence of the primes used. While we employed negative and neutral images only, positive primes have also been shown to disrupt task performance (Mitchell et al., 2006; Blair et al., 2007). Therefore, the addition of positive images should be considered in future studies aiming at characterizing the emotion-cognition interaction. However, due to practical challenges when conducting pediatric neuroimaging studies (particularly time constraints; for a discussion see for example (Raschle et al., 2009)) we decided that it is of importance to keep the task as short as possible and gain maximum power for the emotional condition chosen. Additionally, since the processing of negative affect is a particular problem in disruptive behavior disorders, a focus on this emotion made most sense. Secondly, we here used DAPS images as primes. This system was developed as an adaptation of the International Affective Picture System (IAPS, (Lang, 2008)) in order to be suitable for children and adolescents. The DAPS includes images from the IAPS series as well as additional stimulus material. We here only used images that were part of the IAPS and DAPS system, which can thus be considered suitable for evoking negative affect in both populations. However, IAPS images with the strongest negative affect were excluded within this process. Therefore, the images implemented here may have had a reduced impact on the young adults performing our task. Our decision to employ a child-friendly image system is due to our aim of testing our task for future use in clinical populations involving children and adolescents with disruptive behavior disorders. While effects of negative priming were observable in the young adults sample investigated here, we believe the same images may lead to stronger behavioral and neural effects in younger participants as investigated in the future. Finally, while we implemented an automatic stochastic schedule for optimal event presentation and null trials for jittering, the inter-trial intervals may gain from additional variance (i.e., variations in inter-trial intervals around for example 500-1500 ms).

Conclusion

Converging evidence points towards the importance of a balanced handling of both emotional and cognitive information in our everyday life. Here we present data that validates the usefulness of the emotional number Stroop task in fMRI settings aiming to assess the neural

correlates of the influence of emotion on cognition. More specifically, we show an impact in behavior and the associated neural networks depending on emotional prime and cognitive demand. The respective influence of the emotion and cognition network in the brain may therefore be seen as a dynamic process which is modulated by the executive resources available. Moreover, emotion and cognition seem to be tightly related to each other, as indicated by shared neural networks involved in both of these processes. A failure to successfully integrate emotional and cognitive demands is characteristic to many psychiatric disorders. Future studies may thus further investigate the neural characteristics of children and adolescents that fail to successfully process emotional/cognitive demand, as for example seen in disruptive behavior disorders.

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Author contributions

Conception and design of the experiments: CS, PS, NR, FE, WM. Data collection: LF, WM, NR. Data analysis and interpretation: NR, CS, PS, LF, WM. Drafting the paper: NR, CS, LF, WM. Revision and final approval of the version to be published: NR, CS, PS, LF, WM, FE.

References

Achenbach, T.M. (1991). Manual for the Youth Self-Report and 1991 Profile. Burlington, VT: University of Vermont Department of Psychiatry.

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

Arnsten, A.F., and Goldman-Rakic, P.S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry 55(4), 362-368.

Aron, A.R., Robbins, T.W., and Poldrack, R.A. (2014). Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci 18(4), 177-185. doi: 10.1016/j.tics.2013.12.003.

Beer, J.S., John, O.P., Scabini, D., and 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.

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

Buhle, J.T., Silvers, J.A., Wager, T.D., Lopez, R., Onyemekwu, C., Kober, H., et al. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb Cortex 24(11), 2981-2990. doi: 10.1093/cercor/bht154.

Caplan, B., and Mendoza, J.E. (2011). "Edinburgh handedness inventory," in Encyclopedia of Clinical Neuropsychology. Springer), 928-928.

Cohen, N., and Henik, A. (2012). Do irrelevant emotional stimuli impair or improve executive control? Front Integr Neurosci 6, 33. doi: 10.3389/fnint.2012.00033.

Cordon, I.M., Melinder, A.M., Goodman, G.S., and Edelstein, R.S. (2013). Children's and adults' memory for emotional pictures: examining age-related patterns using the Developmental Affective Photo System. J Exp Child Psychol 114(2), 339-356. doi: 10.1016/j.jecp.2012.08.004.

Cromheeke, S., and Mueller, S.C. (2014). Probing emotional influences on cognitive control: an ALE meta-analysis of cognition emotion interactions. Brain Struct Funct 219(3), 995-1008. doi: 10.1007/s00429-013-0549-z.

Davidson, R.J., Putnam, K.M., and Larson, C.L. (2000). Dysfunction in the neural circuitry of emotion regulation - A possible prelude to violence. Science 289(5479), 591-594. doi: DOI 10.1126/science.289.5479.591.

Dolan, R.J. (2002). Emotion, cognition, and behavior. Science 298(5596), 1191-1194. doi: 10.1126/science.1076358.

Dolcos, F., and McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. J Neurosci 26(7), 2072-2079. doi: 10.1523/jneurosci.5042-05.2006.

Dunbar, R.I.M., and Shultz, S. (2007). Evolution in the social brain. Science 317(5843), 1344-1347. doi: 10.1126/science.1145463.

Eickhoff, S.B., Laird, A.R., Fox, P.T., Bzdok, D., and Hensel, L. (2016). Functional Segregation of the Human Dorsomedial Prefrontal Cortex. Cerebral Cortex 26(1), 304-321. doi: 10.1093/cercor/bhu250.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., and 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., Sterzer, P., and Stadler, C. (2014). Cognitive control under distressing emotional stimulation in adolescents with conduct disorder. Aggress Behav 40(2), 109-119. doi: 10.1002/ab.21508.

Ferri, F., Frassinetti, F., Ardizzi, M., Costantini, M., and Gallese, V. (2012). A sensorimotor network for the bodily self. J Cogn Neurosci 24(7), 1584-1595. doi: 10.1162/jocn_a_00230.

Gee, D.G., Gabard-Durnam, L.J., Flannery, J., Goff, B., Humphreys, K.L., Telzer, E.H., et al. (2013). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 110(39), 15638-15643. doi: 10.1073/pnas.1307893110.

Giedd, J.N., Raznahan, A., Mills, K.L., and Lenroot, R.K. (2012). Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. Biol Sex Differ 3(1), 19. doi: 10.1186/2042-6410-3-19.

Gray, J.R., Braver, T.S., and Raichle, M.E. (2002). Integration of emotion and cognition in the lateral prefrontal cortex. Proc Natl Acad Sci U S A 99(6), 4115-4120. doi: 10.1073/pnas.062381899.

Gross, J.J. (2002). Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 39(3), 281-291. doi: 10.1017.S0048577201393198.

Gu, X., Liu, X., Van Dam, N.T., Hof, P.R., and Fan, J. (2013). Cognition-emotion integration in the anterior insular cortex. Cereb Cortex 23(1), 20-27. doi: 10.1093/cercor/bhr367.

Gupta, R., and Deak, G.O. (2015). Disarming smiles: irrelevant happy faces slow post-error responses. Cogn Process 16(4), 427-434. doi: 10.1007/s10339-015-0664-2.

Gupta, R., Hur, Y.J., and Lavie, N. (2016). Distracted by pleasure: Effects of positive versus negative valence on emotional capture under load. Emotion 16(3), 328-337. doi: 10.1037/emo0000112.

Gupta, R., and Raymond, J.E. (2012). Emotional distraction unbalances visual processing. Psychon Bull Rev 19(2), 184-189. doi: 10.3758/s13423-011-0210-x.

Hart, S.J., Green, S.R., Casp, M., and Belger, A. (2010). Emotional priming effects during Stroop task performance. Neuroimage 49(3), 2662-2670. doi: 10.1016/j.neuroimage.2009.10.076.

Hartikainen, K.M., Ogawa, K.H., and Knight, R.T. (2000). Transient interference of right hemispheric function due to automatic emotional processing. Neuropsychologia 38(12), 1576-1580.

Homack, S., and Riccio, C.A. (2004). A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. Arch Clin Neuropsychol 19(6), 725-743. doi: 10.1016/j.acn.2003.09.003.

Janak, P.H., and Tye, K.M. (2015). From circuits to behaviour in the amygdala. Nature 517(7534), 284-292. doi:

10.1038/nature14188.

Janke, W.D., G. (1978). Die Eigenschaftswörterliste (EWL). Handanweisung. Göttigen: Hogrefe.

Jednorog, K., Altarelli, I., Monzalvo, K., Fluss, J., Dubois, J., Billard, C., et al. (2012). The Influence of Socioeconomic Status on Children's Brain Structure. Plos One 7(8). doi: ARTN e4248610.1371/journal.pone.0042486.

John, O.P., and Gross, J.J. (2004). Healthy and unhealthy emotion regulation: personality processes, individual differences, and life span development. J Pers 72(6), 1301-1333. doi: JOPY298 [pii]10.1111/j.1467-6494.2004.00298.x.

Kanske, P. (2012). On the influence of emotion on conflict processing. Front Integr Neurosci 6, 42. doi: 10.3389/fnint.2012.00042.

Kanske, P., and Kotz, S.A. (2011). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? Cereb Cortex 21(4), 911-919. doi: 10.1093/cercor/bhq157.

Kellermann, T.S., Sternkopf, M.A., Schneider, F., Habel, U., Turetsky, B.I., Zilles, K., et al. (2012). Modulating the processing of emotional stimuli by cognitive demand. Soc Cogn Affect Neurosci 7(3), 263-273. doi: 10.1093/scan/nsq104.

Kuhlmann, M., Hofmann, M.J., Briesemeister, B.B., and Jacobs, A.M. (2016). Mixing positive and negative valence: Affective-semantic integration of bivalent words. Sci Rep 6, 30718. doi: 10.1038/srep30718.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., and Eickhoff, S.B. (2010). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Structure & Function 214(5-6), 519-534. doi: 10.1007/s00429-010-0255-z.

Laird, A.R., McMillan, K.M., Lancaster, J.L., Kochunov, P., Turkeltaub, P.E., Pardo, J.V., et al. (2005). A comparison of label-based review and ALE meta-analysis in the Stroop task. Hum Brain Mapp 25(1), 6-21. doi: 10.1002/hbm.20129.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (2008). "International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8.". (Gainesville, FL.: University of Florida).

Leech, R., and Sharp, D.J. (2014). The role of the posterior cingulate cortex in cognition and disease. Brain 137(Pt 1), 12-32. doi: 10.1093/brain/awt162.

Leonard, C.M., Towler, S., Welcome, S., Halderman, L.K., Otto, R., Eckert, M.A., et al. (2008). Size matters: cerebral volume influences sex differences in neuroanatomy. Cereb Cortex 18(12), 2920-2931. doi: 10.1093/cercor/bhn052.

Livingstone, K., Harper, S., and Gillanders, D. (2009). An Exploration of Emotion Regulation in Psychosis. Clinical Psychology & Psychotherapy 16(5), 418-430. doi: 10.1002/cpp.635.

Luders, E., Gaser, C., Narr, K.L., and Toga, A.W. (2009). Why sex matters: brain size independent differences in gray matter distributions between men and women. J Neurosci 29(45), 14265-14270. doi: 10.1523/jneurosci.2261-09.2009.

Luders, E., Toga, A.W., and Thompson, P.M. (2014). Why size matters: Differences in brain volume account for apparent sex differences in callosal anatomy The sexual dimorphism of the corpus callosum. Neuroimage 84, 820-824. doi: 10.1016/neuroimage.2013.09.040.

Martin, G.N., and Clarke, R.M. (2017). Are Psychology Journals Anti-replication? A Snapshot of Editorial Practices. Front Psychol 8, 523. doi: 10.3389/fpsyg.2017.00523.

Matthew Brett, J.-L.A., Romain Valabregue, Jean-Baptiste Poline (2002). "Region of interest analysis using an SPM toolbox", in: Functional Mapping of the Human Brain. (Sendai, Japan: Neuroimage).

Melcher, T., Born, C., and Gruber, O. (2011). How negative affect influences neural control processes underlying the resolution of cognitive interference: an event-related fMRI study. Neurosci Res 70(4), 415-427. doi: 10.1016/j.neures.2011.05.007.

Mitchell, D.G., Richell, R.A., Leonard, A., and Blair, R.J. (2006). Emotion at the expense of cognition: psychopathic individuals outperform controls on an operant response task. J Abnorm Psychol 115(3), 559-566. doi: 10.1037/0021-843X.115.3.559.

Monk, C.S. (2008). The development of emotion-related neural circuitry in health and psychopathology. Dev Psychopathol 20(4), 1231-1250. doi: 10.1017/S095457940800059X.

Murray, R.J., Brosch, T., and Sander, D. (2014). The functional profile of the human amygdala in affective processing: insights from intracranial recordings. Cortex 60, 10-33. doi: 10.1016/j.cortex.2014.06.010.

Nieuwenhuys, R. (2012). The insular cortex: a review. Prog Brain Res 195, 123-163. doi: 10.1016/B978-0-444-53860-4.00007-6.

Ochsner, K.N., Bunge, S.A., Gross, J.J., and Gabrieli, J.D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 14(8), 1215-1229. doi: 10.1162/089892902760807212.

Ochsner, K.N., and Gross, J.J. (2005). The cognitive control of emotion. Trends Cogn Sci 9(5), 242-249. doi: 10.1016/j.tics.2005.03.010.

Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 23(2), 483-499. doi: 10.1016/j.neuroimage.2004.06.030.

Okon-Singer, H., Lichtenstein-Vidne, L., and Cohen, N. (2013). Dynamic modulation of emotional processing. Biol Psychol 92(3), 480-491. doi: 10.1016/j.biopsycho.2012.05.010.

Pessoa, L. (2008). On the relationship between emotion and cognition. Nature Reviews Neuroscience 9(2), 148-158. doi: Doi 10.1038/Nrn2317.

Pessoa, L. (2009). How do emotion and motivation direct executive control? Trends Cogn Sci 13(4), 160-166. doi: 10.1016/j.tics.2009.01.006.

Petermann, F.E. (2012). Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV). Deutschsprachige adaptation der WAIS-IV von D. Wechsler. [German adaptation of the WAIS-IV by D. Wechsler]. Frankfurt, Germany: Pearson Assessment.

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(2), 331-348. doi: 10.1006/nimg.2002.1087.

Pitskel, N.B., Bolling, D.Z., Kaiser, M.D., Crowley, M.J., and Pelphrey, K.A. (2011). How grossed out are you? The neural bases of emotion regulation from childhood to adolescence. Dev Cogn Neurosci 1(3), 324-337. doi: 10.1016/j.dcn.2011.03.004.

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 (29). doi: 10.3791/1309.

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(9), e0136553. doi: 10.1371/journal.pone.0136553.

Reid, A.T., Bzdok, D., Langner, R., Fox, P.T., Laird, A.R., Amunts, K., et al. (2016). Multimodal connectivity mapping of the human left anterior and posterior lateral prefrontal cortex. Brain Struct Funct 221(5), 2589-2605. doi: 10.1007/s00429-015-1060-5.

Rogers, J.C., and 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. doi:

10.1001/jamapsychiatry.2015.2423.

Schupp, H.T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A.I., and Hamm, A.O. (2007). Selective visual attention to emotion. J Neurosci 27(5), 1082-1089. doi: 10.1523/jneurosci.3223-06.2007.

Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., and 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.

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., and 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., and 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.

Stokes, M.G., Kusunoki, M., Sigala, N., Nili, H., Gaffan, D., and Duncan, J. (2013). Dynamic coding for cognitive control in prefrontal cortex. Neuron 78(2), 364-375. doi: 10.1016/j.neuron.2013.01.039.

Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Kawashima, R., et al. (2011). Correlations among Brain Gray Matter Volumes, Age, Gender, and Hemisphere in Healthy Individuals. Plos One 6(7). doi: ARTN e2273410.1371/journal.pone.0022734.

Thompson, L.A., Malloy, D.M., Cone, J.M., and Hendrickson, D.L. (2010). The Face-to-Face Light Detection Paradigm: A New Methodology for Investigating Visuospatial Attention Across Different Face Regions in Live Face-to-Face Communication Settings. Interact Stud 11(2), 336-348. doi: 10.1075/is.11.2.22tho.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (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.

Uddin, L.Q., Kinnison, J., Pessoa, L., and Anderson, M.L. (2014). Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. J Cogn Neurosci 26(1), 16-27. doi: 10.1162/jocn_a_00462.

Uher, R., Brooks, S.J., Bartholdy, S., Tchanturia, K., and Campbell, I.C. (2014). Increasing cognitive load reduces interference from masked appetitive and aversive but not neutral stimuli. PLoS One 9(4), e94417. doi: 10.1371/journal.pone.0094417.

Van Dillen, L.F., Heslenfeld, D.J., and Koole, S.L. (2009). Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. Neuroimage 45(4), 1212-1219. doi: 10.1016/j.neuroimage.2009.01.016.

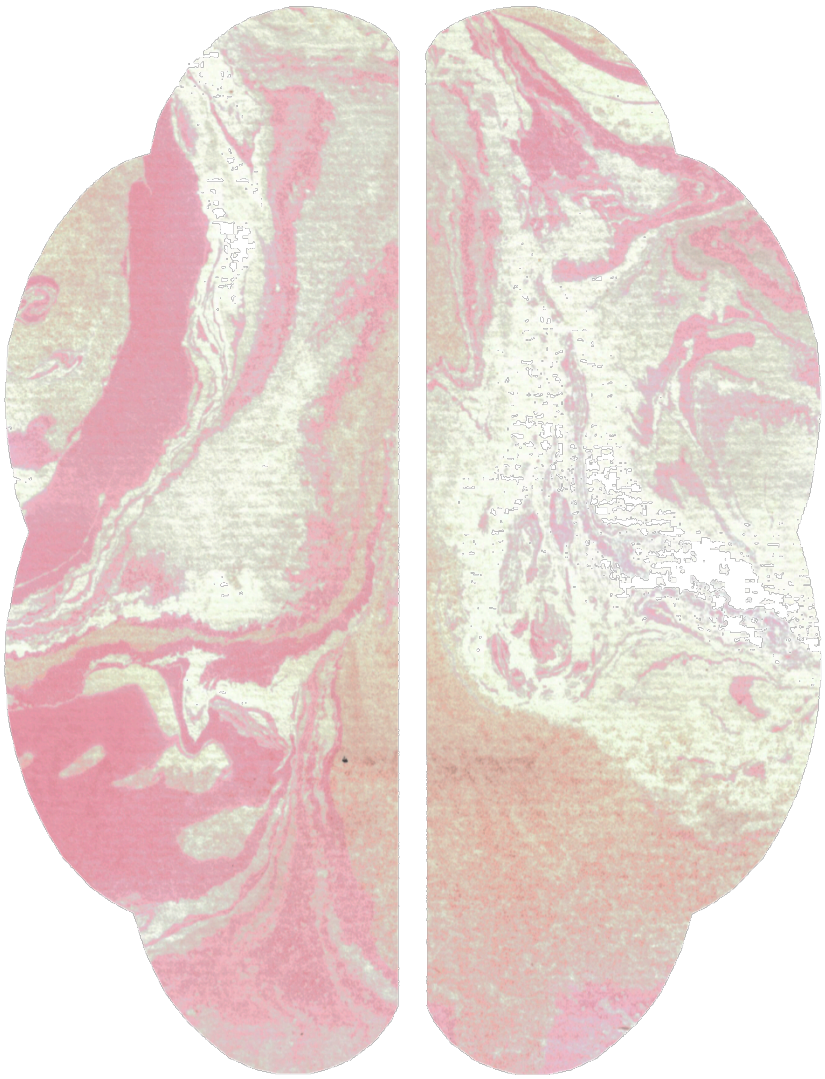
Walcott, C.M., and Landau, S. (2004). The relation between disinhibition and emotion regulation in boys with attention deficit hyperactivity disorder. J Clin Child Adolesc Psychol 33(4), 772-782. doi: 10.1207/s15374424jccp3304_12.

Zinchenko, A., Kanske, P., Obermeier, C., Schroger, E., and Kotz, S.A. (2015). Emotion and goal-directed behavior: ERP evidence on cognitive and emotional conflict. Soc Cogn Affect Neurosci 10(11), 1577-1587. doi: 10.1093/scan/nsv050.

Supplementary material is available in Appendix B.

4 Study 3

Altered neuronal responses during an affective Stroop task in adolescents with conduct disorder



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Abstract

Conduct disorder (CD) is a psychiatric disorder of childhood and adolescence which has been linked to deficient emotion processing and regulation. The behavioral and neuronal correlates targeting the interaction of emotion processing and response inhibition are still investigated. Whole-brain event-related fMRI was applied during an affective Stroop task in 39 adolescents with CD and 39 typically developing adolescents (TD). Participants were presented with an emotional stimulus (negative/neutral) followed by a Stroop task with varying cognitive load (congruent/incongruent/blank trials). fMRI analysis included standard preprocessing, region of interest analyses (amygdala, insula, ventromedial prefrontal cortex) and whole-brain analyses based on a 2(*group*)x2(*emotion*)x3(*task*) full-factorial ANOVA. Adolescents with CD made significantly more errors, while reaction times did not significantly differ compared to TD. Additionally, we observed a lack of downregulation of left amygdala activity in response to task trials and decreased dorsoanterior/posterior insula and increased ventroanterior insula activity for CD relative to TD during affective Stroop task (cluster-level FWE-corrected (p<.05)).The findings presented provide evidence for the neuronal underpinnings of altered interaction of emotion processing and response inhibition in CD. Moreover, our results corroborate previous evidence of emotion dysregulation as a core dysfunction in CD. Future studies shall focus on CD subgroups (e.g., CU-traits or anxiety).

Keywords: Conduct disorder, emotion processing, response inhibition, amygdala, insula

Introduction

Conduct disorder (CD) is a psychiatric disorder of childhood and adolescence marked by aggressive behavior outside of the age-appropriate norm (American Psychiatric Association, 2013). CD youths are more likely to engage in antisocial behavior (e.g., rule breaking, stealing, and lying (Lahey & Waldman, 2012), and are at risk for academic failure, delinquency, and mental disorders in adulthood (Biederman et al., 2008; Erskine et al., 2016; Fergusson, John Horwood, & Ridder, 2005; Swanson, 1994). Antisocial youths are phenotypically characterized by a heterogeneous symptomatology, reflected in different aetiological paths and variations in response to treatment (Steiner, Daniels, Stadler, & Kelly, 2017). Four main forms of neurocognitive dysfunctions relating to the development, heterogeneity, and core impairments of CD have been proposed: reduced affective empathy, threat sensitivity, decision-making, and response inhibition (Blair, Veroude, & Buitelaar, 2016). In particular, mechanisms underlying deficient emotion processing and response inhibition have been hypothesized to increase the risk for antisocial behavior (Campbell, Shaw, & Gilliom, 2000; Davidson, Putnam, & Larson, 2000; Wang, Chassin, Lee, Haller, & King, 2017; Young et al., 2009).

While altered response inhibition has been observed in adolescents with CD and disruptive behavior disorders (DBD; (Hwang et al., 2016; Prateeksha, Roopesh, & Vijayasagar, 2014), results are inconsistent in regards to the direction of findings. Some studies measuring response inhibition report no differences in performance of CD or DBD youths (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia et al., 2008). Others indicate higher error rates and/or longer reaction times (RTs) (Euler, Sterzer, & Stadler, 2014; Hwang et al., 2016; Prateeksha et al., 2014; Rubia, Halari, et al., 2009). Importantly, when response inhibition is preceded by emotional stimuli, decreases in performance are more commonly reported (Euler et al., 2014; Hwang et al., 2016; Prateeksha et al., 2014).

Studies using functional magnetic resonance imaging (fMRI) have shed light on the neuronal phenotype characteristic for CD youths. Most commonly, alterations in neural recruitment in frontal and limbic lobes (including insula, amygdala, and anterior cingulate) are reported (Blair, 2010; Hwang et al., 2016; Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015; Rubia, 2011; Stadler et al., 2007; Sterzer & Stadler, 2009). Studies investigating response inhibition (e.g., stop, Simon, switch, or Stroop tasks) in CD have revealed decreased and increased neuronal activity in medial prefrontal cortex, insula, cingulate gyrus,

temporoparietal junction, subcortical regions, and occipital lobe (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008). To our knowledge, only one study has yet directly tested the interaction between emotion processing and response inhibition in DBD youths. In this study Hwang et al. (2016) detected reduced ventromedial prefrontal cortex (vmPFC) and amygdala activity in response to negative affective stimuli and reduced insula activity with increasing cognitive load in DBD compared to typically developing (TD) youths.

The present study aims at adding to this first evidence in DBD by investigating the neuronal and behavioral correlates of the interaction between emotion processing and response inhibition in CD youths through fMRI during affective Stroop task performance. Using both region of interest and whole-brain approaches, we hypothesized (I) to observe emotion by task interactions for the Stroop effect (i.e., delayed RTs for trials with increased cognitive load and prior negative stimulation) in CD compared to TD youths, in line with previous work (Euler et al., 2014); (II) to detect reduced neuronal activity within brain regions involved in emotion processing and response inhibition (amygdala, insula, and vmPFC) during the affective Stroop task in CD relative to TD youths in line with previous findings (Hwang et al., 2016).

Methods

Participants

Seventy-eight youths (39CD/39TD) were included in the present analyses (age range: 10.1-19.1 years, mean age: 15.7 years, 10 females in each group). CD was diagnosed according to DSM-5 criteria. Seventeen CD youths (43.6%) additionally met DSM-5 criteria for present attention-deficit hyperactivity disorder (ADHD), while 20 CD youths (51.3%) additionally met diagnostic criteria for oppositional defiant disorder (ODD). TD were included if no current psychiatric diagnosis was reported by either the participant and/or the parents/legal guardians. CD and TD groups were matched for age ($t(76)=.87$, $p=.390$) and non-verbal IQ ($t(76)=-.72$, $p=.472$) (Table 1/SI1). Participants were recruited through referrals from child and adolescent psychiatric institutions, public schools, and the general public through the use of fliers.

Ethical considerations

All adolescents and parents/legal guardians gave written informed consent as approved by the local ethics committee 'Ethikkommission der Nordwest- und Zentralschweiz' and received vouchers for their participation.

Clinical testing and questionnaires

CD youths and their legal guardians completed the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) in order to assess CD criteria and comorbid disorders according to the DSM-5 (Table 1). CD and TD participants completed the Youth Psychopathic traits Inventory (YPI, Andershed, Hodgins, and Tengstrom (2007)) and the matrix reasoning subtest of the WISC-IV (ages ≤16y; Petermann, U. (Eds.) (2011)) and the WAIS-III (ages ≥17y; Petermann (1997)) measuring non-verbal IQ. For 10 participants (9 CD, 1 TD), only a composite IQ score was obtained. CD and TD legal guardians moreover completed a socioeconomic status (SES) questionnaire (SI2). Participants were asked to report any medication administered prior to the MRI session (SI3). Exclusion of participants with medication revealed similar results in significant regions of interest (ROI) and whole-brain analyses.

fMRI task: The affective Stroop task

We applied an affective number Stroop task as previously described in Raschle et al. (2017). Each trial started with an emotional stimulus, i.e., a negative (Neg) or neutral (Neu) stimulus (150ms), followed by a task trial (congruent/incongruent/neutral Stroop trial or a blank screen) and finally a relaxation period, i.e., blank screen (350ms). All pictures were selected from a child-appropriate image system (Developmental Affective Photo System (DAPS); Cordon, Melinder, Goodman, and Edelstein (2013)). During task trials, participants were presented with an array of 1 to 4 digits or a blank screen and were asked to press a button corresponding to the number of items displayed. The number of items was either congruent (C; e.g., number 3 in an array of 3) or incongruent (IC; e.g., number 2 in an array of 3) with the digits presented. Star shaped stimuli (S; as a neutral baseline counting condition) and blank trials (B; no response expected from participants) were used as control conditions (for further details see Raschle et al. (2017)). Trial order and interstimulus intervals (which were 350–1850ms) were randomized using Optseq (http://surfer.nmr.mgh.harvard.edu/optseq) and kept constant across participants. A total of 300 task and 100 blank trials were administered

(100 for C/IC/S trials, 50 with preceding negative images, 50 with neutral images, in 2 runs), with a total scan time of about 16 minutes (7.59min each run).

Behavioral measures: In-scanner performance

All participants scored <60% correct responses per task condition and run. RTs and task accuracy (raw scores) were analyzed using 2x2x2 full-factorial ANOVAs with the between-subject factor *group* (CD, TD) and within-subject factors *emotion* (negative, neutral) and *task* (congruent, incongruent) for RTs and accuracy separately using SPSS, version 24. Data was unavailable for a minority of responses because of technical difficulties with the response box (for a detailed description see SI4).

fMRI data acquisition and analysis

Acquisition parameter. In Basel, whole brain blood oxygen level-dependent (BOLD) fMRI data and structural T1-weighted magnetization prepared rapid gradient echo imaging images were acquired on a Siemens Prisma MRI system using a 20-channel phased-array radio frequency head coil. In Berlin, a Siemens TimTRIO MRI system equipped with a 12-channel head coil was used. At both sites a T2*-weighted EPI (echo-planar imaging) sequence with TR=2000ms, TE=30.0ms, FOV=192mm, image matrix=64x64mm, voxel size=3x3x3mm, and number of slices=37 was used. We further acquired high-resolution T1-weighted structural images for coregistration during fMRI preprocessing using the following specifications: TR=1900.0ms, TE=3.42ms, FOV=256mm, image matrix=256x256, voxel size=1mm.

fMRI Analysis. fMRI data were analyzed using the Statistical Parametric Mapping software, version 12 (SPM12, www.fil.ion.ucl.ac.uk/spm/). Preprocessing of the data included realignment, co-registration to the structural image, segmentation, normalization to the Montreal Neurologic Institute (MNI) standard brain, and spatial smoothing using an 8mm Full Width at Half Maximum Gaussian kernel. Quality control was performed throughout the analysis in order to control for effects of motion.

Single-subject fMRI data was analyzed using the general linear model. The model comprised eight task regressors (each combining a negative or neutral stimulus with congruent, incongruent, or neutral (stars/blank) Stroop trials, namely negative-congruent (NegC), negative-stars (NegS), negative-incongruent (NegIC), negative-blank (NegB), neutral-

congruent (NeuC), neutral-stars (NeuS), neutral-incongruent (NeuIC), neutral-blank (NeuB)), one regressor for incorrect/missed responses, and six motion regressors. The task regressors were modeled as stick functions convolved with the hemodynamic response function as implemented in SPM12.

At the second level, hypothesis-based region-of-interest (ROIs) and whole-brain analyses were performed. A-priori defined ROIs included bilateral amygdala and insula and bilateral vmPFC according to (Hwang et al., 2016; Raschle et al., 2015; Rubia, 2011; Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008) and derived from the automated anatomical labeling atlas (aal; Tzourio-Mazoyer et al. (2002)). Mean parameter estimates were extracted from each ROI using the marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002). A repeated measures ANOVA with the factors *group* (CD, TD), *emotion* (negative, neutral), and *task* (blank, congruent, incongruent) and follow-up pairwise comparisons applying a Bonferroni correction were then computed within SPSS, version 24.

For whole-brain analyses, beta images resulting from first-level model estimation for each regressor and run were submitted to a group-level random-effects analysis using 2x2x3 full-factorial ANOVA with the between-subject factor *group* (CD, TD) and within-subject factors *emotion* (negative, neutral) and *task* (blank, congruent, incongruent).

For all analyses, *site* (Basel, Berlin) was added as an additional factor of no interest. Brain activation was assessed for the main effects of *group*, *emotion*, and *task*, and all possible interactions thereof are reported at a cluster-extent family-wise error (FWE) rate of $p<.05$ (cluster building threshold of $p<.001$). Significant clusters of main effects and interactions were followed up with masked post-hoc *t*-tests.

Results

Questionnaires

Psychometric assessments are reported in Table 1. CD scored significantly higher than TD in the callous-unemotional and impulsive-irresponsible dimensions and the total score of the YPI (all $p<.01$; YPI, Andershed et al. (2007)). Nevertheless, psychopathic traits in our CD group were overall low (YPI total score: $M=11.16$, $SD=2.38$, CU dimension: $M=11.23$, $SD=3.08$; see also Stadlin, Pérez, Schmeck, Gallo, and Schmid (2016)). Nevertheless, CD

scored significantly higher than TD in the callous-unemotional and impulsive-irresponsible dimensions and the total score of the YPI (all $p<.01$; YPI, Andershed et al. (2007)).

Table 1. Behavioral group characteristics.

		CD	TD	*p* Sig. 2-tailed	
		Mean ± SD	Mean ± SD		
Age (in years)		15.94 ± 1.88	15.54 ± 2.15	.390	
Sex (male/female)		29/10	29/10		
No. per site (Basel/Berlin)		11/28	11/28		
Handedness (right/left/both)		36/2/2	37/2/1		
IQ	Matrix reasoning	99.47 ± 12.02	101.54 ± 11.31	.472	
Comorbidities (DSM-5)	Attention-deficit hyperactivity disorder	17	0		
	Oppositional defiant disorder	20	0		
	Major depression	2	0		
	Anxiety disorder	6	0		
YPI		*N*=39	*N*=38		
	Grandiose-manipulative	8.68 ± 2.74	7.89 ± 1.90	.117	
	Callous-unemotional	11.23 ± 3.08	9.55 ± 1.94	.006	**
	Impulsive-irresponsible	13.57 ± 2.80	10.68 ± 1.72	<.001	***
	Total	11.16 ± 2.38	9.37 ± 1.21	<.001	***

*$p<.05$; **$p<.01$; ***$p<.001$
For IQ, standard scores are reported; for YPI, mean scores are reported.
CD=conduct disorder; TD=typically developing adolescents; SD=standard deviation.

Behavioral results: In-scanner performance

Analysis of RTs revealed a significant main effect of *emotion* (Neu>Neg, $F(1,76)=5.74$, $p<.05$), and a main effect of *task* (IC>C, $F(1,76)=615.48$, $p<.001$). There was no main effect of *group* and no interaction effects for RTs. For accuracy, we found a significant main effect of *emotion* (Neu>Neg, $F(1,76)=8.29$, $p<.01$), a main effect of *task* (C>IC, $F(1,76)=118.42$, $p<.001$), and a main effect of *group* (CD<TD, $F(1,76)=6.77$, $p<.05$). There were no significant interaction effects for accuracy (SI4).

Functional MRI results

ROI results. A significant main effect of *emotion* ($F(1,74)=7.12$, $p<.01$) was detected in left amygdala, indicating increased neuronal activity for negative compared to neutral trials (Neg>Neu, $p<.01$) (Figure 1). Moreover, a *group* x *task* interaction was observed in left amygdala ($F(2,73)=4.83$, $p<.05$), reflecting significantly decreased activity for incongruent compared to blank trials in TD (IC<B, $p<.05$), but not CD (all $p>.227$). This effect was independent of emotion (no significant *group* x *emotion* x *task* interaction; $F(2,73)=.73$, $p=.485$). A significant *emotion* x *task* interaction effect was found in right amygdala ($F(2,73)=4.77$, $p<.05$). Across all subjects we observed relatively increased right amygdala activity for blank trials with a prior negative compared to neutral emotion (NegB>NeuB, $p<.05$), but relatively decreased activity in the right amygdala during congruent trials with a prior negative versus neutral emotion (NegC<NeuC, $p<.05$). In addition we observed relatively decreased activity in the right amygdala for during congruent relative to blank trials following negative stimuli (NegC<NegB, $p<.01$). Within right insula, a significant *emotion* x *task* effect was observed ($F(2,73)=5.40$, $p<.01$). This reflected increased activity during congruent trials following negative compared to neutral stimuli (NegC>NeuC, $p<.005$) and increased activity for incongruent compared to congruent trials after negative stimuli (NegIC>NegC, $p=.001$). Decreased right insula activity was moreover detected for congruent compared to blank trials following negative stimuli (NegC<NegB, $p<.001$). A significant main effect of *task* was detected in right ($F(2,73)=5.40$, $p<.01$) and left vmPFC ($F(2,73)=9.36$, $p<.001$) and resulting from relatively decreased activation for incongruent compared to blank and congruent trials (IC<B $p<.001$; IC<C, $p<.005$) on the left and incongruent compared to blank trials on the right (IC<B, $p<.005$).

In order to examine the relationship between psychopathic traits (YPI total score) and left amygdala activity during IC–C (*group* x *task* interaction), follow-up bivariate correlations were computed for CD and TD separately. Results revealed no significant relationships between left amygdala activation and psychopathic traits for CD or TD.

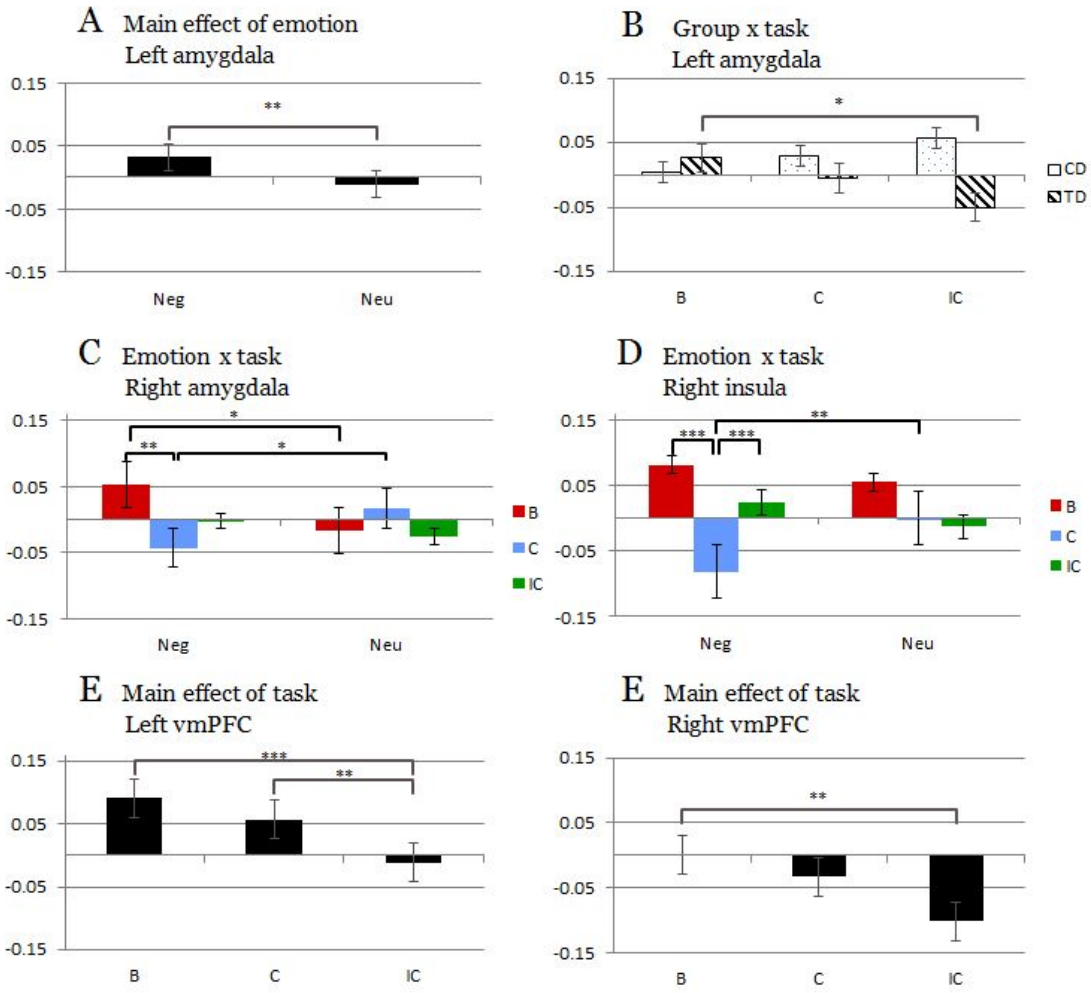

Figure 1. Bar graphs displaying mean values of parameter estimates (mean centered) in predefined ROIs (amygdala, insula, ventromedial prefrontal cortex (vmPFC)) for the main effect of *emotion* and *group* x *task* interaction (left amygdala; A/B), *emotion* x *task* interaction (right amygdala and insula; C/D), and main effect of *task* (left and right vmPFC; E/F). CD=conduct disorder; TD=typically developing adolescents, **p*<.05; ***p*<.01; ****p*<.001, two-tailed *t*-test; all other *t*-tests non-significant at threshold *p*=.05.

Whole-brain results. Whole-brain analysis of brain activation during affective Stroop task processing revealed significant main effects of *group* and *task* (Table 2), but no significant main effect of *emotion.* There were no significant two- or three-way interaction effects. All images are neurologically displayed using the Multi-image Analysis GUI as available at http://ric.uthscsa.edu/mango/mango.html.

Table 2. MNI coordinates, cluster size and Z-scores for whole-brain results using a FWE cluster level correction of $p<.05$ (cluster building threshold of $p<.001$) for the main effect of *group* and main effect of *task* during the affective Stroop task.

Brain Region	Hem	k	Z_0	MNI coordinates [mm]		
				x	y	z
Main effect of *group*						
CD<TD						
supramarginal gyrus, middle frontal gyrus, including insula and precentral gyrus	R	1035	7.19	40	-10	20
postcentral gyrus	L	392	6.04	-62	-2	26
middle/superior temporal gyrus, hippocampus	R	335	6.66	50	-18	-4
pallidum, thalamus	R/L	309	6.68	16	-16	-2
CD>TD						
inferior/superior parietal lobe, middle temporal/occipital lobe	R/L	4310	6.27	-30	-82	26
precentral gyrus, inferior orbitofrontal lobe, caudate, putamen, including insula	R/L	3869	>8	-30	12	22
rolandic operculum, inferior parietal lobe	L	2545	7.71	-32	-44	-26
inferior/middle/superior frontal lobe, precentral gyrus, insula	R	1680	7.44	48	34	28
lingual gyrus, hippocampus, inferior temporal/occipital lobe, cerebelum	R/L	1114	7.04	32	-54	8
middle/superior frontal gyrus, supplementary motor area, anterior/middle cingulate gyrus	R/L	787	6.28	4	26	44
anterior/middle cingulate gyrus, caudate	R/L	391	6.45	4	-2	32
precentral gyrus, superior frontal gyrus	L	343	6.29	-28	-24	30
inferior parietal lobe, angular gyrus	R	339	5.73	54	-34	18
fusiform gyrus, inferior/middle occipital lobe	L	294	6.00	-46	-82	-8
fusiform gyrus, inferior/middle occipital lobe	R	257	5.81	42	-52	-14
supplementary motor area, superior frontal lobe	L	212	5.78	-18	14	62
Main effect of *task*						
IC>C						
calcarine sulcus, lingual gyrus, superior occipital lobe	R/L	385	4.23	4	-82	0
IC<C						
no suprathreshold voxels						
IC>B						
occipital lobe, fusiform gyrus, calcarine sulcus, cerebelum	R/L	9665	>8	34	-86	0
supramarginal gyrus, inferior/superior parietal lobe, middle/superior frontal lobe	L	4888	>8	-46	-36	58
supramarginal gyrus, inferior/superior parietal lobe	R	1118	5.57	42	-40	52

hippocampus, pallidum, putamen, amygdala	L	791	5.53	-24	0	-8
inferior frontal operculum, precentral gyrus	L	291	5.82	-54	8	38
pallidum, caudate, putamen	R	261	4.74	26	6	-8
IC<B						
middle/posterior cingulate gyrus, paracentral lobule, including precuneus	R/L	1850	5.98	-2	-34	44
inferior/middle temporal lobe, inferior parietal lobe, middle occipital lobe	L	872	6.67	-40	-84	28
middle frontal lobe, precentral gyrus	R	832	4.95	36	-16	44
middle/superior temporal lobe, angular gyrus	R	645	4.65	42	-80	30
inferior temporal lobe, including fusiform gyrus	L	232	4.70	-28	-36	-18
C>B						
supramarginal gyrus, inferior/superior parietal lobe, superior frontal lobe	L	3740	>8	-44	-38	60
cerebelum, occipital lobe, including fusiform gyrus	R	3049	6.71	32	-88	0
cerebelum, occipital lobe, including fusiform gyrus	L	2248	6.99	-38	-90	-8
supramarginal gyrus, inferior/superior parietal lobe	R	747	4.95	44	-40	58
hippocampus, putamen	L	232	4.11	-18	0	14
C<B						
middle cingulate gyrus, precuneus, paracentral lobule	R/L	941	4.96	6	-38	50
postcentral gyrus, precentral gyrus	R	432	4.17	36	-20	56
angular gyrus, middle/superior occipital lobe	L	455	4.81	-44	-82	22
middle/superior temporal lobe	R	312	4.09	64	-52	6
fusiform gyrus, lingual gyrus	R	228	4.48	28	-44	-12
insula, putamen, rolandic operculum	R	221	4.06	36	-12	6

FWE cluster level correction of $p<.05$ (cluster building threshold of $p<.001$)
Hem=hemisphere; k= cluster size; B=blank trial; C=congruent trial; IC=incongruent trial; CD=conduct disorder patients; TD=typically developing adolescents

Main effect of group. A main effect of *group* (Figure 2) was detected for regions including bilateral parietal and middle/inferior temporal and occipital lobes, bilateral precentral and inferior orbitofrontal areas extending into dorsoanterior and posterior insula and striatum, frontal cortices, and anterior/middle cingulate cortex (CD>TD) and regions including right middle frontal and supramarginal gyri (extending into ventroanterior insula), left postcentral gyrus, right middle/superior temporal cortex, and bilateral thalamus (CD<TD).

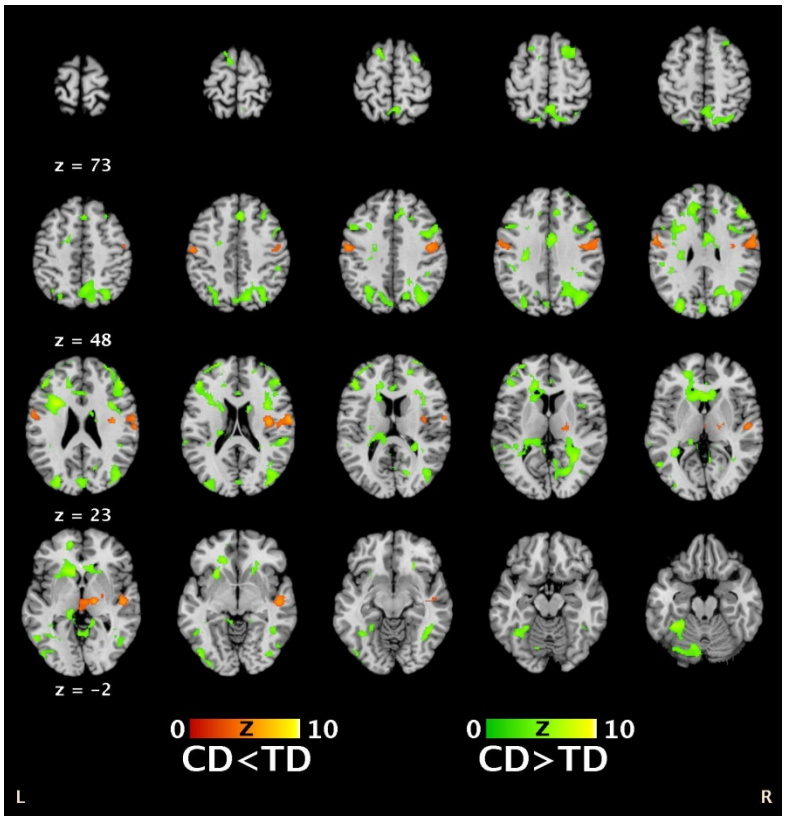

Figure 2. Statistical parametric maps depicting *group* differences between conduct disorder (CD) and typically developing (TD) adolescents in brain activation during the affective Stroop task (masked post-hoc *t*-tests, 39CD/39TD; hypoactivations in CD in red-yellow, hyperactivations in CD in green-yellow) (p<.05, FWE).

Main effect of task. Regions showing a differential BOLD response in response to *task* included bilateral parietal and frontal lobes, supramarginal gyri, occipital, temporal, and cerebellar regions, right middle cingulate cortex, left precuneus, and left amygdala. Bilateral supramarginal, superior frontoparietal, and occipital areas exhibited increased activity for congruent and incongruent relative to blank trials (IC/C>B). Left amygdala and inferior frontal areas exhibited increased activity for incongruent compared to blank trials (IC>B). In contrast, decreased left inferior parietal lobe, right middle frontal and cingulate cortices, and left precuneus activity was detected for congruent and incongruent relative to blank trials (C/IC<B). Decreased activity in left inferior temporal and right middle/superior temporal regions was related to incongruent versus blank trials (IC<B, Figure 3).

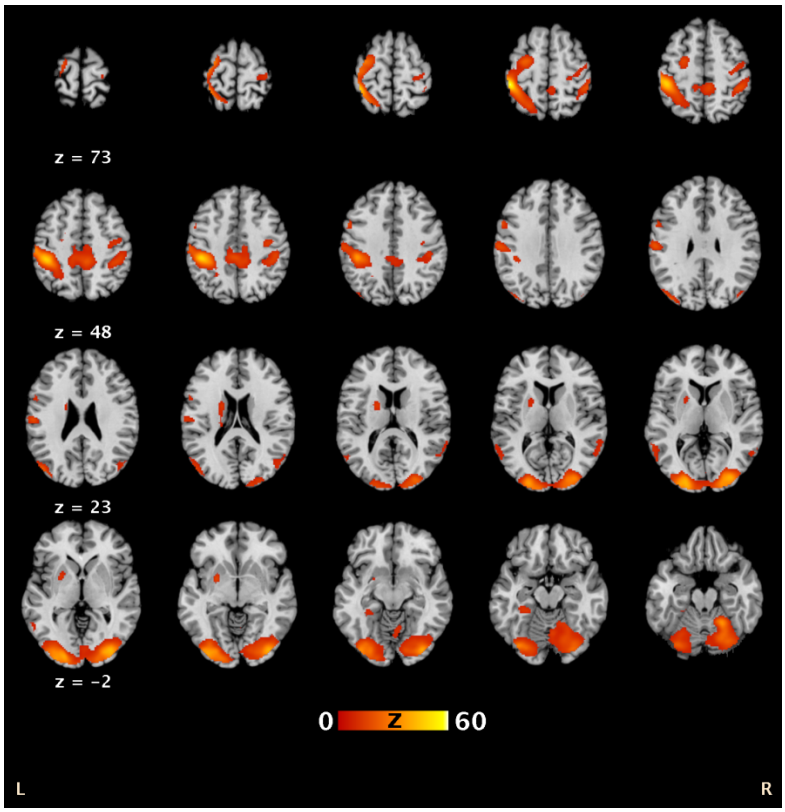

Figure 3. Statistical parametric maps depicting the main effect of *task* during affective Stroop task processing (red-yellow) (p<0.05, FWE).

Discussion

Here we aimed at investigating the interaction of emotion processing and response inhibition in CD youths during an affective Stroop task. ROI analyses revealed a significant *group* x *task* interaction effect reflecting a lack of downregulation of left amygdala activity in response to task trials for CD compared to TD. This effect was independent of the emotion presented prior to Stroop task performance. Additionally, whole-brain analyses revealed a significant main effect of *group* representing decreased dorsoanterior/posterior and increased ventroanterior insula activity for CD relative to TD regardless of emotion and task demands.

Contrary to our hypothesis and some previous investigations (Euler et al., 2014; Prateeksha et al., 2014; Rubia, Smith, et al., 2009) we did not detect group differences in RTs. However, research has not been conclusive to date and the present finding is in accordance with other studies (Banich et al., 2007; Rubia, Halari, et al., 2010; Rubia, Halari, et al., 2009; Rubia et al., 2008). Increased RTs for neutral compared to negative trials and for incongruent compared to congruent trials were detected across all participants. While increased RTs robustly reflect the Stroop effect (Stroop, 1935), shorter RTs for negative compared to neutral stimuli were not expected. However, participants' responses were more accurate after

presentation of neutral relative to negative images. Faster responses at the expense of lower accuracy may be due to heightened stress. Moreover, in line with Rubia, Halari, et al. (2009) CD youths made more errors than TD, which is contrary to other reports in DBD and TD (Banich et al., 2007; Euler et al., 2014; Prateeksha et al., 2014; Rubia, Halari, et al., 2010; Rubia et al., 2008).

In line with our second hypothesis, ROI analyses revealed decreased left amygdala activity during Stroop task trials with a high cognitive load (IC>B) in TD. In contrast, CD youths did not show any downregulation of emotion-related brain areas with increasing task difficulty. Unexpectedly, this group difference was independent of the emotionality. We would have expected to detect a difference depending on the emotion presented (i.e., a downregulation after negative images instead of on any image as observed here). Our data suggests that no task-dependent downregulation of left amygdala response takes place in CD as compared to TD, reflecting altered neuronal functioning of left amygdala which may be linked to altered regulatory processes.

Aberrant amygdala activity in DBD has been previously reported for response inhibition (Hwang et al., 2016), facial emotion processing (Holz et al., 2017; Jones, Laurens, Herba, Barker, & Viding, 2009; Marsh et al., 2008), emotion processing (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005), stimulus-reinforcement learning, and reward processing (Finger et al., 2011). In addition to functional MRI evidence, past research has suggested reduced amygdala volumes in adolescents with conduct problems (Fairchild et al., 2011; Huebner et al., 2008; Rogers & De Brito, 2016; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007; Wallace et al., 2014), supporting a broader view of the amygdala as a key center of alterations in CD.

Whole-brain results provided further insights into right insula activity during the affective Stroop task while distinguishing between insular subdivisions. CD exhibited decreased activity in dorsal anterior and posterior insula, areas involved in response inhibition and sensorimotor processing (Chang, Yarkoni, Khaw, & Sanfey, 2013; Mutschler et al., 2009). Additionally, CD showed increased activity in the ventroanterior insula implicated in affective processing (Chang et al., 2013; Mutschler et al., 2009). Our observations are in line with a broader view of the insula in integrating emotion and cognition in healthy adolescents (Chang et al., 2013; Pavuluri & May, 2015), whereas alterations thereof could be

hypothesized to reflect a failure in recruiting areas for task performance, while allocating neuronal resources for emotion processing instead. However, the observed differences emerged from a main effect of group and therefore need to be interpreted carefully. Future studies shall determine whether right amygdala and insula show significant co-activations (Kober et al., 2008) during task trials following negative stimuli, reflecting on the role of the insula in transferring sensory information to the amygdala (Shelley & Trimble, 2004).

Limitations

For the present study design we used child-appropriate emotional pictures (DAPS; Cordon, Melinder, Goodman, and Edelstein (2013)). However, the short presentation (150ms) and moderate image valence might have resulted in a reduced impact for CD youths. Moreover, we cannot exclude that confounding factors or comorbidities could have influenced the results. Finally, the here presented results characterize a group of CD youths on the lower spectrum of CU traits. Interpretation should therefore be drawn with caution.

Conclusion

We provide evidence for the neuronal characteristics of altered emotion processing and response inhibition interaction in CD. More specifically, we observed a significant lack of downregulation of left amygdala activity in response to task trials and decreased dorsoanterior/posterior and increased ventroanterior insula activity for CD relative to TD during affective Stroop task performance. Behaviorally, CD scored significantly lower than TD youths, while reaction times did not differ. These findings extend knowledge on altered emotion-cognition interaction in CD youths and support emotion dysregulation as a core deficit in CD.

Acknowledgments

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References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Association.

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, 144-154.

Banich, M. T., Crowley, T. J., Thompson, L. L., Jacobson, B. L., Liu, X., Raymond, K. M., & Claus, E. D. (2007). Brain activation during the Stroop task in adolescents with severe substance and conduct problems: A pilot study. Drug and Alcohol Dependence, 90(2-3), 175-182. doi:10.1016/j.drugalcdep.2007.03.009

Biederman, J., Petty, C. R., Dolan, C., Hughes, S., Mick, E., Monuteaux, M. C., & Faraone, S. V. (2008). The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. Psychological Medicine, 38(7), 1027-1036. doi:10.1017/S0033291707002668

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

Blair, R. J., Veroude, K., & Buitelaar, J. K. (2016). Neuro-cognitive system dysfunction and symptom sets: A review of fMRI studies in youth with conduct problems. Neuroscience and Biobehavioral Reviews. doi:10.1016/j.neubiorev.2016.10.022

Brett, Matthew, Anton, Jean-Luc, Valabregue, Romain, & Poline, Jean-Baptiste. (2002). Region of interest analysis using an SPM toolbox. Paper presented at the Functional Mapping of the Human Brain, Sendai, Japan.

Campbell, Susan B, Shaw, Daniel S, & Gilliom, Miles. (2000). Early externalizing behavior problems: Toddlers and preschoolers at risk for later maladjustment. Development and Psychopathology, 12(3), 467-488.

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. Cerebral Cortex, 23(3), 739-749. doi:10.1093/cercor/bhs065

Cordon, I. M., Melinder, A. M., Goodman, G. S., & Edelstein, R. S. (2013). Children's and adults' memory for emotional pictures: examining age-related patterns using the Developmental Affective Photo System. Journal of Experimental Child Psychology, 114(2), 339-356. doi:10.1016/j.jecp.2012.08.004

Davidson, Richard J, Putnam, Katherine M, & Larson, Christine L. (2000). Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. Science, 289(5479), 591-594.

Erskine, H. E., Norman, R. E., Ferrari, A. J., Chan, G. C., Copeland, W. E., Whiteford, H. A., & Scott, J. G. (2016). Long-Term Outcomes of Attention-Deficit/Hyperactivity Disorder and Conduct Disorder: A Systematic Review and Meta-Analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 55(10), 841-850. doi:10.1016/j.jaac.2016.06.016

Euler, F., Sterzer, P., & Stadler, C. (2014). Cognitive control under distressing emotional stimulation in adolescents with conduct disorder. Aggressive Behavior, 40(2), 109-119. doi:10.1002/ab.21508

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. American Journal of Psychiatry, 168(6), 624-633. doi:10.1176/appi.ajp.2010.10081184

Fergusson, David M, John Horwood, L, & Ridder, Elizabeth M. (2005). Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. Journal of child psychology and psychiatry, 46(8), 837-849.

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. American Journal of Psychiatry, 168(2), 152-162. doi:10.1176/appi.ajp.2010.10010129

Holz, N. E., Boecker-Schlier, R., Buchmann, A. F., Blomeyer, D., Jennen-Steinmetz, C., Baumeister, S., . . . Laucht, M. (2017). Ventral striatum and amygdala activity as convergence sites for early adversity and conduct disorder. Social Cognitive and Affective Neuroscience, 12(2), 261-272. doi:10.1093/scan/nsw120

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. Journal of the American Academy of Child and Adolescent Psychiatry, 47(5), 540-547. doi:10.1097/CHI.0b013e3181676545

Hwang, S., Nolan, Z. T., White, S. F., Williams, W. C., Sinclair, S., & Blair, R. J. (2016). Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. Psychological Medicine, 46(7), 1485-1496. doi:10.1017/S0033291716000118

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. American Journal of Psychiatry, 166(1), 95-102. doi:10.1176/appi.ajp.2008.07071050

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. Journal of the American Academy of Child and Adolescent Psychiatry, 36(7), 980-988. doi:10.1097/00004583-199707000-00021

Kober, Hedy, Barrett, Lisa Feldman, Joseph, Josh, Bliss-Moreau, Eliza, Lindquist, Kristen, & Wager, Tor D. (2008). Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. Neuroimage, 42(2), 998-1031.

Lahey, B. B., & Waldman, I. D. (2012). Annual research review: phenotypic and causal structure of conduct disorder in the broader context of prevalent forms of psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines, 53(5), 536-557. doi:10.1111/j.1469-7610.2011.02509.x

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. American Journal of Psychiatry, 165(6), 712-720. doi:10.1176/appi.ajp.2007.07071145

Mutschler, I., Wieckhorst, B., Kowalevski, S., Derix, J., Wentlandt, J., Schulze-Bonhage, A., & Ball, T. (2009). Functional organization of the human anterior insular cortex. Neuroscience Letters, 457(2), 66-70. doi:10.1016/j.neulet.2009.03.101

Pavuluri, Mani, & May, Amber. (2015). I feel, therefore, I am: the insula and its role in human emotion, cognition and the sensory-motor system. AIMS Neuroscience, 2(1), 18-27.

Petermann, F. & Petermann, U. (Eds.). (2011). Wechsler Intelligence Scale for Children (4th ed.). Frankfurt am Main, Germany.: Pearson Assessment.

Petermann, F. (Ed.). (1997). Wechsler Adult Intelligence Scale - Third Edition (WAIS-III). Deutschsprachige Adaptation der

WAIS-III von D. Wechsler. [German adaptation of the WAIS-III by D. Wechsler]. Frankfurt, Germany: Pearson Assessment.

Prateeksha, S., Roopesh, B.N., & Vijayasagar, J.K. (2014). Response inhibition in children with conduct disorder: A preliminary report. Indian Journal of Health and Wellbeing, 5(11), 1325-1330.

Raschle, N. M., Fehlbaum, L. V., Menks, W. M., Euler, F., Sterzer, P., & Stadler, C. (2017). Investigating the Neural Correlates of Emotion–Cognition Interaction Using an Affective Stroop Task. Frontiers in Psychology, 8(1489). doi:10.3389/fpsyg.2017.01489

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

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. doi:10.1001/jamapsychiatry.2015.2423

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

Rubia, K., Cubillo, A., Smith, A. B., Woolley, J., Heyman, I., & Brammer, M. J. (2010). Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Human Brain Mapping, 31(2), 287-299. doi:10.1002/hbm.20864

Rubia, K., Halari, R., Cubillo, A., Mohammad, A. M., Scott, S., & Brammer, M. (2010). Disorder-specific inferior prefrontal hypofunction in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure conduct disorder during cognitive flexibility. Human Brain Mapping, 31(12), 1823-1833. doi:10.1002/hbm.20975

Rubia, K., Halari, R., Smith, A. B., Mohammad, M., Scott, S., & Brammer, M. J. (2009). Shared and disorder-specific prefrontal abnormalities in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure CD during interference inhibition and attention allocation. Journal of Child Psychology and Psychiatry and Allied Disciplines, 50(6), 669-678. doi:10.1111/j.1469-7610.2008.02022.x

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. American Journal of 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. American Journal of Psychiatry, 166(1), 83-94. doi:10.1176/appi.ajp.2008.08020212

Shelley, Bhaskara P, & Trimble, Michael R. (2004). The insular lobe of Reil–its anatamico-functional, behavioural and neuropsychiatric attributes in humans–a review. The World Journal of Biological Psychiatry, 5(4), 176-200.

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. Journal of Psychiatric Research, 41(5), 410-417. doi:10.1016/j.jpsychires.2006.01.006

Stadlin, Christina, Pérez, Tania, Schmeck, Klaus, Gallo, Alain Di, & Schmid, Marc. (2016). Konstruktvalidität und Faktorenstruktur des deutschsprachigen Youth Psychopathic Traits Inventory (YPI) in einer repräsentativen Schulstichprobe. Diagnostica, 62(2), 85-96. doi:10.1026/0012-1924/a000139

Steiner, H., Daniels, W., Stadler, C., & Kelly, M. (2017). Disruptive Behavior: Development, Psychopathology, Crime, and Treatment: Oxford University Press.

Sterzer, P., & Stadler, C. (2009). Neuroimaging of aggressive and violent behaviour in children and adolescents. Frontiers in Behavioral Neuroscience, 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. Biological 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

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 18, 643-662. doi:Doi 10.1037/0096-3445.121.1.15

Swanson, M.C.J., Bland, R.C., Newman, S.C. (1994). Antisocial personality disorders. Acta Psychiatrica Scandinavica, 89(s376), 63-70.

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

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. Journal of the American Academy of Child and Adolescent Psychiatry, 53(4), 456-465 e451. doi:10.1016/j.jaac.2013.12.008

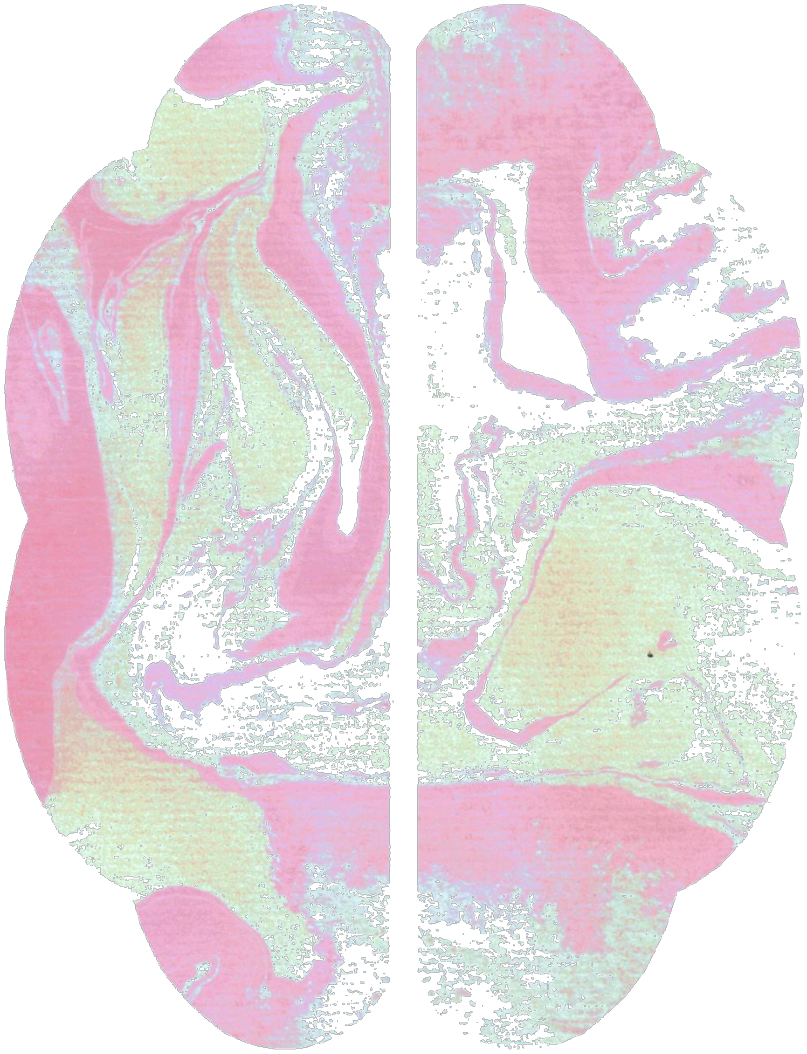
Wang, Frances L, Chassin, Laurie, Lee, Matthew, Haller, Moira, & King, Kevin. (2017). Roles of Response Inhibition and Gene–Environment Interplay in Pathways to Adolescents' Externalizing Problems. Journal of Research on Adolescence 27(2), 258-277.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. Journal of Abnormal Psychology, 118(1), 117-130. doi:10.1037/a0014657

Supplementary material is available in Appendix C.

5 Study 4

Atypical neural correlates during explicit emotion regulation in female youths with conduct disorder



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Abstract submitted to the 73rd Annual Scientific Convention of the Society of Biological Psychiatry (SOBP): Cognitive Neuroscience and Neuroimaging

Background: Conduct disorder (CD) characterized by severe aggressive and antisocial behaviour is commonly associated with emotion regulation deficits, but the associated neural correlates have yet to be investigated.

Methods: We applied whole-brain event-related fMRI during emotion regulation in 60 females with a CD diagnosis (according to DSM-IV guidelines, age range = 14-18 years; *N*=30) and those without (*N*=30). During scanning, participants were asked to look at a negative or neutral image (look_negative/look_neutral) or decrease feelings associated with a negative image (decrease_negative). Each trial was followed by an in-scanner affect rating. fMRI analysis included standard pre-processing steps and random effects analysis according to the GLM. Main regressors of interest were built to assess emotional reactivity (look_negative > look_neutral) and activation or modulation by emotion regulation (decrease_negative >/< look_negative). Results are whole brain FWE-corrected (p<0.05, TFCE).

Results: In-scanner affect ratings confirmed that the stimuli elicited emotional reactivity and all participants regulated their emotions, but emotion regulation success was significantly lower in females with CD compared to TD. Whole-brain findings indicate less neural activation in left angular/temporoparietal and left insula/dorsomedial prefrontal cortex during emotion regulation in female with CD.

Conclusion: We demonstrate for the first time atypical reduced neural response during emotion regulation in limbic and prefrontal regions of females with CD, furthering our understanding of the neural phenotype of CD in females.

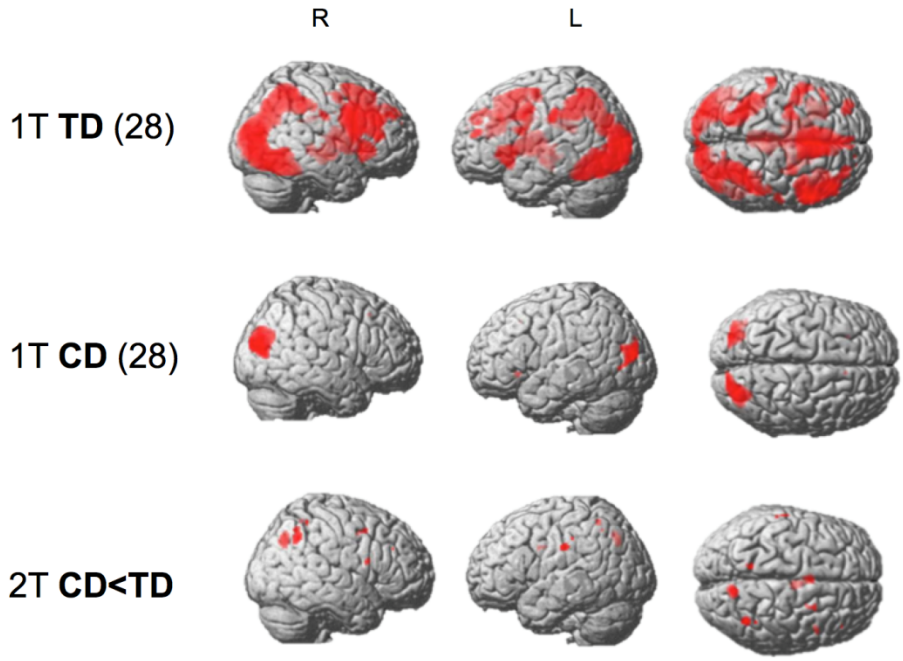

Figure 1. Whole-brain activity for typically developing females (TD), females with conduct disorder (CD), and reduced activity for females with CD compared to TD for emotional reactivity. Displayed at $p<0.001$, FWE corrected.

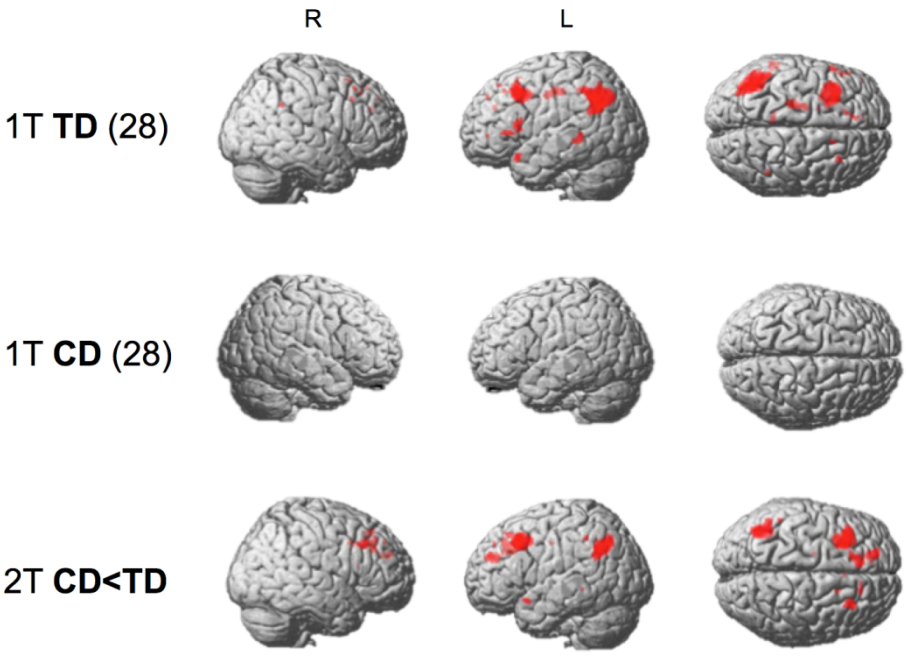

Figure 2. Whole-brain activity for typically developing females (TD), females with conduct disorder (CD), and reduced activity for females with CD compared to TD during cognitive reappraisal. Displayed at $p<0.001$, FWE corrected.

6 Study 5

Emotions and the brain – or how to master “the force”

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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 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).

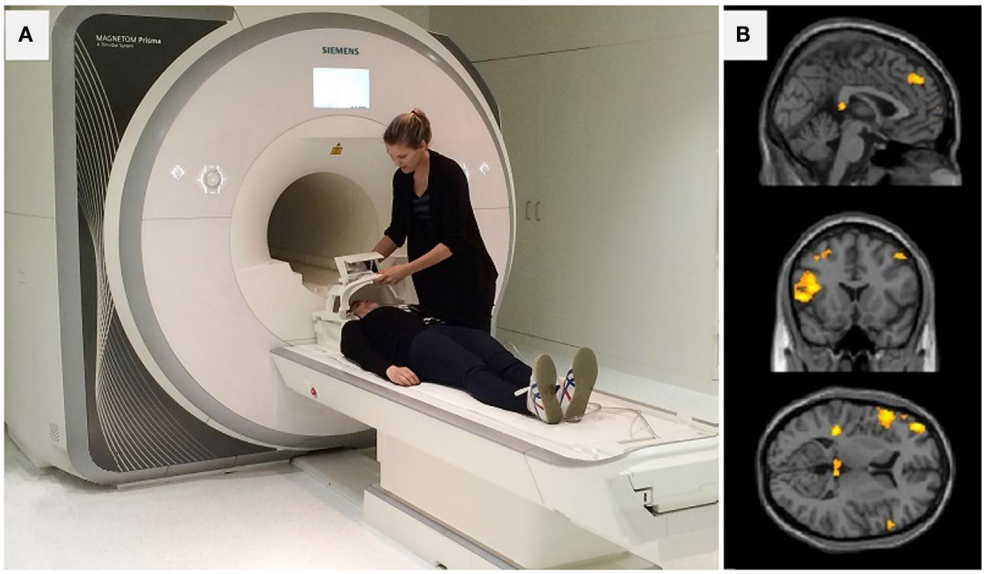

Figure 1. [A] Two of our research team members showing you an MRI camera and how it is used. **[B]** Different views of a child's brain as taken by an MRI camera. The areas that are colored yellow are important for emotion processing and regulation.

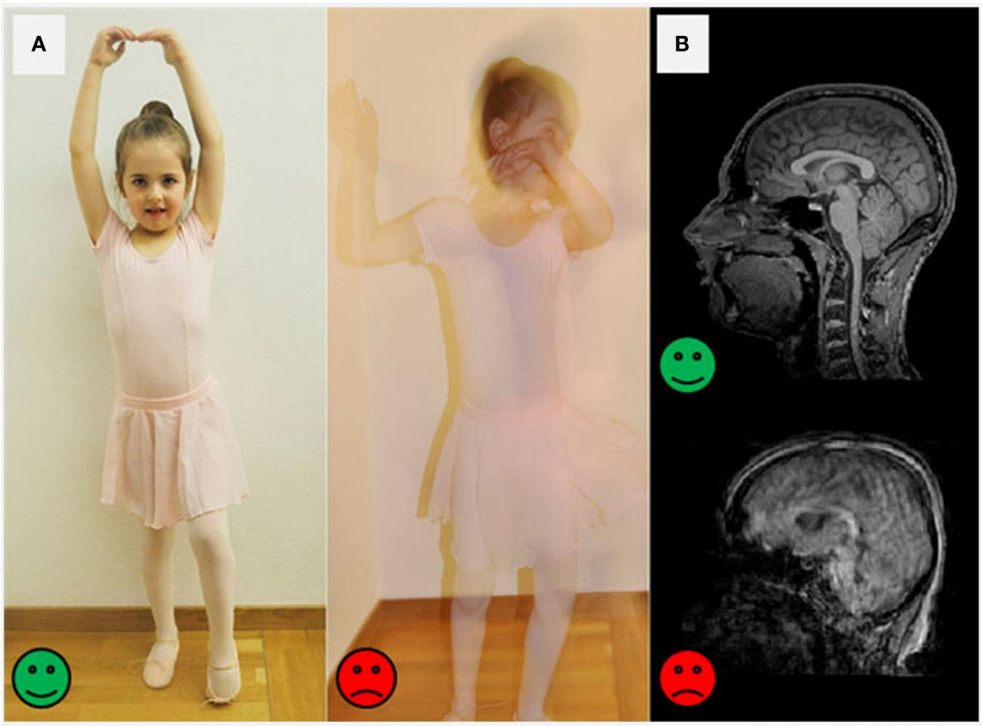

Figure 2. Why staying still during an MRI session is important: **[A]** A picture taken by a regular camera can be very sharp when the person is standing super still (green happy face). But when the person is moving a lot, the picture becomes blurry (red sad face). **[B]** The same is true when taking 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).

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**).

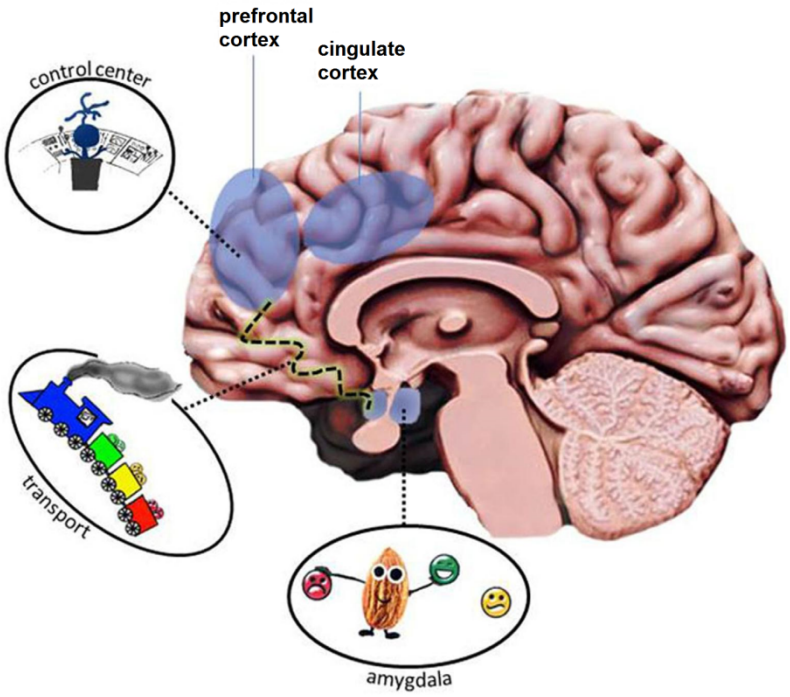

Figure 3. The emotion processing network includes several areas of the brain. Some of these areas are shown here shaded in blue and you can see their different jobs: the amygdala (almond) recognizes and sorts the emotions before transporting them to other areas. In the picture, this transportation is 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”.

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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

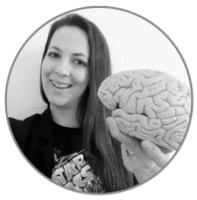
Sterzer, P., Stadler, C., Poustka, F., and Kleinschmidt, A. 2007. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. Neuroimage 37:335–42. doi:10.1016/j.neuroimage.2007.04.043

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.

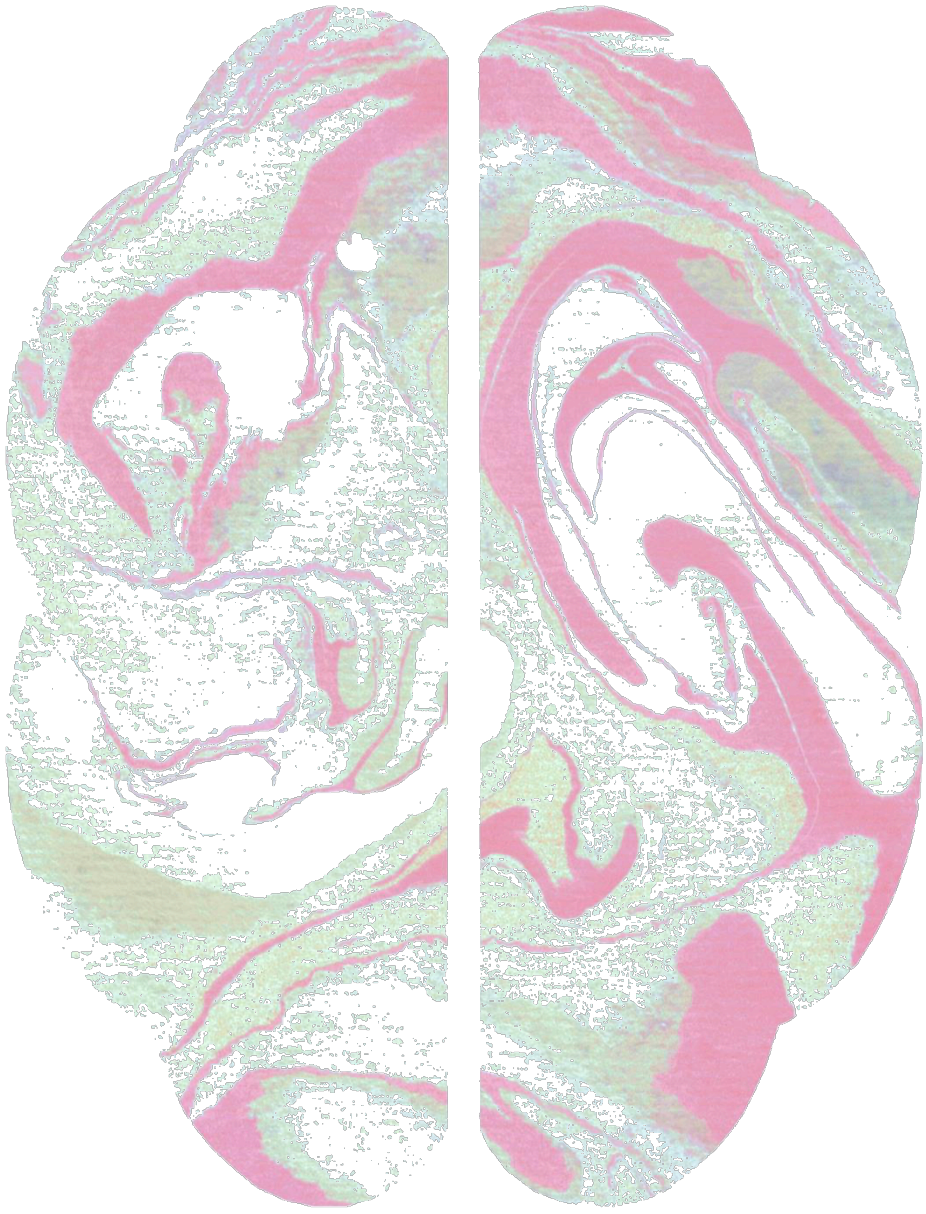
Willeke Martine Menks. I am a biologist from the Netherlands, and I am intrigued by the brain and human behavior. I currently work in Switzerland where I study the brains of children with behavioral problems. With the help of my favorite machine (the MRI scanner), I try to answer difficult questions 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.

7 Study 6

Microstructural white matter alterations in the corpus callosum of girls with conduct disorder



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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 (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).

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

#	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	-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

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.

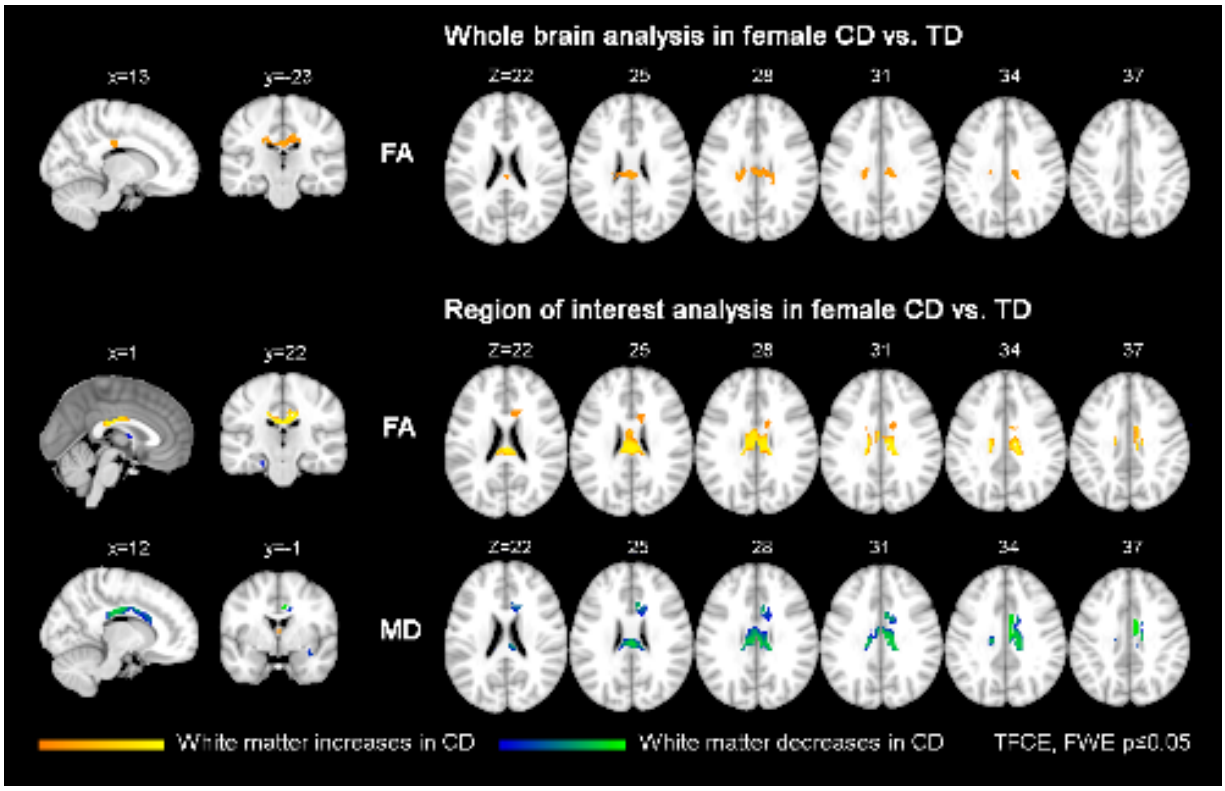


***Figure 1 (top)**. Increased fractional anisotropy (FA) values in the body of the corpus callosum in conduct disorder (CD) girls compared to controls (TD). In a priori defined regions of interest increased FA (**middle**) and mean diffusivity (MD) (**bottom**) alterations in CD were detected in areas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

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).

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

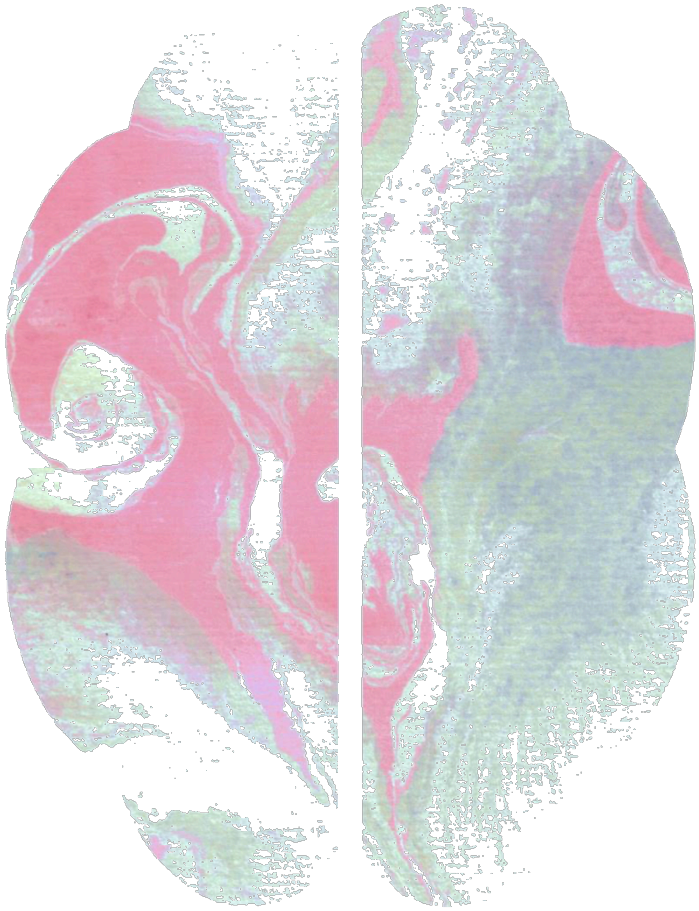
Zhang, J., Gao, J., Shi, H., Huang, B., Wang, X., Situ, W., . . . Yao, S. (2014a). Sex differences of uncinate fasciculus structural connectivity in individuals with conduct disorder. *Biomed Res Int, 2014*, 673165. doi: 10.1155/2014/673165

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 is available in Appendix D.

8 Study 7

Callous-unemotional traits and brain structure: Sex-specific effects in anterior insula of typically-developing youths



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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.

Keywords: Callous-unemotional traits, insula, pediatric neuroimaging, sex differences, voxel-based morphometry.

General scientific summary: This study suggests that callous-unemotional traits have a neuroanatomical correlate within typically developing boys, but not girls. Bilateral anterior insula volume explains up to 19% of the variance in callous-unemotional traits in boys.

Highlights:

- Sex-specific correlations between callous-unemotional (CU) traits and insula volume
- CU-traits are positively linked to anterior insula in typically-developing boys
- Variations in insula volume explained 19% of the variance in CU-traits in boys
- Accounting for sex in neuroanatomical studies of individual differences is important

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Introduction

The term callous-unemotional (CU) traits refers to a pattern of behaviors including a lack of empathy, guilt or remorse, shallow or deficient affect, as well as a lack of concern about the person's actions or one's own and others' feelings (i.e., limited prosocial emotions (American Psychiatric Association 2013)). High levels of CU-traits are often observed in youths with severe aggression and antisocial behavior. Therefore, CU-traits have mostly been studied in children and adolescents with disruptive behavior disorders (DBDs, including oppositional defiant and conduct disorder; (Blair 2013; Frick, et al. 2014c)). 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 (Frick, et al. 2014a; Frick, et al. 2014c; Moffitt, et al. 2008). Devising a meaningful approach to subtyping antisocial behavior has thus been of long-lasting clinical interest (Frick, et al. 2014b). While various approaches have been proposed, separating individuals based on levels of CU-traits is thought to delineate a behaviorally, genetically, and neurobiologically distinct subgroup within antisocial populations ((Barker, et al. 2011; Bezdjian, et al. 2011; Essau, et al. 2006b; Frick, et al. 2003; Rogers and De Brito 2016); for reviews see (Blair 2013; Frick, et al. 2014c; Viding and McCrory 2012). This was likewise recognized within the latest version of the DSM by an additional specifier to the diagnosis of conduct disorder termed *'limited prosocial emotions'* (American Psychiatric Association 2013). Patients qualifying for this specifier (i.e. those with elevated CU-traits) are at high risk for the development of particularly severe, persistent, and treatment-resistant forms of conduct disorder (Frick, et al. 2014c).

While CU-traits have most commonly been studied in DBD populations, there is increasing evidence that CU-traits may be important in community samples without DBDs, and that CU-traits can be elevated in the absence of clinically-significant conduct problems (Fanti, et al. 2013; Frick, et al. 2003; Herpers, et al. 2012; Kumsta, et al. 2012; Rowe, et al. 2010b; Viding and McCrory 2012). CU-traits in youths without DBDs have for example been related to subclinical variations of antisocial behavior, impairments affecting peer relationships, quality of life, hyperactivity and increased risk-taking (Barker, et al. 2011; Frick, et al. 2003; Herpers, et al. 2016; Pardini and Fite 2010); for a review see (Viding and McCrory 2012)). CU-traits in youths with or without conduct problems are highly heritable and may carry independent diagnostic value (Barker, et al. 2011; Frick, et al. 2003; Herpers, et al. 2017; Kumsta, et al. 2012; Rowe, et al. 2010a; Viding and McCrory 2012).

To date, studies investigating the neural correlates of CU-traits have mostly focused on DBD samples. By doing so, functional neuroimaging evidence revealed that among youths with DBD, high levels of CU-traits were associated with reduced brain response during affective processing in several cortical (e.g., anterior insula, anterior cingulate cortices) and subcortical (e.g., amygdala) regions, responsible for empathic behaviours in typically developing youths (Lockwood, et al. 2013; Lozier, et al. 2014; Michalska, et al. 2016). Prefrontal functioning in response to punishment and rewards (e.g. in the caudate and ventromedial prefrontal cortex) has in turn been shown to be increased in DBD, as opposed to a reduction in prefrontal activation typically seen in healthy children and adolescents following punishment learning ((Finger, et al. 2008); for a review see (Viding and McCrory 2017)). Additionally, studies have indicated that the functional connectivity between limbic and prefrontal brain regions, commonly impacted in DBD, was further negatively correlated with callous-unemotional traits (Marsh, et al. 2008), although not all studies were able to replicate this finding (Finger, et al. 2012).

In contrast to functional MRI evidence, the unique associations between CU-traits and brain structure provides mixed findings in regards to the direction and precise location of effects and further investigations in youths with and without conduct problems are needed (Blair 2013; Cohn, et al. 2016). More specifically, 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 (Cohn, et al. 2016; Cope, et al. 2014; De Brito, et al. 2009a; Fairchild, et al. 2013a; Raschle, et al. 2015; Wallace, et al. 2014). Amygdala alterations in correlation with CU-traits are mostly absent (Dalwani, et al. 2011; De Brito, et al. 2009a; Fairchild, et al. 2013a); a modest association was identified by one study reporting a positive association between CU-traits and amygdala gray matter concentration in DBD youths low on CU-traits (Cohn, et al. 2016). Furthermore, a meta-regression study analyzing across five voxel-based morphometry studies on DBDs published to date found that higher CU-traits were associated with a lower reduction in GMV in the putamen and, to a lesser extent, in the right amygdala (Rogers and De Brito 2016).

Overall, structural and functional neuroimaging findings vary with respect to the direction and precise location of the observed associations with CU-traits. This may be due to the choice of assessment tool used, the use of different data analysis packages and strategies, as well as heterogeneity (e.g. differences in demographic and clinical features/diagnoses/comorbidities)

of the groups studied. For example, the mixed nature of previous findings may be related to the various measures employed to assess CU-traits. Research reports have used a range of assessments, such as the Inventory of Callous-Unemotional traits (Essau, et al. 2006a), the Youth Psychopathic traits Inventory (Andershed, et al. 2007), the Psychopathy Checklist: Youth Version (Forth, et al. 2003), or the callous-unemotional scale of the Antisocial Process Screening Device (Frick and Hare 2001) in order to classify participants into those with high versus low CU-traits. Variations in results to date may thus be based on differences in the measure employed, as well as differences between samples in levels of CU-traits which may reflect differences in recruitment sources (e.g., incarcerated offenders versus community samples). In order to maximize reliability of the assessments used to characterize callous-unemotional traits the American Psychiatric Association (American Psychiatric Association 2013) has suggested basing the assessments of limited prosocial emotions or CU-traits on multiple sources of information. However, such comprehensive measures have rarely been implemented in research studies to date.

While all evidence points towards the importance of considering sex as a variable within research designs, the majority of neuroimaging studies, particularly those on CU-traits, focus solely on males (Rogers and De Brito 2016). This may be due to higher levels of crimes, delinquency, or aggressive and antisocial behavior being reported in boys (Loeber, et al. 2013), but nevertheless limits the generalizability of the findings. Longitudinal brain imaging studies in typically developing youths have demonstrated sex-specific differences in brain maturation and cortical trajectories (Giedd and Rapoport 2010; Lenroot, et al. 2007). In fact, cortical and subcortical gray matter development has been suggested to follow an inverted U-shaped pattern with main peaks being reached one to two years earlier in females as compared to males (Lenroot, et al. 2007). Likewise, epidemiologic as well as longitudinal research indicates sex-specific developmental trajectories for neuropsychiatric disorders (Giedd and Rapoport 2010; Moffitt, et al. 2008; Wilke, et al. 2007).

To summarize, the majority of studies to date have only investigated the effects of variation in CU-traits in DBD populations and are thus limited by several factors: (**1**) it remains open whether effects previously attributed to CU-traits were actually driven by the presence of DBDs (i.e., including symptoms and behaviors not associated with CU-traits or common comorbidities such as attention deficit/hyperactivity disorder (ADHD) or anxiety), and also whether associations between CU-traits and brain structure only hold within DBD

populations; (**2**) while epidemiologic as well as longitudinal research indicate sex-specific developmental trajectories for neuropsychiatric disorders (Giedd and Rapoport 2010; Moffitt, et al. 2008), most studies on CU-traits in DBD groups or community samples have focused solely on males, limiting the generalizability of these findings to females; and (**3**) the group classification employed or the measures used to assess CU-traits have varied widely across studies (Essau, et al. 2006a; Kimonis, et al. 2016; Viding and McCrory 2012; Viding and McCrory 2017). These factors, as well as the small samples that have frequently been used, possibly explain the variability in findings reported to date and the lack of replication across studies.

Therefore, the current study aimed at bridging this gap in knowledge resulting from a narrow focus on clinical populations by investigating relationships between CU-traits and brain structure in typically-developing boys and girls without DBDs using whole brain multiple regression analyses. Secondly, we aimed to test whether the association between CU-traits and brain structure differs across boys and girls by including an interaction term for sex and callous-unemotional traits within our multiple regression analysis. Finally, we aimed to implement a comprehensive measure of CU-traits by developing a composite score based on two sources of information (self and others' rating) in order to obtain a robust index for testing for variability in brain structure related to CU-traits. Based on previous evidence in DBD and youths with conduct problems, we expected to find correlations between CU-traits and brain structure in typically-developing youths within limbic and prefrontal brain regions including amygdala, insula, and prefrontal cortex. On the basis of previous findings showing an interaction effect of sex and CU-traits in DBD (Smaragdi, et al. 2017), we expected to observe distinct associations between CU-traits and brain structure in boys and girls.

Method

Participants

For the present analyses, we included 223 typically-developing adolescents (9-18 years), who were a subset of participants from an ongoing European multi-center study investigating female conduct disorder (FemNAT-CD). All adolescents included in the present analyses were explicitly screened to be free of any psychiatric disorder, including DBDs and substance abuse. 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, and the study was 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 included in the present analyses had 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, answered using a three-point Likert scale (Achenbach 1991)). Since we explicitly aimed to study CU-traits in non-aggressive individuals, participants scoring T≥70 on the aggression and/or the delinquency subscales of the CBCL were excluded from our analyses (see **Figure S1**). However, to be even stricter, we also re-ran our analysis with a more stringent criterion (all individuals with a T-score ≤65 on either the delinquency or aggression subscale of the CBCL) and did not observe a change in our main findings. 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 <17 years (WISC-IV, (Petermann and Petermann 2011)) and the Wechsler Adult Intelligence Scale (WAIS-III, (Wechsler 1997)) for sites #01, #02 and #05. All t- and standard scores were first z-transformed prior to any analysis. Empathy scores were measured using the parental report of the Griffith Empathy Measure (GEM: 23 items, answered using a nine-point Likert scale; (Dadds, et al. 2008)).

CU-traits were measured using parent ratings on the Inventory of Callous-Unemotional traits (ICU (Essau, et al. 2006a)) and self-ratings on 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. Reliability values for the ICU lie within the range of acceptable to good (Cronbach alpha range: 0.77-0.89) (Essau, et al. 2006a). 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). Previous 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 aged 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 score 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 found in the present sample. We based CU-traits on multiple sources of information in order to maximize reliability, in line with suggestions by the American Psychiatric Association (American Psychiatric Association 2013). However, it is worth noting 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 correlations between ICU total, YPI callous-unemotional scale and composite CU-traits score and brain structure in separate analyses; and (3) Testing for significant differences between the Cronbach alphas for the old and new CU-traits measures (see **Supplement 2**). The new composite score showed significantly higher internal reliability as compared to the ICU total score or the YPI callous-unemotional dimension. The composite scores were normally distributed and showed sufficient variance to justify a dimensional approach (**Supplement 3**).

ICU and YPI scores, 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 in previous neuroimaging studies (Essau, et al. 2006a; Fairchild, et al. 2013a). Boys scored significantly higher than girls on several subscales of the YPI, ICU or the composite measure as analyzed using two-sample t-tests as implemented in SPSSv23 (IBM Corp., Armonk, N.Y., USA).

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).

Structural image acquisition

Participants completed between one and three functional neuroimaging tasks and/or diffusion tensor imaging scans in addition to structural T1-weighted magnetization prepared rapid gradient echo imaging (MPRAGE) 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 **Table S4).**

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 sex, 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, YPI or ICU subscale data were missing for 16 individuals which were consequently excluded from subsequent analysis. 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. An interaction term for CU-traits and sex was computed by multiplying the z-standardized CU-traits with the dichotomous sex variable. The interaction term between CU-traits and sex was then entered as a covariate within the multiple regression model. Scanning site, age and TIV were added as covariates of no interest and statistics were conducted for gray matter volume only. F-tests were used to assess the main effect of CU-traits and the interaction between CU-traits and sex. Multiple regression analyses in each sex individually were subsequently used to further specify the direction of the results observed. The implemented t-tests were masked for the regions identified through the main analysis. Whole brain results are reported with a $p<0.05$, family-wise error (FWE) correction, using the Threshold-Free Cluster Enhancement technique (TFCE according to (Smith and Nichols 2009) with 10,000 permutations).

Results

Voxel-based morphometry results.

Total intracranial volume was calculated for use as a covariate within the multiple regression analysis of absolute brain 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]). In line with previous findings (e.g. (Giedd and Rapoport 2010)), girls and boys significantly differed in total intracranial volume (for TIV, GM and WM; all $p<0.001$).

Multiple regression analysis across the whole sample.

Across all girls and boys (N=189), there were no significant positive or negative correlations between CU-traits and gray matter volume. However, there was a significant interaction effect for sex and CU-traits in bilateral clusters encompassing anterior insula, claustrum and inferior frontal gyrus (p<0.05; FWE TFCE corrected; see **Figure 1**). In order to assess the direction of this interaction effect further, we performed follow-up analyses in boys and girls individually, with a restricted analysis mask for left and right anterior insula based on the significant clusters identified through the interaction effects across the whole sample.

Multiple regression analysis in boys. For boys, CU-traits were significantly positively correlated with gray matter volume of the previously identified bilateral anterior insular cortices (p<0.05; FWE TFCE corrected; see **Table 2 and Figure 1**).

Table 2. Montreal Neurological Institute neuroanatomical coordinates, cluster size and p-scores representing the peak coordinates for significant interaction effects in all youths and positive associations between callous-unemotional traits and gray matter volume in typically-developing boys, but not girls (p<0.05; FWE TFCE corrected).

		k	MNI coordinates			*p*
			x	y	z	(FWE)
Interaction: callous-unemotional traits x sex						
L insula, claustrum, inferior frontal gyrus		644	-26	22	8	0.003
R insula, claustrum, inferior frontal gyrus		161	28	21	2	0.001
	Direction					
Masked post-hoc analysis in boys (N=81)						
L insula, claustrum, inferior frontal gyrus	*positive*	644	-28	22	3	<0.001
R insula, claustrum, inferior frontal gyrus	*positive*	161	30	21	0	<0.001
Masked post-hoc analysis in females (N=108)						
ns		-	-	-	-	-

k=cluster size; R=right; L=left; ns=no significance

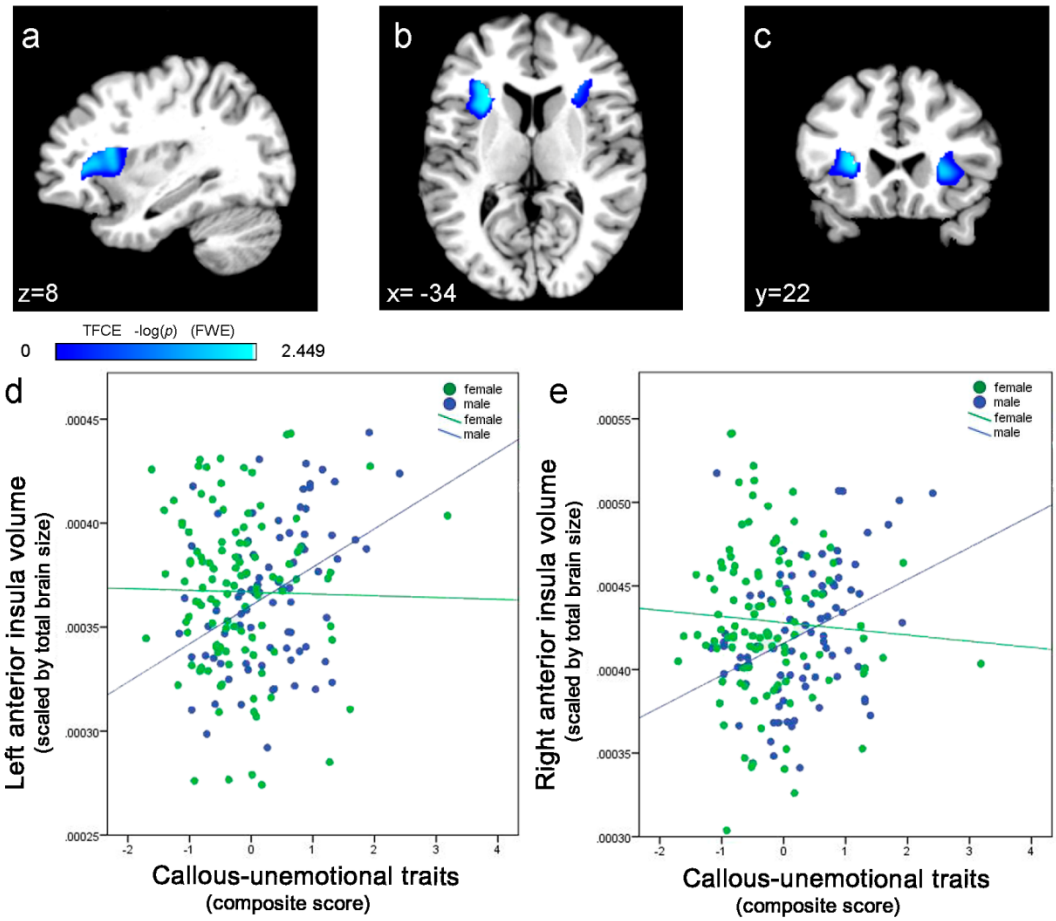

Figure 1. Statistical parametric maps showing a significant positive correlation between callous-unemotional traits and bilateral anterior insula volume in boys (in blue; displayed a=axial, b=sagittal, c=coronal views using the Multi-image Analysis GUI, available at http://ric.uthscsa.edu/mango/mango.html;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

Multiple regression analysis in girls. Within females, there were no significant positive or negative correlations between CU-traits and gray matter volume when restricting the multiple regression model to the bilateral anterior insula as identified by our interaction analysis.

The robustness of the here observed significant interaction effect between CU-traits and sex within bilateral anterior insula across the whole group was further tested by accounting for aggressive behavior. Our results remained significant when a covariate based on scores from the CBCL aggression subscale were added into our multiple regression analysis. Additionally, we assessed a sex-matched group (81:81), excluding participants from centre #5 (only female participants). The analysis resulted in a similar outcome of an interaction effect in bilateral

anterior insula at an uncorrected $p<0.001$ (only left anterior insula remained significant for this group at $p<0.05$; FWE TFCE corrected).

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 v-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 average 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 three post-hoc aims, namely: (**1)** Investigate the specific CU-traits-bilateral insula associations for boys and girls separately; (**2)** Investigate the amount of variance in CU-traits accounted for by variations in bilateral insula volume in boys, as was done previously in adult studies (Cope, et al. 2014; Ermer, et al. 2013); and (**3**) Investigate potential age effects on the bilateral insula findings in boys. Post-hoc results revealed significant positive correlations between left and right insula volumes and CU-traits in boys (**Figure 1d-e**). Although no significant correlations between CU-traits and anterior insula volumes were observed in our whole brain analysis in girls, additional post-hoc region of interest-based analysis were conducted for anatomically defined bilateral anterior insula in order to further evaluate and confirm this null relationship. These findings indicated a trend towards an opposite (negative) association between insular volume and CU-traits in girls, which did not reach formal levels of statistical significance. Additionally, we statistically examined whether the regressions (correlation between CU-traits and left and right anterior insula for boys and girls) significantly differed from each other by calculating Fisher's z (Diedenhofen and Musch 2015). For both left ($z = -3.54$, $p= 0.0004$) and right ($z = -4.38$, $p < 0.0001$) anterior insula, the slopes significantly differed across boys and girls. Secondly, 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 covariates, reached significance ($p<0.001$) and indicated that variations in bilateral anterior volume explained 19.4% of the variance in CU-traits. Finally, within our multiple regression model, we showed that age did not explain any additional variance in bilateral insula volume findings in boys (significant F-change=0.148). This effect was further investigated using an F-test within the multiple regression model in

SPM, plotting positive and/or negative effects of age on bilateral anterior insula volume shown to be associated with CU-traits in boys. No significant effects of age on associations between CU-traits and anterior insula volume were observed.

Discussion

In a sample of typically-developing community boys and girls, we show for the first time that callous-unemotional (CU) traits were correlated with the volume of the anterior insula, independent of disruptive behavior disorders (DBDs). This association was sex-specific, with CU-traits showing a significant positive correlation with bilateral anterior insula volume in boys alone. 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 (Cope, et al. 2014; Ermer, et al. 2013). The present study generated a composite CU-trait score based on multiple sources of information (i.e. self and parent-report). In line with previous authors before and according to psychometric evaluations (American Psychiatric Association 2013; Essau, et al. 2006a), we consider this a potential strength. However, we acknowledge that comparability with previous findings may be impacted as a result of using a newly generated measure of CU-traits..

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 correlation between CU-traits and brain structure observed here was strongest in bilateral anterior insula extending to the inferior frontal gyrus. The anterior insula has consistently been linked to emotion processing and empathy, and is activated in fMRI studies tapping these domains; it has additionally been associated with cognitive control mechanisms (Fan, et al. 2011; Phan, et al. 2002; Sundermann and Pfleiderer 2012).

Past research has revealed structural and functional alterations in the anterior insula of individuals with DBDs (Blair 2013; Cohn, et al. 2013; Fahim, et al. 2011; Raschle, et al. 2015; Rogers and De Brito 2016; Sterzer, et al. 2007). Thereby, functional neuroimaging has linked atypical empathic responding, emotional learning and decision-making to the anterior

insula (Blair 2013; Lockwood, et al. 2013; Michalska, et al. 2016; White, et al. 2012; White, et al. 2016). In DBDs high levels of CU-traits are further positively correlated with the amount neural reduction in limbic areas during affective processing and are considered reflective of a diminished empathy for pain (Lockwood, et al. 2013; Michalska, et al. 2016; Viding and McCrory 2017). However, atypical neural correlates in DBD during reinforcement learning which also implicate insular cortex, have not identified the same (or any) further association based on CU-traits (White, et al. 2012; White, et al. 2016). This may indicate that in DBD impaired insula functioning during affective processing (e.g., (Lockwood, et al. 2013; Michalska, et al. 2016)), but not reinforcement learning is further associated with variations in CU-traits (White, et al. 2012; White, et al. 2016); for a review see (Viding and McCrory 2017)). The association between CU-traits and brain anatomy is still matter of investigations. For example one study reported increases in insular cortex gray matter volume in DBD youths with high CU-traits (De Brito, et al. 2009a), others found a negative correlation between anterior insula volume or concentration and CU-traits in at-risk youths (Cohn, et al. 2013) or DBD girls (Fairchild, et al. 2013a), but the association in the latter study remained non-significant after correcting for CD symptoms (Fairchild, et al. 2013a).

Differences in reports of increased or decreased gray matter in anterior insula in community samples of boys, or boys as compared to girls, with elevated 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 support this hypothesis (Giedd and Rapoport 2010). However, comparability to studies in DBD is complicated since the developmental trajectories between groups of children with and without psychiatric diagnosis may likewise differ (Giedd and Rapoport 2010). Our findings of a positive association between CU-traits and brain structure in boys diverge from studies in DBD that have suggested a negative association between CU-traits and insula volume (i.e. see meta-analysis by (Rogers and De Brito 2016)) or aggression scores and insula volume across both CD and control participants (Sterzer, et al. 2007). This could suggest that the association between CU-traits and brain structure follows a different trajectory in typically-developing youths as compared to those with DBDs. However, differences may also be based on group selection (number of participants, clinical criteria, age, sex-ratio) or construct employed (e.g. measuring CU-traits versus empathy more specifically).

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

We found no significant relationships between CU-traits and gray matter volume in a large sample of girls (N=108). Sex differences in insula structure and function, as well as sex differences in gray matter volume developmental trajectories, as mentioned above, may provide an explanation for this finding (Giedd and Rapoport 2010; Lenroot, et al. 2007). Furthermore, studies investigating the impact of CU-traits in DBD populations have almost exclusively focused on males, and therefore have not allowed 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 apply as well to females (Rogstad and Rogers 2008). We suggest that the fact that did not observe a significant association between CU traits and gray matter volume does not result from measurement issues since the variance in the separate CU-traits subscores are similar within each sex. 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 focus on including and comparing both sexes in order to enhance our understanding of sex differences and apply this information to the study of neurodevelopmental and psychiatric disorders (i.e., DBDs), even if these are more prevalent in males. Ultimately, large-scale longitudinal studies are needed in order to answer the question whether the neuroanatomical differences observed here are of a developmental (e.g. through a time-specific shift in the cortical growth curve of boys and girls) or a fundamental nature (e.g. present across development).

Study limitations

This study had several limitations that should be considered when interpreting the results. First, while multicenter neuroimaging studies do offer considerable advantages in terms of increased sensitivity by including a higher number of participants, they also introduce challenges of inter-site variability which may introduce additional noise and potential systematic errors unless this factor is carefully controlled for (Chen, et al. 2014; Takao, et al. 2014). For example, Takao and colleagues (2014) demonstrate the importance of balanced case and control ratios within structural multicenter neuroimaging analyses by discussing the example of sex differences (Takao, et al. 2014). We cannot fully exclude the possibility that remaining site differences and/or variations in the distribution of CU-traits across sexes have influenced our findings. Furthermore, 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) has or have contributed to the results. For example, in a study comparing youth with conduct disorder and controls, cortical thickness and folding deficits were demonstrated to localize to different (posterior versus anterior) brain structures (Hyatt, et al. 2012). However, an advantage of using a voxel-based morphometry approach is to increase the comparability with past studies. It is also notable that while we assured that the identified insula findings in boys were not influenced by age within the range included, future studies will need to assess more complex issues related to development, which could not be answered using the present sample (e.g. stability of the observed associations across age). Finally, while we have ensured that CU-traits are normally distributed within our sample, thereby allowing us to adopt a dimensional approach, the scores reported here are representative of a community sample and substantially lower than mean CU-traits scores reported in youths with conduct problems (e.g. (Fairchild, et al. 2013a; Marsh, et al. 2008)). While we here demonstrate sex-specific effects of CU traits in typically-developing boys and girls, we note that any comparisons between the present study and the existing literature on DBDs are limited by not including boys and girls with DBDs and varying levels of callous-unemotional traits.

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 to understanding 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 (Garvey, et al. 2016). While our findings of sex-specific positive effects between insula gray matter volume and CU-traits in typically-developing boys but not girls are somewhat surprising given previous opposite findings in DBD boys or mixed gender samples (Lockwood, et al. 2013; Lozier, et al. 2014; Marsh, et al. 2008) or positive findings in DBD girls (Fairchild, et al. 2013a), it is mentionable that the direction of findings across prior studies varies (i.e. increases versus decreases of neural functioning or gray matter volume (e.g. (De Brito, et al. 2009b))). This may indicate a different relationship between CU-traits and brain structures in

typically-developing youths relative to findings obtained in DBD youth. Interestingly, 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, levels of CD symptoms (Cohn, et al. 2016). The study may be interpreted in line with the present analysis in typically developing youths who were deliberately selected to be low in or free of conduct problems and DBD symptoms. However, it is to mention that in the study by Cohn and colleagues (2016) even youths low on CU-traits were childhood arrestees before the age of 12.

Another point to consider is that while CU-traits designate a risk factor for the development of serious conduct problems (e.g., (Frick, et al. 2014a)), the stability of these traits over time is less clear. More specifically, longitudinal research demonstrates that while children high in psychopathic traits at around age 13 have a higher chance to display high psychopathy scores in adulthood, only 9% of the variance in adulthood was actually explained by scores at age 13 (Lynam, et al. 2007). Thus, while high levels of CU-traits may be a risk factor for negative outcomes in some children, they may not remain high over time, and a significant proportion of those with elevated scores will not develop clinically relevant difficulties, such as conduct disorder. In the present analysis, CU-traits were positively associated with bilateral anterior insula volume in boys. While this may be indicative of a heightened risk to develop conduct problems later in life, it is notable that none of the boys had elevated levels of conduct problems or DBD diagnoses at the time of assessment. It is also likely that many of them will not go on to show such difficulties.

Assuming that the present structural variations relate to insula functioning, our findings may be interpreted as consistent with theories implicating atypical insula functioning in populations with CU-traits or antisocial features. However, it remains to be investigated whether variations in CU-traits and insula structure may serve as a potential risk factor for the development of future clinical, social, and psychological problems. However, alterations in brain structure alone may only be a latent or probabilistic risk factor, which, without an environmental trigger, may never manifest as psychopathology (see also (Fairchild, et al. 2013b)).

Future studies will need to examine the relationship between CU-traits and brain structure, not only in typically-developing individuals, but across the whole spectrum, which includes at-

risk children or those with DBDs. By doing so, large-scale neuroimaging studies should investigate whether the structural variations accompanying CU-traits in boys, as identified here, are individually, or in combination with further environmental variables, predictive of 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., S. Hodgins, and A. Tengstrom
2007 Convergent validity of the Youth Psychopathic Traits Inventory (YPI): association with the Psychopathy Checklist: Youth Version (PCL:YV). Assessment 14(2):144-54.

Barker, E. D., et al.
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(8):878-88.

Bezdjian, S, et al.
2011 Psychopathic personality in children: genetic and environmental contributions. Psychological medicine 41(3):589-600.

Blair, R. J.
2013 The neurobiology of psychopathic traits in youths. Nat Rev Neurosci 14(11):786-99.

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

Chang, L. J., et al.
2013 Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb Cortex 23(3):739-49.

Chen, C. C., et al.
2004 Quality assurance of clinical MRI scanners using ACR MRI phantom: Preliminary results. Journal of Digital Imaging 17(4):279-284.

Chen, J., et al.
2014 Exploration of scanning effects in multi-site structural MRI studies. J Neurosci Methods 230:37-50.

Cohn, M. D., 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 254:180-7.

Cohn, MD, et al.
2013 Fear conditioning, persistence of disruptive behavior and psychopathic traits: an fMRI study. Translational psychiatry 3(10):e319.

Cope, L. M., et al.
2014 Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits. J Abnorm Child Psychol 42(4):659-68.

Cosgrove, K. P., C. M. Mazure, and J. K. Staley
2007 Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol Psychiatry 62(8):847-55.

Dadds, Mark R, et al.
2008 A measure of cognitive and affective empathy in children using parent ratings. Child psychiatry and human development 39(2):111-122.

Dalwani, M., et al.
2011 Reduced cortical gray matter volume in male adolescents with substance and conduct problems. Drug Alcohol Depend 118(2-3):295-305.

De Brito, S. A., et al.
2009a Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. Brain 132(Pt 4):843-52.

Diedenhofen, Birk, and Jochen Musch
2015 cocor: A comprehensive solution for the statistical comparison of correlations. PloS one 10(4):e0121945.

Ermer, E., et al.
2013 Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits. J Am Acad Child Adolesc Psychiatry 52(1):94-103 e3.

Essau, C. A., S. Sasagawa, and P. J. Frick
2006a Callous-unemotional traits in a community sample of adolescents. Assessment 13(4):454-69.

Fahim, C., et al.
2011 Neuroanatomy of childhood disruptive behavior disorders. Aggress Behav 37(4):326-37.

Fairchild, G., et al.
2013a Brain structure abnormalities in adolescent girls with conduct disorder. J Child Psychol Psychiatry 54(1):86-95.

Fairchild, Graeme, et al.
2013b Research review: evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. Journal of Child Psychology and Psychiatry 54(9):924-940.

Fan, Y., et al.
2011 Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neuroscience and Biobehavioral Reviews 35(3):903-911.

Fanti, K. A., C. A. Demetriou, and E. R. Kimonis
2013 Variants of Callous-Unemotional Conduct Problems in a Community Sample of Adolescents. Journal of Youth and Adolescence 42(7):964-979.

Finger, E. C., et al.
2008 Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. Arch Gen Psychiatry 65(5):586-94.

Finger, E. C., 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(3):239-44.

Forth, Adelle E, David S Kosson, and Robert D Hare
2003 Hare psychopathy checklist: Youth version: Multi-Health Systems.

Frick, P. J., et al.
2003 Callous-unemotional traits and developmental pathways to severe conduct problems. Dev Psychol 39(2):246-60.

Frick, P. J., et al.
2014a Annual Research Review: A developmental psychopathology approach to understanding callous-unemotional traits in children and adolescents with serious conduct problems. Journal of Child Psychology and Psychiatry 55(6):532-548.

Frickm P. J., et al.
2014b Can callous-unemotional traits enhance the understanding, diagnosis, and treatment of serious conduct problems in children and adolescents? A comprehensive review. Psychol Bull 140(1):1-57.

Frick, P.J., and R.D. Hare
2001 Antisocial Process Screening Device: APSD: Multi-Health Systems.

Garvey, Marjorie, Shelli Avenevoli, and Kathleen Anderson
2016 The national institute of mental health research domain criteria and clinical research in child and adolescent psychiatry. Journal of the American Academy of Child & Adolescent Psychiatry 55(2):93-98.

Giedd, J. N., and J. L. Rapoport
2010 Structural MRI of pediatric brain development: what

have we learned and where are we going? Neuron 67(5):728-34.

Herpers, P. C. M., et al.
2016 Associations between high callous-unemotional traits and quality of life across youths with non-conduct disorder diagnoses. European Child & Adolescent Psychiatry 25(5):547-555.

Herpers, P. C. M., et al.
2017 Taxometric analyses and predictive accuracy of callous-unemotional traits regarding quality of life and behavior problems in non-conduct disorder diagnoses. Psychiatry Research 253:351-359.

Herpers, P. C. M., et al.
2012 Callous-unemotional traits as a cross-disorders construct. Social Psychiatry and Psychiatric Epidemiology 47(12):2045-2064.

Hyatt, C. J., E. Haney-Caron, and M. C. Stevens
2012 Cortical thickness and folding deficits in conduct-disordered adolescents. Biol Psychiatry 72(3):207-14.

Kaufman, J., 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(7):980-8.

Kimonis, E. R., et al.
2016 Can Callous-Unemotional Traits be Reliably Measured in Preschoolers? Journal of Abnormal Child Psychology 44(4):625-638.

Kumsta, R., E. Sonuga-Barke, and M. Rutter
2012 Adolescent callous-unemotional traits and conduct disorder in adoptees exposed to severe early deprivation. Br J Psychiatry 200(3):197-201.

Lenroot, R. K., et al.
2007 Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36(4):1065-73.

Lockwood, Patricia L, et al.
2013 Association of callous traits with reduced neural response to others' pain in children with conduct problems. Current Biology 23(10):901-905.

Loeber, Rolf, Deborah M. Capaldi, and Elizabeth Costello
2013 Gender and the Development of Aggression, Disruptive Behavior, and Delinquency from Childhood to Early Adulthood. In Disruptive Behavior Disorders. H.P. Tolan and L.B. Leventhal, eds. Pp. 137-160. New York, NY: Springer New York.

Lozier, L. M., et al.
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.

Lynam, D. R., et al.
2007 Longitudinal evidence that psychopathy scores in early adolescence predict adult psychopathy. Journal of Abnormal Psychology 116(1):155-165.

Marsh, A. A., 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(6):712-20.

Michalska, Kalina J, Thomas A Zeffiro, and Jean Decety
2016 Brain response to viewing others being harmed in children with conduct disorder symptoms. Journal of child psychology and psychiatry 57(4):510-519.

Moffitt, T. E., et al.
2008 Research review: DSM-V conduct disorder: research needs for an evidence base. J Child Psychol Psychiatry 49(1):3-33.

Panizzon, M. S., et al.
2009 Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19(11):2728-35.

Pardini, Dustin A, and Paula J Fite
2010 Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial maladjustment in boys: advancing an evidence base for DSM-V. Journal of the American Academy of Child & Adolescent Psychiatry 49(11):1134-1144.

Petermann, Franz, and Ulrike Petermann
2011 Wechsler Intelligence Scale for Children®–Fourth Edition.

Phan, K. L., et al.
2002 Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16(2):331-48.

Raschle, N. M., et al.
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.

Rogers, J. C., and S. A. De Brito
2016 Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. JAMA Psychiatry 73(1):64-72.

Rogstad, J. E., and R. Rogers
2008 Gender differences in contributions of emotion to psychopathy and antisocial personality disorder. Clin Psychol Rev 28(8):1472-84.

Rottschy, C., et al.
2012 Modelling neural correlates of working memory: a coordinate-based meta-analysis. Neuroimage 60(1):830-46.

Rowe, R., et al.
2010a The role of callous and unemotional traits in the diagnosis of conduct disorder. J Child Psychol Psychiatry 51(6):688-95.

Rowe, Richard, et al.
2010b The role of callous and unemotional traits in the diagnosis of conduct disorder. Journal of Child Psychology and Psychiatry 51(6):688-695.

Smaragdi, A., et al.
2017 Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents. J Am Acad Child Adolesc Psychiatry 56(8):703-712.

Smith, S. M., and T. E. Nichols
2009 Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44(1):83-98.

Sterzer, P., et al.
2007 A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. Neuroimage 37(1):335-42.

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

Takao, H., N. Hayashi, and K. Ohtomo
2014 Effects of study design in multi-scanner voxel-based morphometry studies. Neuroimage 84:133-40.

van Baardewijk, Y., et al.
2008 Measuring psychopathic traits in children through self-report. The development of the Youth Psychopathic traits Inventory-Child Version. International Journal of Law and Psychiatry 31(3):199-209.

Viding, E., and E. J. McCrory
2012 Why should we care about measuring callous-unemotional traits in children? Br J Psychiatry 200(3):177-8.

Viding, E., and E. J. McCrory
2017 Understanding the development of psychopathy: progress and challenges. Psychol Med:1-12.

Wallace, G. L., et al.
2014 Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. J Am Acad Child Adolesc Psychiatry 53(4):456-65 e1.

Wechsler, David
1997 WAIS-III: Wechsler adult intelligence scale: Psychological Corporation.

Wechsler, David
1999 Wechsler abbreviated scale of intelligence: Psychological Corporation.

White, S. F., 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(7):750-8.

White, S. F., 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(8):938-46.
Wilke, M., et al.
2008 Template-O-Matic: a toolbox for creating customized pediatric templates. Neuroimage 41(3):903-13.
Wilke, M., I. Krageloh-Mann, and S. K. Holland
2007 Global and local development of gray and white matter volume in normal children and adolescents. Experimental Brain Research 178(3):296-307.

Supplementary material is available in Appendix E.

9 General discussion

Past research has revealed behavioral and neuronal alterations in children and adolescents with CD. However, many of the underlying mechanisms of this disorder are yet to be determined. The present dissertation aimed at investigating the in-depth neuronal and behavioral underpinnings of emotion processing and regulation in children and adolescents with a diagnosis of CD. We initially conducted a systematic literature research and ALE meta-analysis in order to determine the state of research on the functional and structural brain correlates of adolescents with aggressive behavior. Next, we designed an affective Stroop task suitable for a paediatric population in order to investigate implicit emotion regulation by emotion-cognition interaction, and validated the task in a sample of adult participants. We then applied the affective Stroop task to children and adolescents with CD, revealing functional atypicalities in CD compared to typically developing adolescents. In a separate study we investigated the neuronal basis of explicit emotion regulation by cognitive reappraisal in female adolescents with CD. Additionally, we translated the results of our meta-analysis on aggressive behavior, neuroimaging methods, and scientific procedure to the general public, we investigated white matter alterations in the corpus callosum in female CD, and we examined the structural correlates of CU traits in typically developing adolescents.

The first aim of our work was to determine the neuronal signature of children and adolescents with aggressive behavior with the use of a coordinate-based ALE meta-analysis approach. Our analysis revealed 19 structural and eight functional foci of alterations within areas responsible for emotion processing and regulation. More specifically, the network included orbitofrontal, dorsomedial prefrontal, and limbic cortices of the brain. Examining the exact locations where functional and structural analyses co-localize (conjunction analysis) revealed significant foci in right dorsomedial prefrontal cortex and left insula (**study 1**). Our results provide an in-depth picture of previous literature reporting alterations in emotion processing brain regions in aggressive adolescents encompassing the orbitofrontal and prefrontal cortex (Blair, 2010b; Fairchild et al., 2014; Lotze, Veit, Anders, & Birbaumer, 2007), insula (Decety, Skelly, & Kiehl, 2013; Lockwood et al., 2013; Michalska, Zeffiro, & Decety, 2016), cingulate cortex (Marsh et al., 2013; Stadler et al., 2007), and amygdala (Marsh et al., 2008; Sterzer et al., 2005).

The second and third aims of this dissertation were to develop and implement a functional neuroimaging task design assessing implicit emotion regulation by emotion-cognition

interaction. This task was likewise required to be suitable for children and adolescents (including those with a psychiatric condition, such as CD). For this purpose, we adapted an affective Stroop task which was used to investigate implicit emotion-cognition interaction in healthy adults by Hart and colleagues (2010). Using a sample of 30 young adults we aimed at validating the task design and re-evaluating previous neuronal findings in healthy adults. We detected emotion-related activity in brain areas responsible for emotion processing, namely the amygdala, insula, and precentral gyrus, and cognition-related activity in left precentral regions, superior frontal cortex, temporal lobe, and insula. Moreover, we found neuronal decreases in left amygdala, right insula, and right precentral gyrus with increasing cognitive load. We concluded that emotion and cognition-related processes are tightly linked with each other as indicated by shared neuronal networks, and that increased cognitive load of a task can lead to a downregulation of emotion-related brain activation in various regions of the brain (**study 2**). Our findings overlap with previous evidence indicating an attenuation of brain activity in response to emotional stimuli with increasing cognitive load (Blair et al., 2007; Hart et al., 2010) and shared neuronal networks for emotion and cognitive processing (Okon-Singer, Hendler, Pessoa, & Shackman, 2015; Pessoa, 2015).

The second study employing the affective Stroop task aimed at exploring the neuronal activity during implicit emotion regulation in adolescents with CD. For this purpose, we compared the neuronal activation in response to implicit emotion-cognition interaction of 39 adolescents with CD with 39 typically developing peers. In line with previous literature (Blair et al., 2007; Hart et al., 2010; Hwang et al., 2014) typically developing adolescents showed a downregulation of emotion-related amygdala activity during task performance. Adolescents with CD, however, demonstrated a similar amount of amygdala activity whether or not a task was presented after emotion stimulation and, therefore, no such downregulation. We hypothesize that this reflects a disruption of typically observed emotion-cognition regulatory processes. We moreover reported decreased neuronal activity in adolescents with CD in areas including the dorsoanterior and posterior insula (responsible for response inhibition and social information processing), and increased activity in the ventroanterior insula (involved in affective processing) during performance of the affective Stroop task (**study 3**).

As a fourth aim of our work, we aimed at investigating the neuronal correlates of explicit emotion regulation by cognitive reappraisal in females with CD. We included 30 females with and 29 females without CD and detected decreased neuronal activation within left insula/dorsolateral frontal cortex, and left temporoparietal regions (angular gyrus) in

adolescents with CD during cognitive reappraisal (**study 4**). We here provide first evidence for atypical neuronal responses in prefrontal and limbic brain regions during cognitive reappraisal in females with CD.

9.1 Neuronal correlates of emotion processing and regulation in conduct disorder

During this dissertation work, we have furthered our understanding of the neuronal correlates of implicit and explicit emotion regulation in healthy young adults and in particular children and adolescents with CD. Furthermore, we have expanded current knowledge on the altered neuronal networks involved in emotion processing in aggressive behavior.

Across our studies, we have consistently detected altered neuronal activity in the insula, amygdala, and frontal cortices in adolescents with CD and aggressive behavior. In line with our findings, previous literature has indicated an involvement of these brain regions in emotion processing and emotion regulation (Baker et al., 2015). We here emphasize the relevance of prefrontal and limbic cortices in tasks involving both emotion and cognition, and brain alterations thereof in CD and aggressive behavior. We especially highlight that brain areas responsible for emotion and cognitive processing cannot be strictly separated but rather form a conjoint network, reflecting their dynamic interplay (Okon-Singer et al., 2015; Pessoa, 2015). **Figure 1** shows the areas in which we consistently found typical and atypical activation patterns during emotion processing and implicit/explicit emotion regulation across our studies, which are further discussed in the upcoming section.

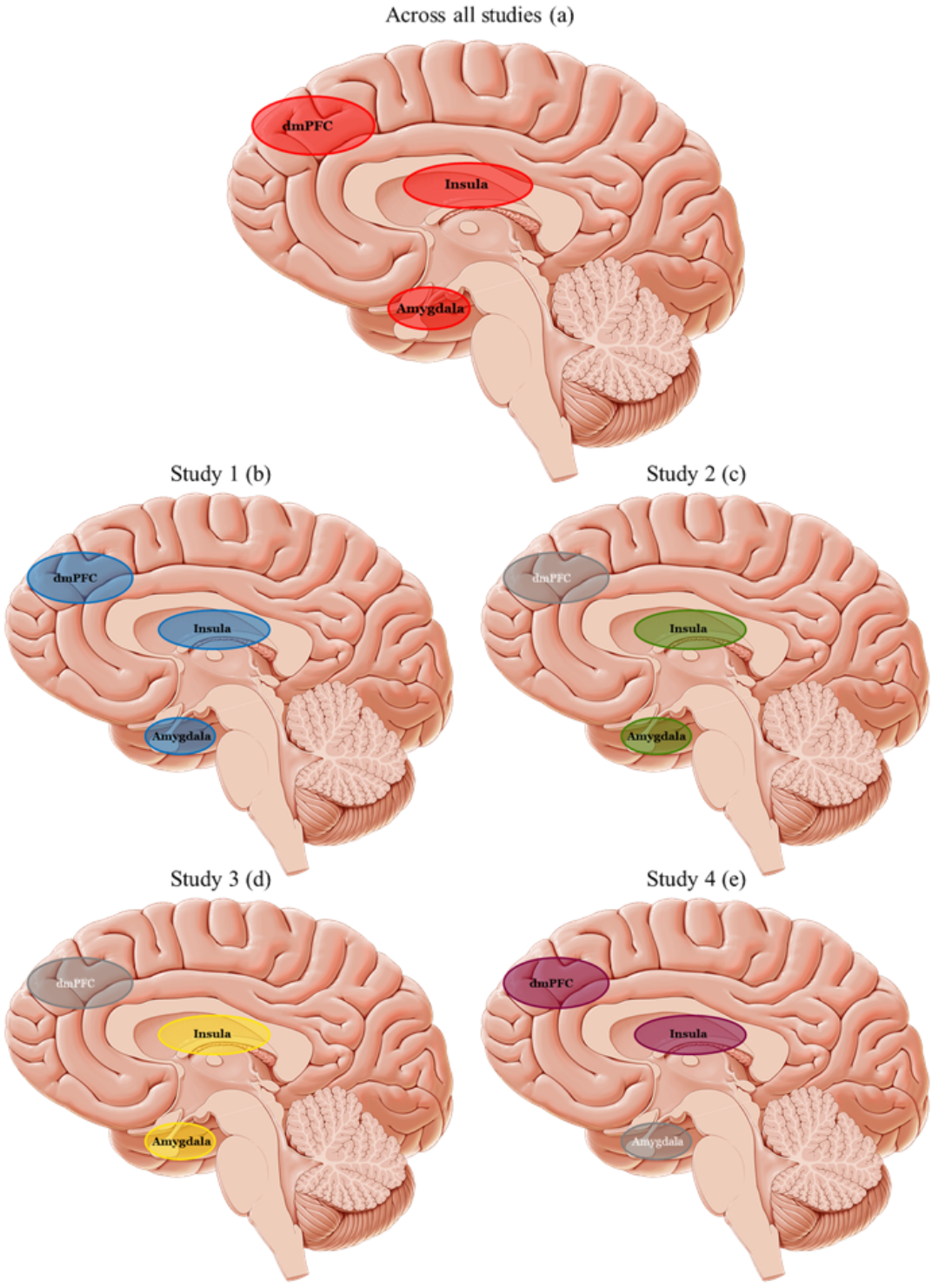

Figure 1. Overview of brain regions consistently detected across the studies included in this dissertation: Insula, amygdala, and dorsomedial prefrontal cortex (dmPFC). **a)** Brain regions consistently detected across all four studies (red). **b)** Brain regions revealed within the meta-analysis on emotion processing in aggressive adolescents (blue). **c)** Brain regions detected during implicit emotion-cognition interaction in healthy young adults (green). **d)** Brain regions detected during implicit emotion-cognition interaction in conduct disorder (yellow). **e)** Brain regions detected during explicit emotion regulation by cognitive reappraisal in female conduct disorder (plum). Areas with a gray background represent brain regions that were not detected in the corresponding study. Image adapted from https://www.kenhub.com/en/ library/anatomy/hypothalamus.

9.1.1 Insula

The insular cortex is a hidden brain structure located deep in the Sylvian fissure implicated in numerous functions, for example emotional recall, empathy, or negative emotion processing (Fan, Duncan, de Greck, & Northoff, 2011; Kirby & Robinson, 2017; Phan, Wager, Taylor, & Liberzon, 2002; Singer, Critchley, & Preuschoff, 2009). This brain region has been attributed an integrative role in which information from major functional systems, e.g., perceptions, sensorimotor information, emotions, and cognitive processes, are linked (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). It is therefore responsible for rather complex processes of the human brain, as for example representations of current emotional states, predicted emotional states, and prediction errors, which are all modulated by individual preferences (Singer et al., 2009). Large-scale meta-analyses have subdivided the human insular cortex into at least three different regions: a dorsoanterior, ventroanterior, and posterior region (Chang, Yarkoni, Khaw, & Sanfey, 2013; Kurth et al., 2010). Each subdivision has been suggested to hold a specific function. As such, the dorsoanterior insula has been suggested to be involved in language-related and cognitive processes such as response inhibition, the ventroanterior insula to process and evaluate affective input, and the posterior regions to be implicated in processing abstract social and sensorimotor information (Chang et al., 2013; Kurth et al., 2010; Mutschler et al., 2009). Interestingly, a conjunction analysis has detected a considerable overlap of social-emotional and cognitive functions in the dorsoanterior insula, most likely representing a hub that integrates all information into a meaningful experience (Kurth et al., 2010).

In line with this view, anatomical connections and co-activations between the insula and other limbic structures (Chang et al., 2013; Höistad & Barbas, 2008; Kober et al., 2008) allow these regions to interact dynamically, enabling e.g. the transfer of sensory input to the amygdala (Shelley & Trimble, 2004) or the regulation of physiological changes and higher-order cognitive functions related to emotion processing (Chang et al., 2013; Phan et al., 2002). It moreover allows the insula to hold important functions in the regulation of social interactions and emotions.

In the current dissertation, we reported alterations in insula functioning in adolescents with CD during performance of emotion processing tasks as indicated by the meta-analysis (**study 1**), implicit emotion regulation by means of an affective Stroop task (**study 3**), and explicit emotion regulation by cognitive reappraisal (**study 4**). More specifically, the results of the explicit emotion regulation task are in line with our ALE meta-analysis by revealing

hypoactivations in the insular cortex in CD. During implicit emotion regulation using the affective Stroop task, however, we reported both hypo- and hyperactivations depending on the exact location within the insula: decreased insular activity in dorsoanterior and posterior regions (response inhibition, abstract social information processing) and increased insular activity in ventroanterior (emotion processing) regions. Our study employing the affective Stroop task in young adults (**study 2**) confirmed the insula as a brain region involved in processing emotional information and integrating emotion and cognitive information as indicated by a downregulation of this area with increased cognitive load during healthy functioning. Our findings are in line with previous literature demonstrating decreases (Fairchild et al., 2014; Lockwood et al., 2013; Passamonti et al., 2010) as well as increases (Decety, Michalska, Akitsuki, & Lahey, 2009; Decety et al., 2013) in insula activity in individuals with CD or severe conduct problems. It is important to note that these studies did not differentiate between the subdivisions of the insula beyond anterior versus posterior insula. In order to gain further knowledge on altered insula function during atypical development, we suggest that future studies should focus on functional parcellation of the insular cortex into three to four subdivisions. Overall, our findings highlight the importance of the insula as a core brain region for functional and structural alterations in adolescents with severely aggressive behavior and CD.

9.1.2 Amygdala

Supported by ample research, the amygdala has traditionally been regarded as the core center for emotion processing. As such, past literature has linked amygdala activity to processing of emotional information across different tasks and types of emotion. As such, increased amygdala activity has been reported for tasks using stimuli with an emotional valence (predominantly negative, but also positive images (Costafreda, Brammer, David, & Fu, 2008; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001)), facial expression of emotion itself (for example fear, anxiety, sadness, disgust, but also positive emotions such as happiness (Harris, Young, & Andrews, 2014; Kirby & Robinson, 2017; Whalen et al., 1998)), emotional words (Hamann & Mao, 2002; Kensinger & Schacter, 2006), or aversive learning (Costafreda et al., 2008; Dunsmoor, Kragel, Martin, & LaBar, 2014). Quantitative meta-analyses have corroborated previous evidence of an involvement of the amygdalae in processing emotional information of negative or positive valence, with a preference for facial expressions (Sergerie, Chochol, & Armony, 2008), in particular for fearful faces (Phan et al., 2002). Beyond emotion processing, the amygdala has been hypothesized to modulate cortical networks by evaluating the affective valence of visual stimuli (Pessoa & Adolphs, 2010), and to be

downregulated when cognitive resources are needed for simultaneous task processing (Blair et al., 2007; Etkin et al., 2006; Hart et al., 2010; Mitchell et al., 2007).

This dissertation work strongly supports suggestions of the amygdala as key to emotion processing and regulation. The amygdala was indeed one of the regions that emerged in our meta-analysis on brain alterations in adolescents with aggressive behavior during emotion processing tasks (**study 1**). In line with previous evidence on implicit emotion regulation through emotion-cognition interaction (Blair et al., 2007; Etkin et al., 2006; Hart et al., 2010; Mitchell et al., 2007) we moreover detected increased amygdala activity in response to emotional images, and a downregulation of emotion-related amygdala activity with increasing cognitive load in healthy adults and adolescents by means of an affective Stroop task (**studies 2 and 3**). In contrast to typically developing peers, increased cognitive load did not lead to decreases in emotion-related amygdala activity in adolescents with CD (**study 3**). This is in line with functional evidence suggesting alterations in amygdala activity in CD and psychopathy (Blair, 2007; Fairchild et al., 2011; Marsh et al., 2008). The current dissertation extends previous knowledge by providing evidence of failed integration of emotion and cognition in adolescents with CD as reflected by lacking adaptation of amygdala activity.

9.1.3 Prefrontal cortex

The prefrontal cortex is a large brain area implicated in higher order cognitive functioning, such as top-down cognitive control and integration of emotion and cognitive processes (Miller & Cohen, 2001). It has been functionally divided into several subregions with distinct functions. Dorsomedial and lateral prefrontal regions have a role in negative emotion generation and evaluation and emotional conflict resolution, whereas ventromedial prefrontal (i.e., orbitofrontal) regions are involved in emotion regulation, empathy, and motivation, and connected with the limbic system (Etkin, Egner, & Kalisch, 2011; Gray et al., 2002; Miller & Cohen, 2001; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003).

The current dissertation provides evidence for an involvement of different regions of the prefrontal cortex, and in particular the dorsomedial prefrontal cortex, in emotion processing and explicit emotion regulation, and alterations thereof in aggressive behavior and CD. We detected decreased neuronal activity in the dorsomedial prefrontal cortex during explicit emotion regulation by cognitive reappraisal in CD (**study 4**), which is in line with our meta-analysis on emotion processing in adolescents with aggressive behavior (**study 1**). Additionally, we detected an implication of more lateral regions of the prefrontal cortex during implicit emotion regulation by means of an affective Stroop task in healthy adults

(**study 2**) and some indication of increased neuronal activity in these regions during an affective Stroop task in CD. This effect was however only observed as a main effect of *group* and not within an interaction effect of *group* by *emotion* by *cognition*, and should therefore be interpreted with caution (**study 3**). Overall, our results suggest that the dorsomedial prefrontal cortex is more extensively recruited during explicit emotion regulation tasks in contrast to the more implicit nature of emotion-cognition interaction, where we observe an implication of lateral prefrontal regions.

Our findings are in line with previous evidence demonstrating altered activity in prefrontal cortex in individuals with CD and psychopathy (Alegria, Radua, & Rubia, 2016; Blair, 2007, 2010b; Finger et al., 2008; Hwang et al., 2016; Rubia et al., 2009; Smaragdi et al., 2017). We suggest that dorsal prefrontal alterations are at least partly related to the role of this area in emotional conflict resolution impaired in CD. Moreover, we propose that prefrontal alterations in aggressive behavior and CD may comprise a broader area including lateral and medial prefrontal areas depending on task and sample characteristics.

Our findings on implicit emotion regulation by emotion-cognition interaction are based on an affective Stroop task developed and implemented within this dissertation. The upcoming section will focus on the task development.

9.2 Task development: The affective Stroop task

The affective Stroop task (Blair et al., 2007; Hart et al., 2010) is an fMRI suitable paradigm designed to assess the implicit interaction between emotion and cognition with the use of emotional images and variations in cognitive task load. It is an adaptation of the number Stroop task (Pansky & Algom, 2002), a variant of the traditional Stroop task (Stroop, 1935), originally developed as a behavioral task to be conducted outside of the MRI environment. After initial validation in healthy adults (Blair et al., 2007), slightly adapted versions of the affective Stroop tasks have been used within the last decade as a measure to study the behavioral and/or neuronal basis of implicit emotion regulation in psychiatric conditions. So far, it has been employed in anxiety disorders (Blair et al., 2012; Hasler et al., 2009), post-traumatic stress syndrome (Mueller-Pfeiffer et al., 2010; Roy et al., 2014; Vythilingam et al., 2007; White et al., 2015), attention-deficit hyperactivity disorder (Hwang et al., 2015), and DBD (Hwang et al., 2016).

Adaptations of the task design of the affective Stroop task include differences in the duration of stimuli presentation, emotional valence of the images, number and duration of trials,

number and duration of task runs, the digits and number of items presented, and the precise task design respectively instruction provided (see **Table 1** for a comparison of the affective Stroop task designs of the most relevant publications and **Appendix F** for a visualization of the task designs).

Table 1. Affective Stroop task designs of the most relevant publications.

	Blair et al., 2007	Hart et al., 2010	Hwang et al., 2016	Raschle et al., 2017
Duration of emotion stimulation (in ms)	400	150	400	150
Duration of Stroop task (in ms)	400	1000	400	1500
Duration of relaxation period (in ms)	400-1000	1500-2500	400-1300	350-1850
Trial duration (in ms)	3000	2650-3650	2900	2000-3500
Valence of emotion stimuli	negative/neutral/positive	negative/neutral	negative/neutral/positive	negative/neutral
Number of runs	4	6	2	2
Duration of runs (in min)	4.39	5.50	8.13	7.59
Number of task trials per run	112	103	288	150
Digits presented	1-6	1-4	3-6	1-4
Number of items presented	2-5	1-4	3-6	1-4
Exact instruction provided (task)	indicate task trial with highest numerosity	indicate number of items presented	indicate number of items presented	indicate number of items presented

For detailed task designs see **Figure 2** and **Appendix F**.

The task designs by Blair et al. (2007) and Hwang et al. (2016) used emotional stimuli both before and after Stroop task performance. The authors were therefore able to additionally investigate effects of cognition on emotion, whereas the task designs of Hart et al. (2010) and our group only allowed to study the influence of emotion on cognition. Moreover, the original task design by Blair et al. (2007) involved a different instruction compared to all subsequently employed tasks. More specifically, participants were asked to indicate which of two task trials had the highest numerosity, whereas all other task designs involved indicating the number of items presented on one particular Stroop trial.

One major aim of this dissertation was to develop an affective Stroop task especially adapted to the needs of children and adolescents with and without DBD. The task developed within this dissertation is based on the affective Stroop task by Hart and colleagues (2010) and was implemented within **studies 2 and 3**. In our task, each trial of the affective Stroop task starts with an emotional stimulus, i.e., an image of negative or neutral content. After emotion stimulation, a number Stroop task is presented, which varies in task difficulty (i.e., cognitive load), eventually followed by a relaxation period, i.e., blank screen. During Stroop trials, participants see an array of one to four digits and are asked to press a button corresponding to the number of items presented. On congruent trials, the number of items displayed corresponds to the actual digit presented (e.g., digit 4 in an array of four, reflecting low cognitive load), whereas on incongruent trials, the number of items presented does not

correspond to the actual digit presented (e.g., digit 2 in an array of four, reflecting increasing cognitive load). An array of star shaped stimuli serving as a neutral counting condition and blank trials during which no response is required are used as control conditions. Child-friendly pictures were selected from the Developmental Affective Photo System (DAPS; Cordon, Melinder, Goodman, and Edelstein (2013)), a child-appropriate subset of pictures of the International Affective Picture System (IAPS; Lang (2008)). While the affective Stroop task developed by our group is very similar to the task design by Hart et al. (2010), it differs in some details. More specifically, our affective Stroop task included child-appropriate images and adaptations in the duration of the response window and the task itself in order to make sure that the task design is suitable even for young children (also see **Table 1** and **Figure 2**).

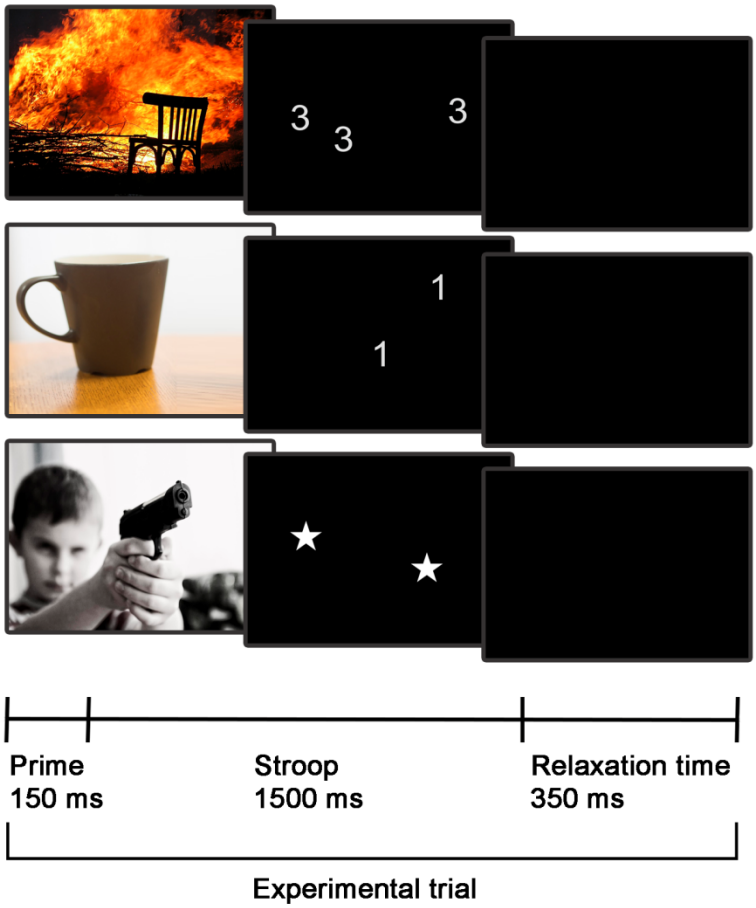

Figure 2. fMRI task design developed within this dissertation (Raschle et al., 2017), including three trials of the affective Stroop task (First row: negative-congruent trial, second row: neutral-incongruent trial, third row: negative-stars trial).

After its validation in healthy adults, the affective Stroop task developed within this dissertation was successfully implemented in children and adolescents with CD and their typically developing peers within a child-appropriate neuroimaging session detailed in the following section.

9.3 Imaging the developing brain

This dissertation work aimed at investigating the neuronal development in typical and atypical children and adolescents with the use of state-of-the-art neuroimaging methods. Investigating the developing brain offers a wide range of possibilities for clarifying important research questions regarding healthy brain development, prediction and development of mental diseases, and investigation of childhood disorders.

Although modern imaging techniques offer a unique possibility of displaying changes in the brain, paediatric neuroimaging is still an emerging field. Specific challenges when imaging a paediatric population have been a source of debate in the past. Primary concerns are related to feasibility and practical reasons, such as maintaining the child's motivation and attention during the session while reducing potential anxiety and motion. The use of child appropriate MR protocols (Raschle et al., 2012; Raschle et al., 2009) and trained staff can however provide children with an optimal experimental environment and make a participation in research fun and enjoyable. A child-friendly procedure does not only include imaging itself, but the whole study setting, including task development, preparation of the scanning session, and adequate data analysis. The experimental task for example needs to be designed according to the fact that children might find it challenging to lie still and concentrate for a long time. As such, the task and neuroimaging session should be kept as short as possible. Moreover, the stimuli should be selected according to the age of the participants (for a child-friendly image system see for example Cordon et al. (2013)). Extensive preparation and training using a mock scanner make the child and its family confident and at ease with the MR environment and scanning procedure. Furthermore, it is essential that the language used is age-appropriate, positive, and well understandable for the participants and family. By providing sufficient time to ask questions and get familiar with the new environment, potential anxiety can be reduced. Moreover, the procedure should be flexible, which enables the researcher to adapt the approach depending on the participant's mood, anxiety, and overall state. During neuroimaging, offering breaks and communicating on a regular basis with the child increases comfort. Ear protection protects the child from MR-related noise and a pre-heated blanket keeps it warm and cozy. Providing feedback (either indirectly through communication during breaks or directly by a gentle hand press on the leg by a staff member in the MRI room) helps to reduce motion-related artifacts, which can, when needed, additionally be accounted for during data preprocessing (e.g., using ArtRepair; Mazaika, Whitfield-Gabrieli, Reiss, and Glover (2007)).

A special challenge within paediatric neuroimaging is given if the participant is not only of a young age, but moreover presents with a psychiatric condition such as CD. Here, it is of particular importance to know the characteristics of the participant as for example indicated by previous study sessions (e.g., behavioral testing) in order to predict possible defiant behavior or compliancy issues, and ensure the safety of the participant itself and staff involved within the neuroimaging setting. Children's and adolescents' responses during the training and imaging should be (even more) closely monitored in order to confirm that the participants have understood the task and to improve data quality.

In conclusion, appropriate paediatric imaging protocols make participation in neuroimaging studies fun for children and adolescents and offer unique possibilities of studying the developing brain. This in turn has important implications including possible prevention of the development of mental diseases early in age or increasing chances of rapid remission.

9.4 Strengths and caveats

The current dissertation work informed about the neuronal mechanisms underlying altered emotion processing and implicit and explicit emotion regulation in CD.

The most important strength of the present dissertation represents the effort to examine children and adolescents that meet a clinical diagnosis of CD. As such, two out of three of the studies conducted with clinical samples included adolescents with CD only (**studies 2 and 4**), focusing on rather small, but more homogeneous samples. This allowed us to provide a line of evidence demonstrating neuronal alterations during implicit and explicit emotion regulation in adolescents with a strict diagnosis of CD. Notably, the third study including a clinical sample was a meta-analysis (**study 1**) that required a minimum number of studies in order to result in reliable findings. Our first priority was, however, to pursue an optimal analytical approach by applying strict methodological inclusion criteria. This required a trade-off that led to our decision of not including only CD, but also adolescents with ODD or community samples characterized by conduct problems and/or high levels of CU traits.

A further strength of this dissertation derives from the development and implementation of a child-friendly affective Stroop task as discussed above. In order to study the effects of implicit emotion regulation by emotion-cognition interaction, the task includes a selection of negative images from the DAPS system (Cordon et al., 2013), pictures which have proven to be adequate for children. We moreover adapted the duration of the trials, of the task itself, and also of the neuroimaging session by making sure that the questionnaires and other behavioral

data were acquired during another session prior to neuroimaging. Based on a child-appropriate protocol (Raschle et al., 2012; Raschle et al., 2009) highly trained staff members prepared the participating children and adolescents for the neuroimaging session and conducted the experiments in a child-friendly manner. The affective Stroop task developed by our group was moreover extensively validated with a sample of 30 young adults prior to its use on children and adolescents (**study 2**).

Nevertheless, a few limitations have to be highlighted. One limitation concerns the choice of images used in the affective Stroop task (**studies 2 and 3**). Our priority was to make sure to use pictures that are approved for its use for experiments with children in order to avoid negative consequences for our participants. It is likely that, as a consequence, the impact of the images used was reduced for some of the children, especially in those with a high probability of already being accustomed to images with a highly negative valence, e.g., high on violence. We cannot exclude that choosing child-appropriate images might have influenced our results (**study 3**).

Another limitation refers to the aforementioned heterogeneity of CD. We have aimed at describing our samples as well as possible, taking into account for example the age of onset and an accurate estimation of psychopathic or CU traits, or potential comorbidities (**studies 3 and 4**). Particularly within **study 3**, we were however not able to investigate CU traits in more detail due to the fact that most of the adolescents (also those with CD) were characterized by low CU scores, leaving few possibilities of investigating effects related to variations in CU traits due to a small sample size. Considering previous findings of altered amygdala activation during emotion processing in dependence of CU trait levels (Baker et al., 2015; Blair, 2010a), future studies should consider focusing on groups with a higher variance in CU traits. This moreover applies to other important research questions which we were not able to focus on, such as sex and age differences, or effects of anxiety and attention.

9.5 Clinical implications and outlook

This dissertation work extends previous knowledge on neuronal alterations in adolescents with CD and overall suggests the presence of robust neuronal markers in the prefrontal cortex, insula, and amygdala for deficient emotion processing and regulation. It is likely that deficits in emotion processing and regulation impact daily life not only when directly dealing with emotions, but also have consequences when cognitive demands have to be met. Clinical interventions specifically targeted at improving emotion recognition and regulation skills using dialectical and/or cognitive behavior therapy (e.g., as implemented within the START

NOW training program (Kersten et al., 2016; Sampl, Trestman, & Krauss, 2013)) have proven effective in helping these adolescents at reducing externalizing, internalizing, and depressive symptoms, while increasing interpersonal and social problem solving skills (Lochman & Wells, 2004; Nelson-Gray et al., 2006). Furthermore, the development of treatment programs using neurofeedback for self-regulation training, an effective method already used in other psychiatric conditions such as ADHD (Gevensleben et al., 2009; Jacobs, 2006), might provide adolescents with further skills to train the brain to self-regulate. Given the heterogeneity of CD, we overall suggest that intervention programs shall focus on individualized approaches tailored to the specific needs of each patient (Pardini & Frick, 2013).

We here consistently identified alterations in the prefrontal cortex and limbic system (insula, amygdala) in children and adolescents with CD (**studies 3 and 4**), but also in individuals with subclinical features of CD (**study 1**). Our findings make a strong point for a common basis of alterations in aggressive behavior, which is likely to be modulated by the severity of conduct problems. Future studies shall be conducted in order to provide even more detailed information about the neuronal phenotype of adolescents with CD, and the underlying mechanisms responsible for emotion processing and regulation. More specifically, we suggest following up on the here observed neuronal alterations during implicit emotion regulation by emotion-cognition interaction (**study 3**) and explicit emotion regulation by cognitive reappraisal (**study 4**) in adolescents with CD. Ideally, future studies should aim at investigating the implication of the amygdala, insula, and prefrontal cortex on a more detailed basis by distinguishing between the functionally divided subregions of the areas implicated in emotion processing and regulation (see e.g., Han, Lee, Kim, and Kim (2013)).

The findings of this dissertation have furthered our knowledge on psychiatric disorders displaying aberrant neuronal activation during affective Stroop task processing in CD, which was already observed in other psychiatric disorders including ADHD (Hwang et al., 2015), affective disorders (Blair et al., 2012), post-traumatic stress disorders (Roy et al., 2014; White et al., 2015), and DBD (Hwang et al., 2016). A direct cross-disorder comparison is, however, yet missing and of high clinical relevance in order to determine the underlying neuronal mechanisms and development of different emotion-related psychiatric disorders. Depending on the exact aims of future investigations, an improvement of the affective Stroop paradigm used to investigate implicit emotion regulation as presented in **studies 2 and 3** of this dissertation should be considered. Changes could potentially include the addition of images of positive valence in order to increase the knowledge deriving from the task, and increasing the duration of the emotion presented (to for example 400 instead of 150ms, see for example

Blair et al. (2007) or Hwang et al. (2016)) in order to being able to clearly distinguish effects of emotion and cognition. Furthermore, future studies using the affective Stroop task but also other tasks would clearly benefit from increased sample sizes and therefore larger variance. This would allow to investigate subgroups of CD, such as those with childhood-onset or adolescent-onset, comorbidities such as ADHD, anxiety, or ODD, symptom severity, those with high versus low CU traits, different age ranges, sex differences, or even cultural differences (e.g., within the frame of the European-wide consortium project FemNAT-CD, https://www.femnat-cd.eu, part of aim 4). With the use of increased sample sizes, future studies could potentially benefit by the use of a so-called RDoC approach focusing on dimensions of functioning across disorders rather than DSM diagnoses (Blair, 2015; Blair, White, Meffert, & Hwang, 2013; Fonagy & Luyten, 2017). Longitudinal studies and investigations on brain structure and connectivity would moreover add to the knowledge gained within this dissertation by providing a more comprehensive picture of the neuronal underpinnings of CD and related developmental research questions in health and disease.

9.6 Conclusion

CD is a psychiatric disorder of childhood and adolescence marked by severely aggressive behavior lying outside of the age-appropriate norm, leading to substantial economic costs and negative social consequences (Merikangas, Nakamura, & Kessler, 2009). Ample evidence has indicated atypical brain structure and function in adolescents with CD in prefrontal and limbic regions related to deficient emotion processing and regulation. However, the exact neuronal mechanisms underlying the observed altered emotion processing and regulation skills remain largely unknown. The present dissertation extends previous knowledge by providing a new line of evidence that aims to fill this gap in research. We report meta-analytic evidence for a network of functional alterations in aggressive behavior located in the prefrontal and limbic cortices, including the insula and amygdala. Our study in young adults demonstrated that emotion-related neuronal activity in prefrontal and limbic areas decreases in order to meet cognitive demands during implicit emotion regulation. In adolescents with CD, however, increased cognitive load did not lead to decreases in emotion-related amygdala activity. Moreover, adolescents with CD showed decreased prefrontal and insula activity during explicit emotion regulation by cognitive reappraisal. Our findings likely reflect a failure in adequate regulatory processes in CD. Overall, the results of this dissertation provide novel evidence on the neuronal characteristics of implicit and explicit emotion regulation in adolescents with CD, and align with the behaviorally observed deficits. Future investigations

shall further investigate emotion regulation in specific subgroups of conduct disorder, for example those with psychopathic traits or high levels of anxiety. Increased knowledge about the underlying neuronal and behavioral markers of CD is crucial for developing programs of early intervention and treatment targeting emotion processing and regulation skills, which shall ultimately influence the child's immediate environment, but also public health and society as a whole.

TAKE HOME MESSAGE

Conduct disorder (CD) is a psychiatric condition of childhood and adolescence characterized by aggressive behavior and alterations in brain function related to emotion processing and regulation deficits. This dissertation presents novel evidence for altered neuronal activity in prefrontal and limbic brain regions during implicit and explicit emotion regulation in adolescents with CD compared to typically developing adolescents. The observed alterations in brain function align with the behaviorally observed deficits. Future studies shall inform further about the neuronal mechanisms in adolescents with CD by building up on the results of the present dissertation and ultimately influence social and economic outcomes.

10 References

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. doi:10.1176/appi.ajp.2016.15081089

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

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

Banich, M. T., Crowley, T. J., Thompson, L. L., Jacobson, B. L., Liu, X., Raymond, K. M., & Claus, E. D. (2007). Brain activation during the Stroop task in adolescents with severe substance and conduct problems: A pilot study. *Drug and Alcohol Dependence, 90*(2-3), 175-182. doi:10.1016/j.drugalcdep.2007.03.009

Biederman, J., Petty, C. R., Dolan, C., Hughes, S., Mick, E., Monuteaux, M. C., & Faraone, S. V. (2008). The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychological Medicine, 38*(7), 1027-1036. doi:10.1017/S0033291707002668

Blair, C. (2002). School readiness: Integrating cognition and emotion in a neurobiological conceptualization of children's functioning at school entry. *American Psychologist, 57*(2), 111.

Blair, K. S., Geraci, M., Smith, B. W., Hollon, N., DeVido, J., Otero, M., . . . Pine, D. S. (2012). Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. *Biological Psychiatry, 72*(6), 476-482. doi:10.1016/j.biopsych.2012.04.013

Blair, K. S., Newman, C., Mitchell, D. G., Richell, R. A., Leonard, A., Morton, J., & Blair, R. J. (2006). Differentiating among prefrontal substrates in psychopathy: neuropsychological test findings. *Neuropsychology, 20*(2), 153-165. doi:10.1037/0894-4105.20.2.153

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

Blair, R. (2015). Psychopathic traits from an RDoC perspective. *Current Opinion in Neurobiology, 30*, 79-84.

Blair, R., White, S. F., Meffert, H., & Hwang, S. (2013). Disruptive behavior disorders: taking an RDoC (ish) approach *The Neurobiology of Childhood* (pp. 319-336): Springer.

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

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

Blair, R. J. (2010b). Psychopathy, frustration, and reactive aggression: the role of ventromedial prefrontal cortex. *British Journal of Psychology, 101*(Pt 3), 383-399. doi:10.1348/000712609X418480

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

Blakemore, S. J., & Mills, K. L. (2014). Is Adolescence a Sensitive Period for Sociocultural Processing? *Annual Review of Psychology, Vol 65, 65*, 187-207. doi:10.1146/annurev-psych-010213-115202

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., . . . Ochsner, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex, 24*(11), 2981-2990. doi:10.1093/cercor/bht154

Bunte, T. L., Schoemaker, K., Hessen, D. J., van der Heijden, P. G., & Matthys, W. (2014). Stability and change of ODD, CD and ADHD diagnosis in referred preschool children. *Journal of Abnormal Child Psychology, 42*(7), 1213-1224. doi:10.1007/s10802-014-9869-6

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafo, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews: Neuroscience, 14*(5), 365-376. doi:10.1038/nrn3475

Campbell, S. B., Shaw, D. S., & Gilliom, M. (2000). Early externalizing behavior problems: Toddlers and preschoolers at risk for later maladjustment. *Development and Psychopathology, 12*(3), 467-488.

Capaldi, D. M., Crosby, L., & Stoolmiller, M. (1996). Predicting the timing of first sexual intercourse for at-risk adolescent males. *Child Development, 67*(2), 344-359. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8625717

Castellanos-Ryan, N., Rubia, K., & Conrod, P. J. (2011). Response inhibition and reward response bias mediate the predictive relationships between impulsivity and sensation seeking and common and unique variance in conduct disorder and substance misuse. *Alcoholism: Clinical and Experimental Research, 35*(1), 140-155.

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. *Cerebral Cortex, 23*(3), 739-749. doi:10.1093/cercor/bhs065

Chen, J. E., & Glover, G. H. (2015). Functional Magnetic Resonance Imaging Methods. *Neuropsychology Review, 25*(3), 289-313. doi:10.1007/s11065-015-9294-9

Cohen, N., & Henik, A. (2012). Do irrelevant emotional stimuli impair or improve executive control? *Frontiers in Integrative Neuroscience, 6*, 33. doi:10.3389/fnint.2012.00033

Cordon, I. M., Melinder, A. M., Goodman, G. S., & Edelstein, R. S. (2013). Children's and adults' memory for emotional pictures: examining age-related patterns using the Developmental Affective Photo System. *Journal of Experimental Child Psychology, 114*(2), 339-356. doi:10.1016/j.jecp.2012.08.004

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews, 58*(1), 57-70. doi:10.1016/j.brainresrev.2007.10.012

Cromheeke, S., & Mueller, S. C. (2014). Probing emotional influences on cognitive control: an ALE meta-analysis of cognition emotion interactions. *Brain Structure and Function, 219*(3), 995-1008. doi:10.1007/s00429-013-0549-z

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.

Decety, J., Michalska, K. J., Akitsuki, Y., & Lahey, B. B. (2009). Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. *Biological Psychology, 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

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience, 18*(1), 193-222.

Dodge, K. A., Lansford, J. E., Burks, V. S., Bates, J. E., Pettit, G. S., Fontaine, R., & Price, J. M. (2003). Peer rejection and social information-processing factors in the development of aggressive behavior problems in children. *Child Development, 74*(2), 374-393. doi:Doi 10.1111/1467-8624.7402004

Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience, 26*(7), 2072-2079. doi:10.1523/jneurosci.5042-05.2006

Dunsmoor, J. E., Kragel, P. A., Martin, A., & LaBar, K. S. (2014). Aversive learning modulates cortical representations of object categories. *Cerebral Cortex, 24*(11), 2859-2872. doi:10.1093/cercor/bht138

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. *Human Brain Mapping, 30*(9), 2907-2926.

Eiden, R. D., Edwards, E. P., & Leonard, K. E. (2007). A conceptual model for the development of externalizing behavior problems among kindergarten children of alcoholic families: role of parenting and children's self-regulation. *Developmental Psychology, 43*(5), 1187-1201. doi:10.1037/0012-1649.43.5.1187

Eisenberg, N., Spinrad, T. L., & Eggum, N. D. (2010). Emotion-related self-regulation and its relation to children's maladjustment. *Annual Review of Clinical Psychology, 6*, 495-525.

Erskine, H. E., Norman, R. E., Ferrari, A. J., Chan, G. C., Copeland, W. E., Whiteford, H. A., & Scott, J. G. (2016). Long-Term Outcomes of Attention-Deficit/Hyperactivity Disorder and Conduct Disorder: A Systematic Review and Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(10), 841-850. doi:10.1016/j.jaac.2016.06.016

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 85-93. doi:10.1016/j.tics.2010.11.004

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., Sterzer, P., & Stadler, C. (2014). Cognitive control under distressing emotional stimulation in adolescents with conduct disorder. *Aggressive Behavior, 40*(2), 109-119. doi:10.1002/ab.21508

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

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. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(6), 677-687. e675.

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. *American Journal of Psychiatry, 168*(6), 624-633. doi:10.1176/appi.ajp.2010.10081184

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*(3), 903-911. doi:10.1016/j.neubiorev.2010.10.009

Fergusson, D. M., John Horwood, L., & Ridder, E. M. (2005). Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *Journal of Child Psychology and Psychiatry, 46*(8), 837-849.

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. *Archives of General Psychiatry, 65*(5), 586-594. doi:10.1001/archpsyc.65.5.586

Fletcher, P. C., & Grafton, S. T. (2013). Repeat after me: replication in clinical neuroimaging is critical. *NeuroImage: Clinical, 2*, 247.

Fonagy, P., & Luyten, P. (2017). Conduct problems in youth and the RDoC approach: A developmental, evolutionary-based view. *Clinical Psychology Review*.

Foster, E. M., & Jones, D. E. (2005). The high costs of aggression: public expenditures resulting from conduct disorder. *American Journal of Public Health, 95*(10), 1767-1772. doi:10.2105/AJPH.2004.061424

Frick, P. J., & Dickens, C. (2006). Current perspectives on conduct disorder. *Current Psychiatry Reports, 8*(1), 59-72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16513044

Frick, P. J., & Morris, A. S. (2004). Temperament and developmental pathways to conduct problems. *Journal of Clinical Child and Adolescent Psychology, 33*(1), 54-68.

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. doi:10.1097/00001756-200108280-00036

Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., . . . Heinrich, H. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. *Journal of Child Psychology and Psychiatry, 50*(7), 780-789.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biological Psychiatry, 63*(6), 577-586.

Gowers, S. (2005). Development in adolescence. *Psychiatry, 4*(6), 6-9.

Gray, J. R., Braver, T. S., & Raichle, M. E. (2002). Integration of emotion and cognition in the lateral prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 99*(6), 4115-4120. doi:10.1073/pnas.062381899

Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology, 2*(3), 271.

Gu, X., Liu, X., Van Dam, N. T., Hof, P. R., & Fan, J. (2013). Cognition-emotion integration in the anterior insular cortex. *Cerebral Cortex, 23*(1), 20-27. doi:10.1093/cercor/bhr367

Gupta, R., & Deák, G. O. (2015). Disarming smiles: irrelevant happy faces slow post-error responses. *Cognitive Processing, 16*(4), 427-434.

Gupta, R., Hur, Y. J., & Lavie, N. (2016). Distracted by pleasure: Effects of positive versus negative valence on emotional capture under load. *Emotion, 16*(3), 328-337. doi:10.1037/emo0000112

Gyurak, A., Gross, J. J., & Etkin, A. (2011). Explicit and implicit emotion regulation: a dual-process framework. *Cognition & Emotion, 25*(3), 400-412. doi:10.1080/02699931.2010.544160

Hamann, S., & Mao, H. (2002). Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport, 13*(1), 15-19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11924878

Han, H. J., Lee, K., Kim, H. T., & Kim, H. (2013). Distinctive amygdala subregions involved in emotion-modulated Stroop interference. *Social Cognitive and Affective Neuroscience, 9*(5), 689-698.

Harris, R. J., Young, A. W., & Andrews, T. J. (2014). Dynamic stimuli demonstrate a categorical representation of facial expression in the amygdala. *Neuropsychologia, 56*, 47-52. doi:10.1016/j.neuropsychologia.2014.01.005

Hart, S. J., Green, S. R., Casp, M., & Belger, A. (2010). Emotional priming effects during Stroop task performance.

Neuroimage, 49(3), 2662-2670. doi:10.1016/j.neuroimage.2009.10.076

Hartikainen, K. M., Ogawa, K. H., & Knight, R. T. (2000). Transient interference of right hemispheric function due to automatic emotional processing. *Neuropsychologia, 38*(12), 1576-1580. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11074080

Hasler, G., Mondillo, K., Drevets, W. C., & Blair, J. R. (2009). Impairments of probabilistic response reversal and passive avoidance following catecholamine depletion. *Neuropsychopharmacology, 34*(13), 2691-2698.

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. *Journal of Child Psychology and Psychiatry, 49*(7), 781-791.

Hiatt, K. D., Schmitt, W. A., & Newman, J. P. (2004). Stroop tasks reveal abnormal selective attention among psychopathic offenders. *Neuropsychology, 18*(1), 50-59. doi:10.1037/0894-4105.18.1.50

Höistad, M., & Barbas, H. (2008). Sequence of information processing for emotions through pathways linking temporal and insular cortices with the amygdala. *Neuroimage, 40*(3), 1016-1033.

Hwang, S., Nolan, Z. T., White, S. F., Williams, W. C., Sinclair, S., & Blair, R. J. (2016). Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. *Psychological Medicine, 46*(7), 1485-1496. doi:10.1017/S0033291716000118

Hwang, S., White, S. F., Nolan, Z. T., Craig Williams, W., Sinclair, S., & Blair, R. J. (2015). Executive attention control and emotional responding in attention-deficit/hyperactivity disorder--A functional MRI study. *Neuroimage Clin, 9*, 545-554. doi:10.1016/j.nicl.2015.10.005

Hwang, S., White, S. F., Nolan, Z. T., Sinclair, S., & Blair, R. J. (2014). Neurodevelopmental changes in the responsiveness of systems involved in top down attention and emotional responding. *Neuropsychologia, 62*, 277-285. doi:10.1016/j.neuropsychologia.2014.08.003

Jacobs, E. H. (2006). Neurofeedback treatment of two children with learning, attention, mood, social, and developmental deficits. *Journal of Neurotherapy, 9*(4), 55-70.

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. *American Journal of Psychiatry, 166*(1), 95-102. doi:10.1176/appi.ajp.2008.07071050

Kanske, P., & Kotz, S. A. (2011). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? *Cerebral Cortex, 21*(4), 911-919. doi:10.1093/cercor/bhq157

Kazdin, A. E. (1995). *Conduct disorders in childhood and adolescence* (Vol. 9): Sage.

Kazdin, A. E. (1997). Practitioner review: Psychosocial treatments for conduct disorder in children. *Journal of child psychology and Psychiatry, 38*(2), 161-178.

Kellermann, T. S., Sternkopf, M. A., Schneider, F., Habel, U., Turetsky, B. I., Zilles, K., & Eickhoff, S. B. (2011). Modulating the processing of emotional stimuli by cognitive demand. *Social Cognitive and Affective Neuroscience, 7*(3), 263-273.

Kempes, M., Matthys, W., De Vries, H., & Van Engeland, H. (2005). Reactive and proactive aggression in children A review of theory, findings and the relevance for child and adolescent psychiatry. *European Child and Adolescent Psychiatry, 14*(1), 11-19.

Kensinger, E. A., & Schacter, D. L. (2006). Processing emotional pictures and words: effects of valence and arousal. *Cognitive, Affective & Behavioral Neuroscience, 6*(2), 110-126. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17007232

Kersten, L., Prätzlich, M., Mannstadt, S., Ackermann, K., Kohls, G., Oldenhof, H., . . . Popma, A. (2016). START NOW-a comprehensive skills training programme for female adolescents with oppositional defiant and conduct disorders: study protocol for a cluster-randomised controlled trial. *Trials, 17*(1), 568.

Kimonis, E. R., Fanti, K. A., Frick, P. J., Moffitt, T. E., Essau, C., Bijttebier, P., & Marsee, M. A. (2015). Using self-reported callous-unemotional traits to cross-nationally assess the DSM-5 'With Limited Prosocial Emotions' specifier. *Journal of Child Psychology and Psychiatry, 56*(11), 1249-1261.

Kirby, L. A. J., & Robinson, J. L. (2017). Affective mapping: An activation likelihood estimation (ALE) meta-analysis. *Brain and Cognition, 118*, 137-148. doi:10.1016/j.bandc.2015.04.006

Kober, H., Barrett, L. F., Joseph, J., Bliss-Moreau, E., Lindquist, K., & Wager, T. D. (2008). Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *Neuroimage, 42*(2), 998-1031.

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation--an ALE meta-analysis and MACM analysis. *Neuroimage, 87*, 345-355. doi:10.1016/j.neuroimage.2013.11.001

Kross, E., & Ayduk, O. (2008). Facilitating adaptive emotional analysis: Distinguishing distanced-analysis of depressive experiences from immersed-analysis and distraction. *Personality and Social Psychology Bulletin, 34*(7), 924-938.

Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., & Eickhoff, S. B. (2010). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure & Function, 214*(5-6), 519-534. doi:10.1007/s00429-010-0255-z

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. doi:10.1037/0022-006X.73.3.389

Lang, P. J., Bradley, M.M., & Cuthbert, B.N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8.* Gainesville, FL.: University of Florida.

Lochman, J. E., & Wells, K. C. (2004). The coping power program for preadolescent aggressive boys and their parents: outcome effects at the 1-year follow-up. *Journal of Consulting and Clinical Psychology, 72*(4), 571-578. doi:10.1037/0022-006X.72.4.571

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. *Current Biology, 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. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(12), 1468-1484. doi:10.1097/00004583-200012000-00007

Lotze, M., Veit, R., Anders, S., & Birbaumer, N. (2007). Evidence for a different role of the ventral and dorsal medial prefrontal cortex for social reactive aggression: An interactive fMRI study. *Neuroimage, 34*(1), 470-478. doi:10.1016/j.neuroimage.2006.09.028

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. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 54*(8), 900-910. doi:10.1111/jcpp.12063

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. *American Journal of Psychiatry, 165*(6), 712-720. doi:10.1176/appi.ajp.2007.07071145

Mazaika, P., Whitfield-Gabrieli, S., Reiss, A., & Glover, G. (2007). Artifact repair for fMRI data from high motion clinical subjects. *Human Brain Mapping*, 2007.

McLaughlin, K. A., Hatzenbuehler, M. L., Mennin, D. S., & Nolen-Hoeksema, S. (2011). Emotion dysregulation and adolescent psychopathology: a prospective study. *Behaviour Research and Therapy, 49*(9), 544-554. doi:10.1016/j.brat.2011.06.003

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D., Gross, J. J., & Ochsner, K. N. (2010). The neural bases of distraction and reappraisal. *Journal of Cognitive Neuroscience, 22*(2), 248-262.

McRae, K., Ochsner, K. N., Mauss, I. B., Gabrieli, J. J., & Gross, J. J. (2008). Gender differences in emotion regulation: An fMRI study of cognitive reappraisal. *Group Processes & Intergroup Relations, 11*(2), 143-162.

Melcher, T., Born, C., & Gruber, O. (2011). How negative affect influences neural control processes underlying the resolution of cognitive interference: an event-related fMRI study. *Neuroscience Research, 70*(4), 415-427. doi:10.1016/j.neures.2011.05.007

Mennin, D. S., McLaughlin, K. A., & Flanagan, T. J. (2009). Emotion regulation deficits in generalized anxiety disorder, social anxiety disorder, and their co-occurrence. *Journal of Anxiety Disorders, 23*(7), 866-871.

Merikangas, K. R., Nakamura, E. F., & Kessler, R. C. (2009). Epidemiology of mental disorders in children and adolescents. *Dialogues in Clinical Neuroscience, 11*(1), 7-20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19432384

Michalska, K. J., Zeffiro, T. A., & Decety, J. (2016). Brain response to viewing others being harmed in children with conduct disorder symptoms. *Journal of Child Psychology and Psychiatry, 57*(4), 510-519. doi:10.1111/jcpp.12474

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202. doi:10.1146/annurev.neuro.24.1.167

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

Moore, A. A., Silberg, J. L., Roberson-Nay, R., & Mezuk, B. (2017). Life course persistent and adolescence limited conduct disorder in a nationally representative US sample: prevalence, predictors, and outcomes. *Social Psychiatry and Psychiatric Epidemiology, 52*(4), 435-443.

Mueller-Pfeiffer, C., Martin-Soelch, C., Blair, J., Carnier, A., Kaiser, N., Rufer, M., . . . Hasler, G. (2010). Impact of emotion on cognition in trauma survivors: what is the role of posttraumatic stress disorder? *Journal of Affective Disorders, 126*(1), 287-292.

Mutschler, I., Wieckhorst, B., Kowalevski, S., Derix, J., Wentlandt, J., Schulze-Bonhage, A., & Ball, T. (2009). Functional organization of the human anterior insular cortex. *Neuroscience Letters, 457*(2), 66-70. doi:10.1016/j.neulet.2009.03.101

Nelson-Gray, R. O., Keane, S. P., Hurst, R. M., Mitchell, J. T., Warburton, J. B., Chok, J. T., & Cobb, A. R. (2006). A modified DBT skills training program for oppositional defiant adolescents: Promising preliminary findings. *Behaviour Research and Therapy, 44*(12), 1811-1820.

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. *Psychological Medicine, 36*(5), 699-710. doi:10.1017/S0033291706007082

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage, 23*(2), 483-499. doi:10.1016/j.neuroimage.2004.06.030

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage, 23*(2), 483-499.

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. *Annals of the New York Academy of Sciences, 1251*, E1-24. doi:10.1111/j.1749-6632.2012.06751.x

Okon-Singer, H., Hendler, T., Pessoa, L., & Shackman, A. J. (2014). Introduction to the special research topic on the neurobiology of emotion-cognition interactions. *Frontiers in Human Neuroscience, 8*, 1051. doi:10.3389/fnhum.2014.01051

Okon-Singer, H., Hendler, T., Pessoa, L., & Shackman, A. J. (2015). The neurobiology of emotion–cognition interactions: fundamental questions and strategies for future research. *Frontiers in Human Neuroscience, 9*.

Okon-Singer, H., Lichtenstein-Vidne, L., & Cohen, N. (2013). Dynamic modulation of emotional processing. *Biological Psychology, 92*(3), 480-491. doi:10.1016/j.biopsycho.2012.05.010

Pansky, A., & Algom, D. (2002). Comparative judgment of numerosity and numerical magnitude: attention preempts automaticity. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 28*(2), 259.

Pardini, D., & Frick, P. J. (2013). Multiple developmental pathways to conduct disorder: Current conceptualizations and clinical implications. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 22*(1), 20.

Park, N. (2004). The role of subjective well-being in positive youth development. *Annals of the American Academy of Political and Social Science, 591*, 25-39. doi:10.1177/0002716203260078

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. *Archives of General Psychiatry, 67*(7), 729-738. doi:10.1001/archgenpsychiatry.2010.75

Pessoa, L. (2015). Précis on the cognitive-emotional brain. *Behavioral and Brain Sciences, 38*.

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nature Reviews: Neuroscience, 11*(11), 773-783. doi:10.1038/nrn2920

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

Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2011). *Handbook of functional MRI data analysis*: Cambridge University Press.

Prateeksha, S., Roopesh, B. N., & Vijayasagar, J. K. (2014). Response inhibition in children with conduct disorder: A preliminary report. *Indian Journal of Health and Wellbeing, 5*(11), 1325-1330.

Rahm, C., Liberg, B., Wiberg-Kristoffersen, M., Aspelin, P., & Msghina, M. (2013). Rostro-caudal and dorso-ventral gradients in medial and lateral prefrontal cortex during cognitive control of affective and cognitive interference. *Scandinavian Journal of Psychology, 54*(2), 66-71.

Raschle, N., Zuk, J., Ortiz-Mantilla, S., Sliva, D. D., Franceschi, A., Grant, P. E., . . . Gaab, 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.

Raschle, N. M., Fehlbaum, L. V., Menks, W. M., Euler, F., Sterzer, P., & Stadler, C. (2017). Investigating the Neural Correlates of Emotion–Cognition Interaction Using an Affective Stroop Task. *Frontiers in Psychology, 8*(1489). doi:10.3389/fpsyg.2017.01489

Raschle, N. M., Lee, M., Buechler, R., Christodoulou, J. A., Chang, M., Vakil, M., . . . Gaab, N. (2009). Making MR imaging child's play - pediatric neuroimaging protocol, guidelines and procedure. *Journal of Visualized Experiments*(29). doi:10.3791/1309

Roy, M. J., Costanzo, M. E., Blair, J. R., & Rizzo, A. A. (2014). Compelling evidence that exposure therapy for PTSD

normalizes brain function. *Studies in Health Technology and Informatics, 199*, 61-65.

Rubia, K., Halari, R., Cubillo, A., Mohammad, A. M., Scott, S., & Brammer, M. (2010). Disorder-specific inferior prefrontal hypofunction in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure conduct disorder during cognitive flexibility. *Human Brain Mapping, 31*(12), 1823-1833. doi:10.1002/hbm.20975

Rubia, K., Halari, R., Smith, A. B., Mohammad, M., Scott, S., & Brammer, M. J. (2009). Shared and disorder-specific prefrontal abnormalities in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure CD during interference inhibition and attention allocation. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(6), 669-678. doi:10.1111/j.1469-7610.2008.02022.x

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. *American Journal of Psychiatry, 165*(7), 889-897. doi:10.1176/appi.ajp.2008.07071084

Sampl, S., Trestman, R., & Krauss, W. (2013). START NOW facilitator manual. *Farmington, University of Connecticut Health Center*.

Schiffer, B., Pawliczek, C., Mu, B., Forsting, M., Gizewski, E., Leygraf, N., & Hodgins, S. (2014). Neural mechanisms underlying cognitive control of men with lifelong antisocial behavior. *Psychiatry Research: Neuroimaging, 222*(1), 43-51.

Schupp, H. T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. I., & Hamm, A. O. (2007). Selective visual attention to emotion. *Journal of Neuroscience, 27*(5), 1082-1089. doi:10.1523/jneurosci.3223-06.2007

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

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. *Archives of General Psychiatry, 69*(8), 814-822. doi:10.1001/archgenpsychiatry.2011.2070

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 32*(4), 811-830. doi:10.1016/j.neubiorev.2007.12.002

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience, 15*(3), 324-337. doi:10.1162/089892903321593063

Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention deficit hyperactivity disorder. *American Journal of Psychiatry, 171*(3), 276-293.

Shelley, B. P., & Trimble, M. R. (2004). The insular lobe of Reil–its anatamico-functional, behavioural and neuropsychiatric attributes in humans–a review. *The World Journal of Biological Psychiatry, 5*(4), 176-200.

Silk, J. S., Steinberg, L., & Morris, A. S. (2003). Adolescents' emotion regulation in daily life: Links to depressive symptoms and problem behavior. *Child Development, 74*(6), 1869-1880.

Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences, 13*(8), 334-340. doi:10.1016/j.tics.2009.05.001

Smaragdi, A., Cornwell, H., Toschi, N., Riccelli, R., Gonzalez-Madruga, K., Wells, A., . . . Fairchild, G. (2017). Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(8), 703-712. doi:10.1016/j.jaac.2017.05.015

Sommer, M., Hajak, G., Döhnel, K., Meinhardt, J., & Müller, J. L. (2008). Emotion-dependent modulation of interference processes: an fMRI study. *Acta Neurobiologiae Experimentalis, 68*(2), 193-203.

Song, S., Zilverstand, A., Song, H., Uquillas, F. d. O., Wang, Y., Xie, C., . . . Zou, Z. (2017). The influence of emotional interference on cognitive control: A meta-analysis of neuroimaging studies using the emotional Stroop task. *Scientific Reports, 7*.

Stadler, C., Poustka, F., & Sterzer, P. (2010). The heterogeneity of disruptive behavior disorders - implications for neurobiological research and treatment. *Frontiers in Psychiatry, 1*, 21. doi:10.3389/fpsyt.2010.00021

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. *Journal of Psychiatric Research, 41*(5), 410-417. doi:10.1016/j.jpsychires.2006.01.006

Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends in Cognitive Sciences, 9*(2), 69-74.

Steinberg, L. (2014). *Age of opportunity: Lessons from the new science of adolescence*: Houghton Mifflin Harcourt.

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

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*, 643-662. doi:Doi 10.1037/0096-3445.121.1.15

Swanson, M. C. J., Bland, R.C., Newman, S.C. (1994). Antisocial personality disorders. *Acta Psychiatrica Scandinavica, 89*(s376), 63-70.

Szasz, P. L., Szentagotai, A., & Hofmann, S. G. (2011). The effect of emotion regulation strategies on anger. *Behaviour Research and Therapy, 49*(2), 114-119.

Teisl, M., & Cicchetti, D. (2008). Physical abuse, cognitive and emotional processes, and aggressive/disruptive behavior problems. *Social Development, 17*(1), 1-23.

Tugade, M. M., Fredrickson, B. L., & Feldman Barrett, L. (2004). Psychological resilience and positive emotional granularity: Examining the benefits of positive emotions on coping and health. *Journal of Personality, 72*(6), 1161-1190.

Uher, R., Brooks, S. J., Bartholdy, S., Tchanturia, K., & Campbell, I. C. (2014). Increasing cognitive load reduces interference from masked appetitive and aversive but not neutral stimuli. *PloS One, 9*(4), e94417. doi:10.1371/journal.pone.0094417

van der Meer, D.-J., & van der Meere, J. (2004). Response inhibition in children with conduct disorder and borderline intellectual functioning. *Child Neuropsychology, 10*(3), 189-194.

Van Dillen, L. F., Heslenfeld, D. J., & Koole, S. L. (2009). Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. *Neuroimage, 45*(4), 1212-1219. doi:10.1016/j.neuroimage.2009.01.016

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. *American Journal of Psychiatry, 169*(10), 1109-1116. doi:10.1176/appi.ajp.2012.12020191

Vitaro, F., Brendgen, M., & Barker, E. D. (2006). Subtypes of aggressive behaviors: A developmental perspective. *International Journal of Behavioral Development, 30*(1), 12-19. doi:10.1177/0165025406059968

Vythilingam, M., Blair, K., McCaffrey, D., Scaramozza, M., Jones, M., Nakic, M., . . . Mitchell, D. (2007). Biased emotional attention in post-traumatic stress disorder: a help as well

as a hindrance? *Psychological Medicine, 37*(10), 1445-1455.

Wang, F. L., Chassin, L., Lee, M., Haller, M., & King, K. (2017). Roles of Response Inhibition and Gene–Environment Interplay in Pathways to Adolescents' Externalizing Problems. *Journal of Research on Adolescence 27*(2), 258-277.

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. *Journal of Neuroscience, 18*(1), 411-418. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9412517

White, S. F., Costanzo, M. E., Blair, J. R., & Roy, M. J. (2015). PTSD symptom severity is associated with increased recruitment of top-down attentional control in a trauma-exposed sample. *Neuroimage: Clinical, 7*, 19-27. doi:10.1016/j.nicl.2014.11.012

Wolgast, M., Lundh, L.-G., & Viborg, G. (2011). Cognitive reappraisal and acceptance: An experimental comparison of two emotion regulation strategies. *Behaviour Research and Therapy, 49*(12), 858-866.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of Abnormal Psychology, 118*(1), 117-130. doi:10.1037/a0014657

Zinchenko, A., Kanske, P., Obermeier, C., Schroger, E., & Kotz, S. A. (2015). Emotion and goal-directed behavior: ERP evidence on cognitive and emotional conflict. *Social Cognitive and Affective Neuroscience, 10*(11), 1577-1587. doi:10.1093/scan/nsv050

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Curriculum Vitae

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Education

02/2014 –	**PhD in Psychology** at the University of Basel and Psychiatric University Clinics, UPK (Research Department of the Child and Adolescent Psychiatry) Research interests: Investigation of the neural and behavioral basis of child and adolescent psychiatric disorders such as conduct disorder
01/2011 – 07/2013:	**Master of Science in Psychology** (minor subject: Popular Culture Studies) at the University of Zurich Specialization: Cognitive Psychology and Cognitive Neuroscience Master thesis with the title "Neural basis of individual differences in reading: Effects of poor reading, socioeconomic status, bilingualism and sex on third graders' specialization for print"
10/2006 – 01/2011:	**Bachelor of Science in Psychology** (minor subject: Popular Culture Studies) at the University of Zurich Bachelor thesis with the title "Spiegelneurone und ihr Einfluss auf die Symptomatik der Schizophrenie" („Mirror neurons and their effect on the symptomatology of schizophrenia")
09/1999 – 05/2005:	**Secondary school** at the Swiss School of Barcelona (bilingual education: Spanish and German) Swiss Maturity Diploma with emphasis on modern languages Spanish university entrance examination (selectividad)

Practical experience

04/2016 – 05/2016:	**Research visit (1 month, 100%)** in the group of Prof. Dr. Margaret Sheridan, University of North Carolina at Chapel Hill, Psychology Department
02/2014 –	**Project collaborator (100%)** in the study *Neural correlates of emotional processes in adolescents with conduct disorder* (Prof. Dr. Dr. Christina Stadler), funded by the Swiss National Science Foundation (SNSF) and the study *Neurobiology and treatment of adolescent female conduct disorder: The central role of emotion (FemNAT-CD)*, funded by the EU 7th Framework Programme for Research and Technological Development (FP7), at the Research Department of the Child and Adolescent Psychiatry of Psychiatric University Clinics, UPK, Basel (direction: Prof. Dr. Dr. Christina Stadler)
12/2013:	**Scientific assistant** for the dissertation project *Arbeitsbedingungen und Gesundheit des Kita-Personals in der Stadt Zürich* (*Working conditions and health of the day-care center staff in Zurich)* at the division of Public and Organisational Health of the Institute of Social and Preventive Medicine at the University of Zurich (direction: lic.phil. Olivia Blöchliger)
02/2012 – 07/2013:	**Project collaborator** for the study *Frühenglisch im Gehirn (Early education of English in the brain,* Prof. Dr. Urs Maurer), funded by the Swiss National Science Foundation (SNSF) at the chair of Cognitive Neuroscience at the University of Zurich (direction: Prof. Dr. Urs Maurer)
11/2012 – 01/2013:	**Scientific assistant** for the dissertation project *Plastizität neurophysiologischer Korrelate der Sprachverarbeitung über die Lebensspanne (Plasticity of*

neurophysiologic correlates of language processing throughout lifespan, direction: lic. phil. Katharina Rufener) at the chair of Neuropsychology at the University of Zurich

07/2011 – 03/2013: **Project collaborator** for the study *PROGRESS* at the Military Academy at ETH Zurich (MILAK) by the Armed Forces College (direction: Dr. H. Annen). Principal: Swiss Federal Office of Sport (BASPO) in cooperation with the University of Zurich, chair of Clinical Psychology and Psychotherapy (direction: Prof. Dr. Ulrike Ehlert)

09/2011 – 12/2011: **Research internship** at the chair of Cognitive Psychology at the University of Zurich. Collaborator for the study *Switching personality* regarding the relationship between cognition, heart rate, and personality (direction: Dr. Miriam Gade)

02/2011 – 05/2011: **Internship** at the Department of Neurology at the Charité Universitätsmedizin, Berlin, with focus on neuropsychological diagnostics (division manager of neuropsychology: Dr. rer. nat. Ute Kopp)

09/2004 – 05/2016: **Tutor** for Spanish, English, French, and German (beginner to advanced levels)

Trainings in academia

01/2015 – 11/2015: **antelope@university** career program, funded by the Equal Opportunities Office of University of Basel

Scientific courses:

06/2017: **MRI safety** certificate, Radiology & Nuclear Medicine Clinic, University Hospital Basel (**advanced** course)

05/2015: "How to **publish** in peer-reviewed journals" course (Dr. Gunther Tress, TRESS & TRESS GbR), within the framework of antelope@university

04/2015: **MRI safety** certificate, Radiology & Nuclear Medicine Clinic, University Hospital Basel (**basic** course)

02/2015: Statistical Parametric Mapping (**SPM**) course at the Translational Neuromodeling Unit, University of Zurich & ETH Zurich

09/2014: Good Clinical Practice (**GCP**) basic course at University Hospital Basel

12/2012: Continuation Course **SPSS** (direction: Dr. Jürg Schwarz), IT Training and Development, University of Zurich

06/2011 – 07/2011: **Observer training** and one and a half day observation of participants at an assessment center at the chair of Work and Organizational Psychology at the University of Zurich (Prof. Dr. Martin Kleinmann)

Skills courses:

11/2015: "Keeping your talk fresh: **Storytelling** techniques" (Julie Stearns, impulsplus), within the framework of antelope@university

10/2015: „**Oral presentations**: methods and self-confidence" course (Susanne Matuschek, MATUSCHEK CONSULTING) at the University of Basel

09/2015: "**Negotiation strategies**: fair and systematic" course (Jasmin Döhling-Wölm, karrierekunst), within the framework of antelope@university

04/2015: "**Successful self-marketing**" course (Dr. Petra Wüst, Wüst Consulting), within the framework of antelope@university

02/2015: "How to become a more **efficient researcher**" training (Dr. Bärbel Tress, TRESS & TRESS GbR), within the framework of antelope@university

Skills

Research skills: Paediatric neuroimaging, fMRI, VBM, EEG, neurophysiology (e.g., HRV), neuropsychological testing, clinical interviews (e.g., K-SADS), statistics, oral presentations, scientific writing, participant recruitment, project coordination

Teaching skills:	Supervision of a master student (MSc. Letizia Wyss) and interns/research assistants (all part of the neuroimaging team within the group of Prof. Dr. Dr. Stadler), school teaching (within the framework of "School and Researchers meet") for Gymnasium Liestal (03/2015) and Gymnasium Leonhard, Basel (04/2015)
Computer skills:	SPM, MATLAB, GingerALE meta-analysis software, Mango (Multi-image Analysis GUI), SPSS, BESA, Brain Vision Analyzer, Microsoft Office
Language skills:	German (native speaker), Spanish (second language), English (fluent), French (good), Catalan (basics), Italian (basics)

Grants and awards

02/2017:	Grant of the Freiwillige Akademische Gesellschaft (**FAG**) Basel supporting PhD completion (CHF 7'000)
07/2016:	Invitation for workshop „Human Brain Projects and Public Health" by WHO
04/2016:	Grant of the Freiwillige Akademische Gesellschaft (**FAG**) Basel supporting a one-month research stay in Chapel Hill, North Carolina, USA, in the group of Prof. Dr. Margaret Sheridan (CHF 2'500)
04/2016:	Travel grant provided within the framework of **antelope@university** career program, funded by the Equal Opportunities Office of University of Basel, supporting travel costs for academic exchange with Prof. Dr. Margaret Sheridan (CHF 1'040)
01/2015:	**Poster award** at the Clinical Research Day of University Hospital Basel, Basel

Memberships

2016 –	Freiwillige Akademische Gesellschaft (FAG) Basel
03/2016 –	Organization for Human Brain Mapping (OHBM)
10/2015 –	Cognitive Neuroscience Society (CNS)

Publications

2017:

Fehlbaum, L.V., Raschle, N.M., Menks, W.M., Prätzlich, M., Flemming, E., Wyss, L., Euler, F., Sheridan, M., Sterzer, P., & Stadler, C. (submitted to *Social Cognitive and Affective Neuroscience*). Altered neuronal responses during an affective Stroop task in adolescents with conduct disorder.

Rogers, J.C., Gonzalez-Madruga, K., Baker, R., Clanton, R., Pauli, R., Birch, P., Chowdhury, A., Kirchner, M., Andersson, J., Smaragdi, A., Puzzo, I., Baumann, S., Kohls, G., Raschle, N.M., **Fehlbaum, L.V.**, Menks, W.M., Stadler, C., Konrad, K., Freitag, C., Fairchild, G., & De Brito, S.A. (submitted to *The American Journal of Psychiatry*). White matter in youths with conduct disorder: Effects of sex and variation in callous traits.

Prätzlich, M., Oldenhof, H., Steppan, M., Ackermann, K., Baker, R., Batchelor, M., Baumann, S., Bernhard, A., Clanton, R., Dikeos, D., Dochnal, R., **Fehlbaum, L.V.**, … & Stadler, C. (under review in *Journal of Criminal Justice*). Resting autonomic nervous system activity is unrelated to antisocial behavior dimensions in adolescents: Cross-sectional findings from a European multi-centre study.

Oldenhof, H., Prätzlich, M., Ackermann, K., Baker, R., Batchelor, M., Baumann, S., Bernhard, A., Clanton, R., Dikeos, D., Dochnal, R., **Fehlbaum, L.V.**, … & Popma, A. (under review in *Journal of Criminal Justice*). Baseline autonomic nervous system activity in female children and adolescents with conduct disorder: Psychophysiological findings from the FemNAT-CD study.

Raschle, N.M., Menks, W.M., **Fehlbaum, L.V.**, Steppan, M., Smaragdi, A., Gonzalez-Madruga, K., Rogers, J., Clanton, R., Kohls, G., Martinelli, A., Bernhard, A., Konrad, K., Herpertz-Dahlmann, B., Freitag, C.M., Fairchild, G., de Brito, S., & Stadler, C. (in press). Callous-unemotional traits and brain structure: Sex-specific effects in anterior insula of typically-developing youths. *Neuroimage: Clinical*. doi: 10.1016/j.nicl.2017.12.015

Raschle, N.M.*, **Fehlbaum, L.V.***, Menks, W.M., Euler, F., Sterzer, P., & Stadler, C. (2017). Investigating the neural correlates of emotion-cognition interaction using an affective Stroop task. *Frontiers in Psychology, 8*, 1489. doi: 10.3389/fpsyg.2017.01489

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. doi: 10.1016/j.jaac.2016. 12.006

2016:

Raschle, N.M., Tshomba, E., Menks, W.M., **Fehlbaum, L.V.**, & Stadler, C. (2016). Emotions and the brain – or how to master 'The Force'. *Frontiers for Young Minds*, 4:16. doi: 10.3389/frym.2016.00016

Eberhard-Moscicka, A.K., Jost, L.B., **Fehlbaum, L.V.**, Pfenninger, S.E., & Maurer, U. (2016). Temporal dynamics of early visual word processing - Early versus late N1 sensitivity in children and adults. *Neuropsychologia, 91*, 509-518. doi: 10.1016/j.neuropsychologia. 2016.09.014

2015:

Raschle, N.M., Becker, B.L.C., Smith S., **Fehlbaum, L.V.**, Wang, Y., Gaab, N. (2015). Investigating the influences of language delay and/or familial risk for dyslexia on brain structure in 5-year-olds. *Cerebral Cortex,* 1–13. doi: 10.1093/cercor/bhv267

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

* indicates shared first authorship

Conference abstracts and posters

2017:

Fehlbaum, L.V., Raschle, N.M., Menks, W.M., Euler, F., Sterzer, P. & Stadler, C. (2017). Neuronal basis of emotion processing and cognitive control in healthy young adults and adolescents with and without conduct disorder. Poster abstract accepted to the 4th FemNAT-CD General Assembly Meeting, Budapest, February 2017.

2016:

Fehlbaum, L.V., Menks, W.M., Euler, F., Flemming, E., Sterzer, P., Stadler, C. & Raschle, N.M. (2016). Frontotemporal and limbic gray matter volume reductions in youths with conduct disorder. Poster abstract accepted to the Organization for Human Brain Mapping (OHBM) Annual Meeting, Geneva, June 2016.

Fehlbaum L.V., Raschle, N.M., Menks, W.M., Euler, F. & Stadler, C. (2016). Neuronal basis of emotion and cognitive processing in young adults and adolescents. Poster abstract accepted to the Cognitive Neuroscience (CNS) Annual Meeting, New York, April 2016.

2015:

Fehlbaum, L.V., Prätzlich, M., Raschle, N.M., Menks, W.M., Kersten L., Mannstadt S., Dietrich C. & Stadler C. (2015). Linking heart rate variability to psychological health and brain structure in female adolescents with and without conduct disorder. Poster abstract accepted to the 3rd FemNAT-CD General Assembly Meeting, Bilbao, November 2015.

Fehlbaum, L.V., Raschle, N.M., Menks, W.M., Euler, F., & Stadler, C. (2015). Emotion processing and emotion regulation in youths with empathy deficits. Poster abstract accepted to the Clinical Research Day of University Hospital Basel, Basel, January 2015. *Awarded CHF 300 poster price.*

2014:

Fehlbaum, L.V., Raschle, N.M., Menks, W.M., Euler, F., & Stadler, C. (2014). Emotion processing and emotion regulation in youths with empathy deficits. Poster abstract accepted to the 1st Computational Psychiatry Meeting, Zurich, May 2014.

Basel, December 2017

L. Fehl

Declaration by candidate

I declare that this dissertation has been composed independently. All research articles have been published in or submitted to peer-reviewed journals and were written in collaboration with the listed co-authors. All citations are referenced and only the mentioned sources were used.

The dissertation includes the following articles:

Fehlbaum, L.V., Raschle, N.M., Menks, W.M., Prätzlich, M., Flemming, E., Wyss, L., Euler, F., Sheridan, M., Sterzer, P., & Stadler, C. (submitted to *Social Cognitive and Affective Neuroscience*). Altered neuronal responses during affective Stroop task performance in adolescents with conduct disorder.
Data acquisition, data analysis and interpretation, drafting the manuscript

Raschle, N.M.*, **Fehlbaum, L.V.***, Menks, W.M., Euler, F., Sterzer, P., & Stadler, C. (2017). Investigating the neural correlates of emotion-cognition interaction using an affective Stroop task. *Frontiers in Psychology, 8*(1489). doi:10.3389/fpsyg.2017.01489
* indicates shared first authorship
Data acquisition, data analysis and interpretation, drafting the manuscript, critical revision

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
Data acquisition, data analysis and interpretation, drafting the manuscript, critical revision

Additional articles:

Raschle, N.M., Tshomba, E., Menks, W.M., **Fehlbaum, L.V.**, & Stadler, C. (2016). Emotions and the brain – or how to master 'The Force'. *Frontiers for Young Minds*, 4:16. doi: 10.3389/frym.2016.00016
Critical revision of the manuscript

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. doi: 10.1016/j.jaac.2016. 12.006
Data acquisition, critical revision of the manuscript

Raschle, N.M., Menks, W.M., **Fehlbaum, L.V.**, Steppan, M., Smaragdi, A., Gonzalez-Madruga, K., Rogers, J., Clanton, R., Kohls, G., Martinelli, A., Bernhard, A., Konrad, K., Herpertz-Dahlmann, B., Freitag, C.M., Fairchild, G., de Brito, S., & Stadler, C. (in press). Callous-unemotional traits and brain structure: Sex-specific effects in anterior insula of typically-developing youths. *Neuroimage: Clinical*. doi: 10.1016/j.nicl.2017.12.015
Data acquisition, data analysis and interpretation, critical revision of the manuscript

Appendices

Appendix A

Supplementary material to study 1:

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

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.

Appendix B

Supplementary material to study 2:

Investigating the neural correlates of emotion-cognition interaction using an affective Stroop task

1.1 Negative and neutral images used in the emotional priming task. All images are part of the DAPS (Cordon et al., 2013), mirroring the IAPS commonly used in adults (Lang, 2008). Numbers correspond to DAPS coding.

1300	2222	2400	3180	6510	9007	9530
1410	2273	2487	3250	6830	9040	9570
1441	2274	2488	3500	6831	9050	9571
1500	2299	2506	3530	7002	9120	9600
1540	2302	2515	5201	7004	9140	9620
1620	2308	2518	5202	7081	9180	9622
1670	2314	2560	5390	7090	9181	9630
1850	2342	2580	5870	7130	9230	9910
1942	2382	2593	5940	7242	9250	9911
2018	2383	2594	6190	7440	9400	9912
2026	2384	2691	6210	7492	9420	9921
2032	2385	2791	6211	7509	9421	
2036	2388	2800	6250	7512	9430	
2037	2390	2870	6260	7595	9440	
2053	2393	2900	6300	7820	9470	
2058	2396	3030	6312	8230	9490	
2205	2398	3160	6370	8480	9500	

Cordon, I.M., Melinder, A.M., Goodman, G.S., and Edelstein, R.S. (2013). Children's and adults' memory for emotional pictures: examining age-related patterns using the Developmental Affective Photo System. *J Exp Child Psychol* 114(2)**,** 339-356. doi: 10.1016/j.jecp.2012.08.004.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (2008). "International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8.". (Gainesville, FL.: University of Florida).

1.2. Behavioral pilot study assessing in-scanner task

A pilot study was run to validate the neuroimaging task behaviorally in 8 healthy adults (1 dataset was discarded due to incomplete data). Data was analyzed with regards to accuracy and reaction times with two separate 2 (emotion: Neg, Neu) by 3 (task: C, S, IC) repeated measures ANOVAs. Pilot data assessment indicated a significant emotion by cognition interaction on both accuracy measures ($F(2,5)=9.224$, $p=.021$) and reaction times

(F(2,5)=14.451, p=.008). Moreover, a significant main effect of cognition was detected in accuracy measures (F(2,5)=182.542, p<0.001) and reaction times (F(1,6)=30.470, p=0.002).

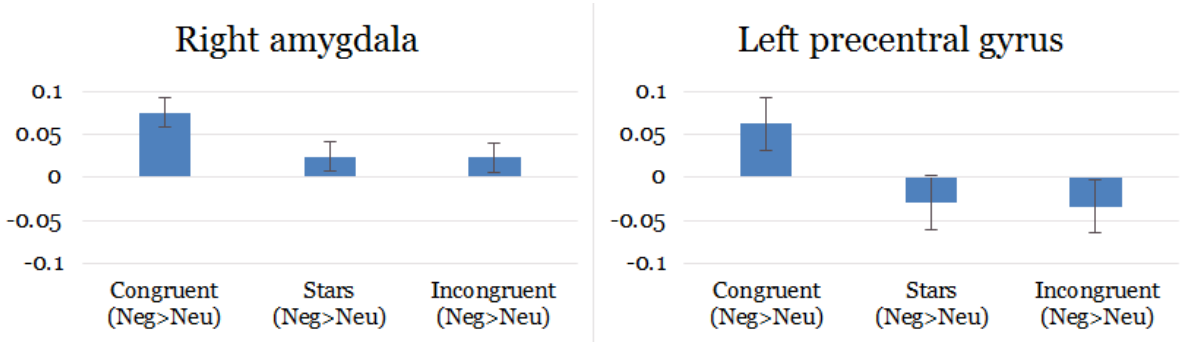
		Congruent [±SD]	**Stars [±SD]**	**Incongruent [±SD]**
Accuracy [raw scores]	Negative prime	50.0 [1.5]	42.9 [1.07]	46.0 [2.9]
	Neutral prime	49.4 [1.7]	40.6 [2.4]	46.6 [3.36]
Reaction Times [ms]	Negative prime	672.4 [82.7]	684.9 [89.5]	761.4 [113.3]
	Neutral prime	663.7 [91.0]	696.8 [102.0]	784.0 [109.3]

Supplementary Figures and Tables

2.1 Emotional valence rating (N=30, raw scores).

	Range	**Mean**	**Standard Deviation**
Negative primes	1.75	-1.20	0.44
Neutral primes	2.13	0.66	0.46

2.2 Supplementary Figure 1. Additional graphs displaying follow-up investigations on the influence of emotion on cognition within regions of interests (right amygdala, left precentral gyrus).



Appendix C

Supplementary material to study 3:

Altered neuronal responses during affective Stroop task performance in adolescents with conduct disorder

SI1. Additional information on participants

All adolescents were invited to take part in two separate sessions including psychometric testing and magnetic resonance imaging. Clinical and behavioral assessments were conducted at the Department of Child and Adolescent Psychiatric Center in Basel or at the Department of Psychiatry and Psychotherapy at Charité – Universitätsmedizin Berlin, Campus Mitte, while neuroimaging took place at the University Hospital of Basel or at the Berlin Center of Advanced Neuroimaging at the Charité – Universitätsmedizin Berlin. We excluded subjects with an IQ score below 70. Adolescents with CD were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL, Kaufman et al. (1997) and were excluded if they did not meet the DSM-5 diagnostic criteria for CD.

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. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(7), 980-988. doi:10.1097/00004583-199707000-00021

SI2. Psychometric testing: Socioeconomic status

Conduct disorder (CD) and typically developing (TD) adolescents did not differ in socioeconomic status as indexed by mothers' education and family income earned within the last 12 months. However, they did differ with regards to fathers' education (U=298.00, p=.017). Furthermore, CD and TD did not differ in subjective social status as assessed by the MacArthur Community ladder measuring social status within their community, but did differ in the MacArthur SES ladder assessing social status within their country (U=196.50, p=.026).

		CD	TD	*p*	
		[%]	[%]	**Sig. 2-tailed** *Mann-Whitney test*	
Mother characteristics					
	N=	28	38		
Education (highest degree earned)	Pre-primary education (ISCED 0)	0.00%	0.00%	.356	
	Primary education or first stage of basic education (ISCED 1)	3.60%	2.60%		
	Lower secondary or second stage of basic education (ISCED 2)	14.30%	5.30%		
	(Upper) secondary education (ISCED 3)	60.70%	65.80%		
	Post-secondary non-tertiary education (ISCED 4)	3.60%	5.30%		
	First stage of teritary education (ISCED 5)	17.90%	21.10%		
	Second stage of tertiary education (doctoral level) (ISCED 6)	0.00%	0.00%		
Father characteristics					
	N=	24	37		
Education (highest degree earned)	Pre-primary education (ISCED 0)	4.20%	0.00%	.017	*
	Primary education or first stage of basic education (ISCED 1)	4.20%	0.00%		
	Lower secondary or second stage of basic education (ISCED 2)	4.20%	5,4%		
	(Upper) secondary education (ISCED 3)	62.50%	37.80%		
	Post-secondary non-tertiary education (ISCED 4)	0.00%	2.70%		
	First stage of tertiary education (ISCED 5)	25.00%	54.10%		
	Second stage of tertiary education (doctoral level) (ISCED 6)	0.00%	0.00%		
Family characteristics					
	N=	23	33		
Income earned within the past 12 months	less than 4'500 CHF	4.30%	3.00%	.224	
	4500 CHF - 10'699 CHF	4,3%	3.00%		
	10'700 CHF - 15'199 CHF	8,7%	3.00%		
	15'200 CHF - 22'299 CHF	4,3%	3.00%		
	22'300 CHF - 31'249 CHF	8,7%	3.00%		
	31'250 CHF - 44'599 CHF	8,7%	3.00%		
	44'599 CHF - 66'999 CHF	13.00%	12.10%		
	67'000 CHF - 88'999 CHF	8,7%	9.10%		
	89'000 and greater	13.00%	39.40%		
	I don't know	17,4%	6.10%		
	No response	4,3%	15.20%		

		[Mean ± SD]	[Mean ± SD]		
Subjective socioeconomic status (MacArthur)	*N*=	20	31		
	SES Ladder	5.35±2.08	6.68±1.96	.026	*
	N=	21	30		
	SES Comunity ladder	6.57±2.16	7.13±1.78	.346	

* p<.05; two-tailed t-test; all other t-tests non-significant at threshold of p<.05
Education ranking according to ISCED97

SI3. Medication of adolescents with CD (N=35) and typically developing controls (N=39) at MRI session

		CD	TD
		N=35	*N*=39
ADHD medication	Methylphenidate	6	0
	Atomoxetine	1	0
Pain medication	Paracetamol	1	0
Depression/bipolar disorder medication	Quetiapine	1	0
	Valproate	1	0
Allergy medication	Montelukast	0	1
	Antihistamines	0	1

CD=conduct disorder patients; TD=typically developing adolescents

SI4. Button box responses

In the course of the study we faced technical problems with the recording of button #3 of the button box used to record the responses resulting in missing data for six controls and two patients (within the participants included in the present paper) for button number three only. Each file affected by this problem was individually evaluated with regards to whether the missing responses consistently represented correct answers. Only if we were certain that we are able to interpret the missing answers correctly, we proceeded with including the respective file into further MRI analyses (all other data were discarded).

SI5. In-scanner performance (accuracy, reaction times) for adolescents with CD (N=39) and typically developing controls (N=39)

			CD Mean ± SD	TD Mean ± SD
Reaction times [ms]	Negative prime			
		Congruent	758.8 [98.8]	739.3 [101.3]
		Incongruent	857.9 [115.5]	848.2 [99.3]
	Neutral prime			
		Congruent	767.9 [96.1]	749.0 [99.7]
		Incongruent	872.5 [107.4]	852.2 [111.2]
Accuracy [raw scores]	Negative prime			
		Congruent	46.6 [2.8]	48.0 [2.3]
		Incongruent	43.2 [3.8]	44.8 [3.6]
	Neutral prime			
		Congruent	47.0 [2.9]	48.6 [1.5]
		Incongruent	43.9 [3.6]	45.3 [3.6]

Appendix D

Supplementary material to study 6:

Microstructural white matter alterations in the corpus callosum of girls with conduct disorder

Supplementary Table 1. *Means and standard deviations (SD) for the λ1, λ2, λ3 eigenvalues (10-3 mm2/s) in the corpus callosum (body) of female adolescents with conduct disorder (CD) and typically developing controls (TD).*

	λ1 (SD)	λ2 (SD)	λ3 (SD)
CD	1.34 (0.03)	0.63 (0.03)	0.53 (0.03)
TD	1.35 (0.05)	0.65 (0.04)	0.55 (0.04)

Supplementary table 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).*

		coordinates of peak location[a]			Cluster size (number of	
# Brain region	L/R	X	Y	Z	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≤0.05 FWE-corrected. [c] Region of interest

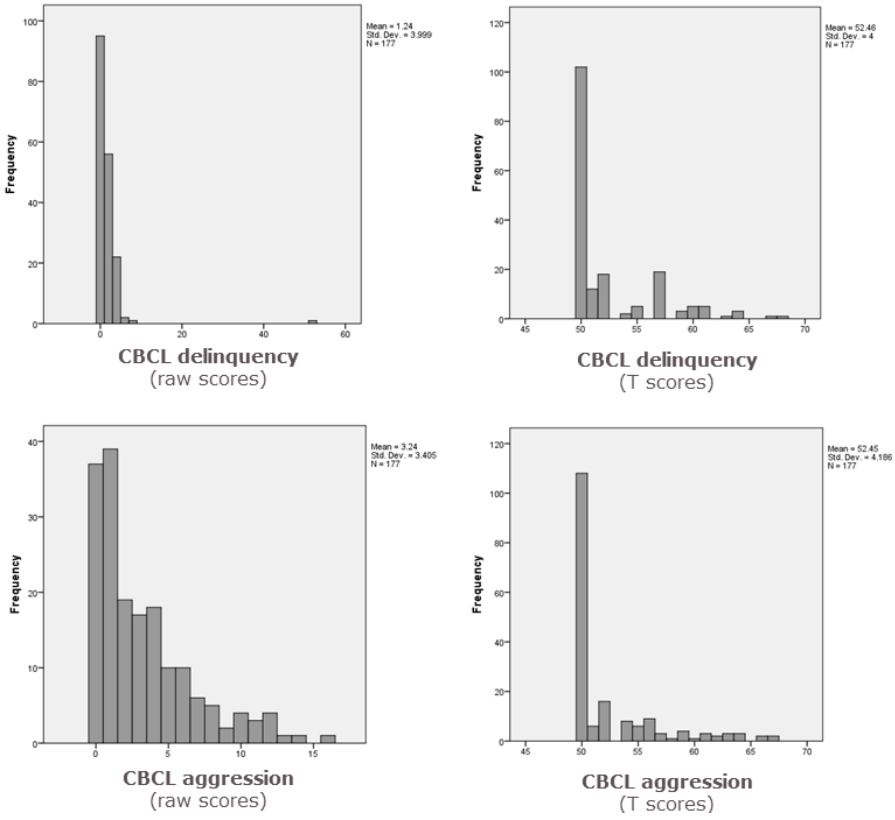
Appendix E

Supplementary material to study 7:

Callous-unemotional traits and brain structure: Sex-specific effects in anterior insula of typically-developing youths

Figure S1

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. Furthermore, previous work has indicated that CU-traits are negatively correlated with empathy (Kahn, et al. 2017; Pasalich, et al. 2014), which has been additionally tested, see point (**5**), by correlating the new composite score and data obtained using the Griffith Empathy Measure. Furthermore, mean gray matter volume parameter estimates from

independent bilateral anterior insula regions of interest were correlated with total empathy scores.

(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.

(2) Between-assessments correlations

		YPI (callous-unemotional)	ICU (total)	CU-traits (composite)
All	YPI (callous-unemotional)	1		
	ICU (total)	0.324**	1	
	CU-traits (composite)	0.768**	0.853**	1
Girls	YPI (callous-unemotional)	1		
	ICU (total)	0.276**	1	
	CU-traits (composite)	0.741**	0.850**	1
Boys	YPI (callous-unemotional)	1		
	ICU (total)	0.280*	1	
	CU-traits (composite)	0.737**	0.851**	1

Note. Pearson correlations (r). ** p<.01.

(3) Testing changes in Cronbach's alpha between assessments

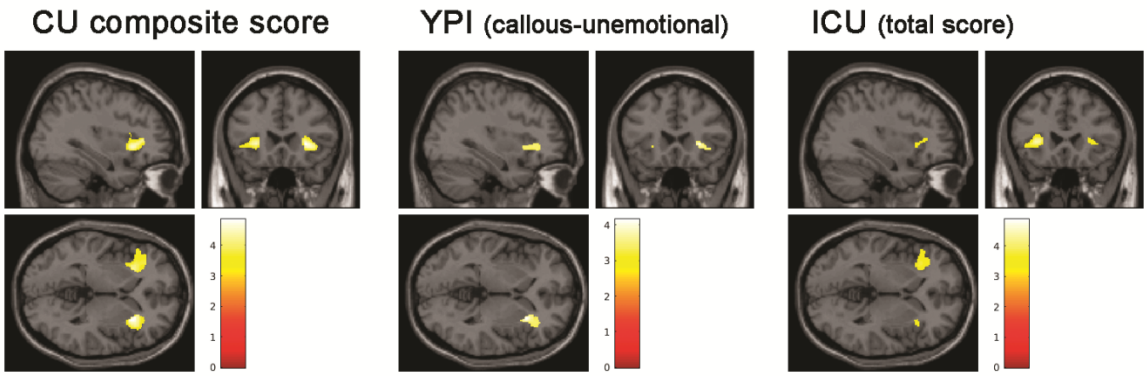
		YPI (callous-unemotional)	ICU (total)
All	YPI (callous-unemotional)		
	ICU (total)	p < 0.8460	
	CU-traits (composite)	**p < 0.0058****	**p < 0.0120***
Girls	YPI (callous-unemotional)		
	ICU (total)	p < 0.8423	
	CU-traits (composite)	p < 0.1956	p < 0.0846
Boys	YPI (callous-unemotional)		
	ICU (total)	p < 0.4509	
	CU-traits (composite)	**p < 0.0343***	p < 0.1725

Note. Difference in Cronbach's Alpha (statistical inference based on cocron[1,2]). * p <.05; ** p<.01

[1]Diedenhofen, B. (2013). cocron: Statistical comparisons of two or more alpha coefficients (Version 1.0-0). Available from http://r.birkdiedenhofen.de/pckg/cocron/

[2]Feldt, L. S., Woodruff, D. J., & Salih, F. A. (1987). Statistical inference for coefficient alpha. Applied Psychological Measurement, 11, 93-103.

(4) Replication of correlational findings in boys for ICU total, YPI callous-unemotional and composite score (p<0.001, uc).



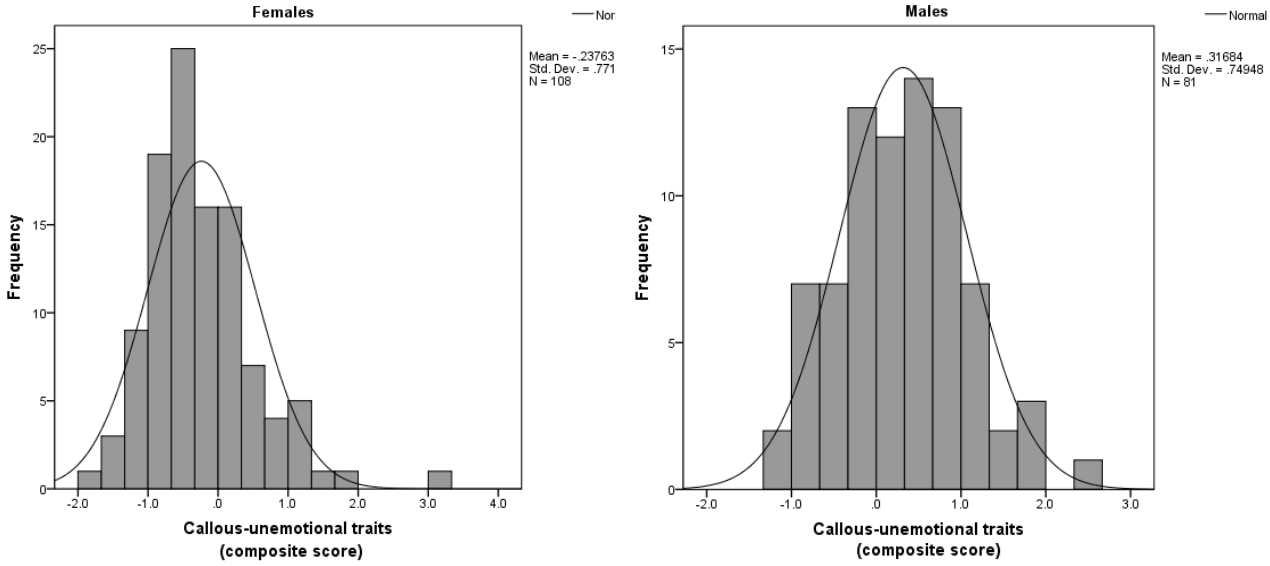
(**5**) Correlational analysis linking the new CU-composite score and empathy (as based on the total score of the Griffith Empathy Measure) indicate a significant negative relationship for both typically developing boys and girls (r=-0.526 and r=-0.485 ; both *p*<0.001). Furthermore, partial correlation analysis (considering the main covariates age, TIV, site) between mean parameter estimates derived from independent bilateral anterior insula regions of interest and empathy scores reveal a negative relationship. However, findings only reached formal levels of statistical significance for the right anterior insula (r=-0.236; *p*<0.040).

Kahn, R. E., et al. (2017). The Moderating Role of Anxiety in the Associations of Callous-Unemotional Traits with Self-Report and Laboratory Measures of Affective and Cognitive Empathy. J Abnorm Child Psychol 45(3):583-596.

Pasalich, D. S., M. R. Dadds, and D. J. Hawes (2014). Cognitive and affective empathy in children with conduct problems: additive and interactive effects of callous-unemotional traits and autism spectrum disorders symptoms. Psychiatry Res 219(3):625-30.

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.

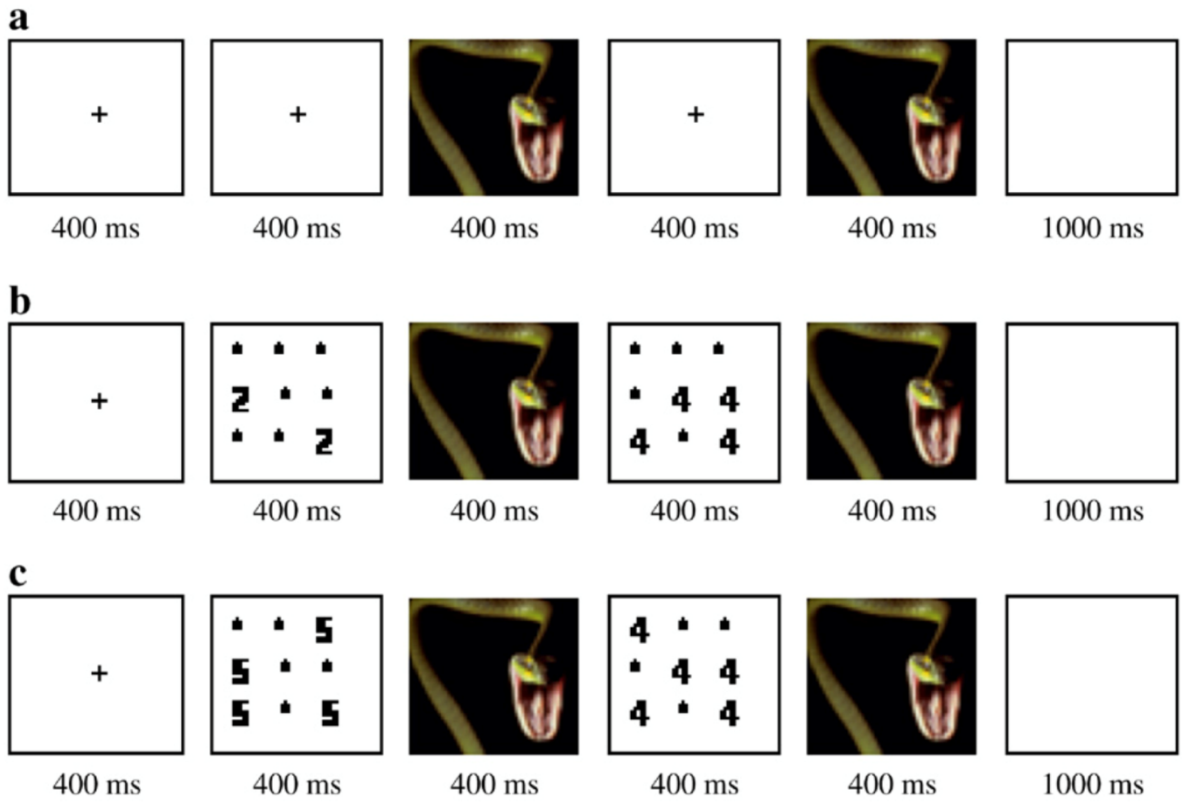
Site #	01	02	04	05	07
#of participants	36	41	44	18	50
[girls/boys]	[16/20]	[22/19]	[22/22]	[18/0]	[30/20]
scanner model	Siemens Trio	Siemens Prisma	Siemens Trio	Siemens Prisma	Phillips
#of slices	192	192	192	192	192
TR	1900ms	1900ms	1900ms	1900ms	1900ms
TE	2.74ms	3,42ms	4.1ms	3.42ms	3.7ms
TI	900ms	900ms	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.

Appendix F

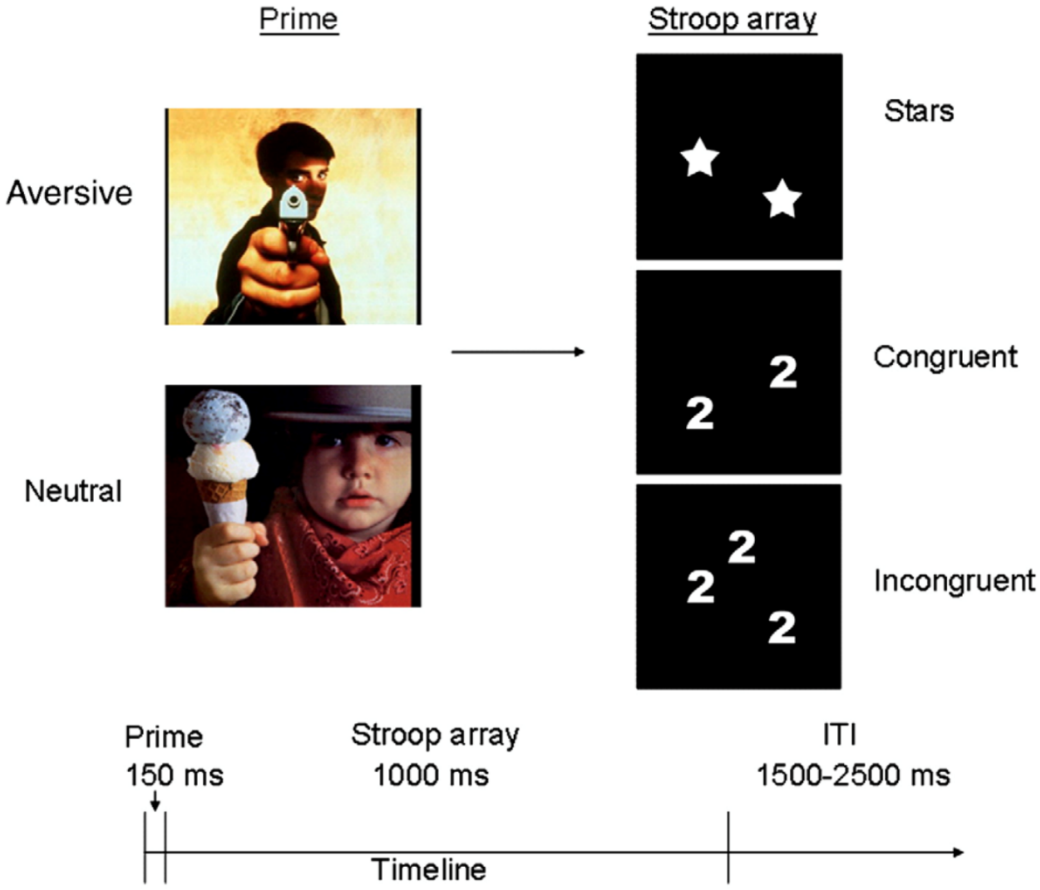
Previously used affective Stroop task designs

I) Task design by Blair and colleagues (2007). a) negative view trial, b) negative congruent trial, c) negative incongruent trial.



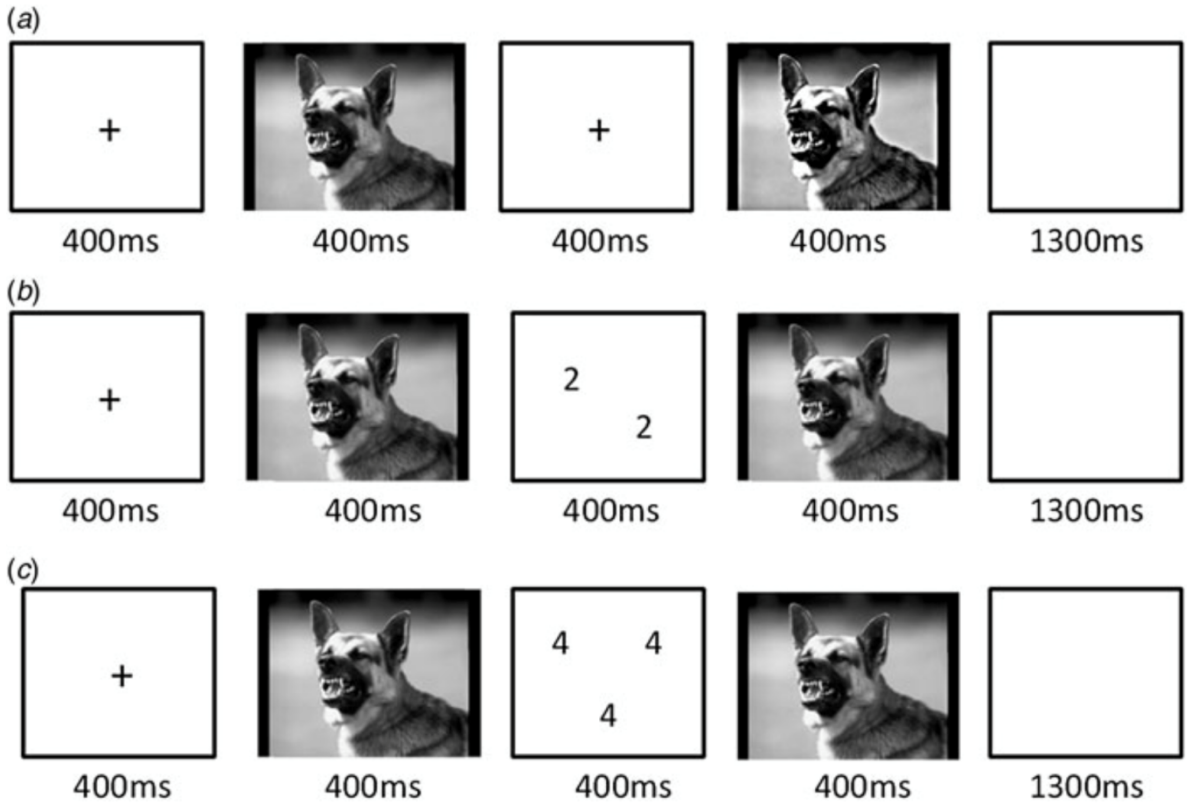
Blair, K. S., Smith, B. W., Mitchell, D. G., Morton, J., Vythilingam, M., Pessoa, L., Fridberg, D., Zametkin, A., Sturman, D., Nelson, E. E., Drevets, W.C., Pine, D. S., Martin, A., & Blair, R. J. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage*, 35(1), 430-440. doi:10.1016/j.neuroimage.2006.11.048

II) Task design by Hart and colleagues (2010). Aversive or neutral prime followed by a Stroop array (stars, congruent, or incongruent). ITI=intertrial interval.



Hart, S. J., Green, S. R., Casp, M., & Belger, A. (2010). Emotional priming effects during Stroop task performance. Neuroimage, 49(3), 2662-2670. doi:10.1016/j.neuroimage.2009.10.076

III) Task design by Hwang and colleagues (2016). a) negative view trial, b) negative congruent trial, c) negative incongruent trial.



Hwang, S., Nolan, Z. T., White, S. F., Williams, W. C., Sinclair, S., & Blair, R. J. (2016). Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. Psychol Med, 46(7), 1485-1496. doi:10.1017/S0033291716000118

Right side:

Word cloud based on this dissertation. Words with greater prominence appear more frequently in the text. Image generated using www.wordle.net.


main
Basel
control
typically
activity
areas
adolescents
gray
anterior
neuronal
superior
YPI
differences
Stadler
Sterzer
scores
traits
aggressive
example
results
evidence
Psychology
Brain
tasks
Rubia
compared
lobe
neuroimaging
analysis
effect
neutral
problems
load
participants
previous
Blair
left
interest
boys
callous-unemotional
CU-traits
However
interaction
research
Raschle
emotion
significant
ALE
right
trials
meta-analysis
gyrus
fMRI
youths
role
callosum
analyses
frontal
disorder
task
cortex
different
temporal
negative
also
emotions
clinical
individuals
emotion-cognition
Stroop
studies
alterations
matter
line
corpus
increased
structural
conduct
response
development
activation
volume
brain
developing
data
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findings
affective
Fairchild
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cognition
study
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structure
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regulation
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emotional
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CD
disorders
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regions
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number
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used
inferior
TD
antisocial