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**Evaluating self-regulation in adolescents with conduct
problems or severe disruptive behavior disorders - possible
neural targets for future interventions**

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“And now that you don’t have to be perfect, you can be good.”

John Steinbeck (East of Eden)

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TABLE OF ABBREVIATIONS

ACC = anterior cingulate cortex

AMG = amygdala

ANOVA = analysis of variance

APA = American Psychological Association

APD = antisocial personality disorder

AI = anterior insula

BOLD = blood oxygen level dependent

CBCL = child behavior checklist

CD = conduct disorder

CP = conduct problems

CU = callous unemotional

DBD = disruptive behavior disorder

dlPFC = dorsolateral prefrontal cortex

dmPFC = dorsomedial prefrontal cortex

DSM = diagnostic and statistical manual

EEG = electroencephalography

EMG = electromyography

EPI = echo-planar imaging

EU = European Union

fMRI = functional magnetic resonance imaging

FEW = family wise error

ICD = international classification of disease

ICU = inventory of callous unemotional traits

INS = insula

IQ = intelligence quotient

LOCF = last observation carried forward

LPE = limited prosocial emotions

MATRICES = multidisciplinary approaches to translational research in conduct syndromes

MP-RAGE = magnetization-prepared rapid gradient echo

MRI = magnetic resonance imaging

MST = multisystemic therapy

NEO = neuroticism, extraversion, openness

NF = neurofeedback

OFC = orbitofrontal cortex

ODD = oppositional defiant disorder

PDS = pubertal development scale

PTSD = posttraumatic stress disorder

PFC = prefrontal cortex

RCT = randomized controlled trial

RPQ = reactive proactive questionnaire

ROI = region of interest

rtfMRI = real-time functional magnetic resonance imaging

SAD = substance use disorder

SDQ = strengths and difficulties questionnaire

SPM = statistical parametric mapping

TAU = treatment as usual

TFCO = treatment foster care Oregon

TRF = teacher report form

vmPFC = ventromedial prefrontal cortex

WHO = World Health Organization

WISC = Wechsler intelligence scale for children

1. Introduction

Disruptive behavior is a common phenomenon in human nature and frequently occurs during adolescence. It is associated with conduct problems (CP) in healthy as well as clinical populations. When CP exceed the normal range and disruptive behaviors are severe, Disruptive Behavior Disorder (DBD), including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), is often diagnosed. The prevalence of any DBD during childhood and adolescence was estimated globally up to 6.1% (predominantly in western cultures (O'Connell, Boat, & Warner, 2009)), with an estimated prevalence of around 2.1% for CD and 3.6% for ODD (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Children and Adolescents with DBD (CD/ODD) show ongoing patterns of uncooperative and defiant behavior such as violation of the rights of others and physical aggression, which can seriously impact their daily and future lives and also frequently impacts those around them, including teachers, peers, and family members (Coghill, 2013; Odgers et al., 2007). This is of considerable importance as DBDs create a burden not only on the affected patients and their families, but they are also associated with an exceptionally high societal and economic burden affecting healthcare, educational and justice systems (Erskine et al., 2014).

Individuals who fulfill diagnostic criteria of DBD also frequently display a conspicuous pattern of behavior that is characterized by a callous, uncaring and unemotional interpersonal style, including deficits in empathy, emotional affectivity and conscientiousness. These behaviors have been labeled the *affective dimension of psychopathy* (Hare & Neumann, 2008) or *callous-unemotional traits* (CU traits) in research (Frick & Ray, 2015). The growing clinical and scientific interest in subtypes of DBD recently led to the introduction of a Limited Prosocial Emotions (LPE) specifier to the diagnosis of CD in the DSM-5, and, in the upcoming ICD-11, also to the diagnosis of ODD (APA, 2013; WHO, 2018). The LPE specifier is designated to be applied to those individuals who exhibit high CU traits in addition to the diagnosis of DBD, allowing for subtype-specific treatment.

Overall, evidence-based psychological treatments for DBD only reach small to moderate effect sizes in teacher, parent, children and blinded observer ratings and there is currently not enough evidence to support one specific form of treatment over another (Bakker, Greven, Buitelaar, & Glennon, 2017). Additionally, psychopharmacological treatment effectively reduce symptoms of DBD, but is only indicated when patients show high reactive aggression or severe emotion dysregulation (Gorman et al., 2015; Pilling, Gould, Whittington, Taylor, & Scott, 2013). Further, pharmacologic treatment is usually used only in parallel with psychosocial interventions and is often accompanied by adverse effects (Loy, Merry, Hetrick, & Stasiak, 2017a; Pilling et al., 2013). Moreover, children and adolescents with a diagnosis of DBD who fulfill the criteria of the LPE specifier appear to represent a more severe phenotype with more stable behavior problems, more severe aggressive behavior and poorer response to treatment than those diagnosed without this specifier (low CU traits) (Frick, Ray, Thornton, & Kahn, 2014; Hawes, Price, & Dadds, 2014). However, independently from the severity of CU traits, a recent meta-analysis revealed that effect-sizes are generally small for psychological interventions for DBD (Bakker et al., 2017) and less than a quarter of CD/ODD patients have received effective help yet (Coghill, 2013). As a consequence, there is a considerable need for new, innovative, non-pharmacological and customizable treatment strategies for individuals with diagnosis of DBD, especially for those exhibiting high CU traits.

Interestingly, in adult normative populations, disruptive (antisocial) behavior and psychopathic traits have been associated with altering subcortical reactivity in affective processing of negative faces (angry and fearful) (Hyde, Byrd, Votruba-Drzal, Hariri, & Manuck, 2014). Further, emotion recognition deficits associated with CU traits in older children with diagnosis of DBD can already be detected in healthy preschoolers displaying low concern (White, Briggs-Gowan, et al., 2016). Moreover, longitudinal studies of healthy development found that less subcortical reactivity to negative emotional faces was associated with increased risk for antisocial behavior and CU traits (Gard et al., 2017; Holz et al., 2017). These findings in healthy individuals are in line with clinical findings in clinical groups with a diagnosis of DBD (compared to controls) during affective

processing, comprising subcortical and cortical regions, such as the amygdala, the anterior insula (AI) and the anterior cingulate cortex (ACC) (Viding & McCrory, 2018). To date, there exists no cross-sectional study investigating affective processing in healthy adolescents in the range from low to increased levels of CP and at a tight span of age. Such an investigation could offer insights into neurophysiological changes happening in the subclinical range of DBD at the particularly critical period of adolescence and might be informative for the development of future prevention- and intervention-strategies.

Importantly, individuals with a diagnosis of DBD also show deficits in the emotional self-regulation of negative affect (Graziano et al., 2019), which can be further differentiated into emotional reactivity (cortical and subcortical) on the one hand and into prefrontal cognitive control of emotions on the other hand (Achterberg, van Duijvenvoorde, Bakermans-Kranenburg, & Crone, 2016). Thus, brain-based measures of CP in adolescence should also focus on prefrontal control, and brain-based treatment strategies targeting areas involved in affective processing and aiming at the improvement of self-regulation of reactivity or cognitive control of emotions may be a promising treatment-strategy for adolescents with DBD and high CU traits.

1.1 Symptoms and diagnosis of DBD

CD and ODD are usually preceded and accompanied by CP, which occur to some degree also in typically developing adolescents and are characterized by less obedience, frequent fits of rage, verbal and physical aggression and delinquency. As long as the diagnostic criteria for any DBD discussed below are not fully met, such behavior is normal or subclinical.

1.1.1 Conduct Disorder

CD is characterized by a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated (meeting at least three symptoms from table 1). Further, the disturbance in behavior has to cause clinically significant impairments in social, academic, or occupational functioning (APA, 2013).

Table 1. Diagnostic criteria of CD

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others
2. Often initiates physical fights
3. Has used a weapon that can cause serious physical harm to others
4. Has been physically cruel to others
5. Has been physically cruel to animals
6. Has stolen while confronting a victim
7. Has forced someone into sexual activity

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage
9. Has deliberately destroyed others' property (other than by fire setting)

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car
11. Often lies to obtain goods or favors or to avoid obligations
12. Has stolen items of nontrivial value without confronting a victim

Serious Violation of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 years
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period
15. Is often truant from school, beginning before age 13 years

The prevalence of CD has been estimated to be approximately twice as high in males (around 3-4%) as in females (around 1-2%) and the etiology of CD is thought to be multifactorial with a cumulative nature. Environmental influences have been estimated in twin studies to account for around 50% of the variance in CD phenotypes with prenatal, perinatal, familial, and neighborhood risk factors are considered to play roles (Jaffee, Strait, & Odgers, 2012; Latimer et al., 2012). Further, poverty, low socio-economic status, defiant peers and community violence have been identified as substantial environmental risk factors (Boden, Fergusson, & Horwood, 2010; Price, Drabick, & Ridenour, 2019; Trudeau, Mason, Randall, Spoth, & Ralston, 2012).

1.1.2 Oppositional Defiant Disorder

Oppositional Defiant Disorder is characterized by a pattern of angry or irritable mood, argumentative or defiant behavior, or vindictiveness (meeting at least four symptoms from table

2). Additionally, the disturbance in behavior need to be associated with distress in the individual or others in his or her immediate social context (e.g. family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other areas of functioning.

Table 2. Diagnostic criteria of ODD

Angry and Irritable Mood

1. Often loses temper
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 months.

The prevalence of ODD has been estimated to be slightly higher in boys (around 2.2%) than in girls (around 1.5%) before adolescence, whereas this difference seems to resolve during adolescence (Boylan, Vaillancourt, Boyle, & Szatmari, 2007; Loeber, Burke, Lahey, Winters, & Zera, 2000). The etiology of ODD is also thought to be multifactorial and shares environmental risk factors and genetic variance with CD, e.g. a unique genetic influence that increases the tendency for externalizing behaviors (Azeredo, Moreira, & Barbosa, 2018; Ghosh & Sinha, 2012; Tuvblad, Zheng, Raine, & Baker, 2009). However, the majority of studies support a distinction between ODD and CD, because ODD typically has its onset before the onset of CD and many children with ODD never meet full criteria of CD and similarly, many children with CD are not diagnosed with ODD (D. M. Fergusson, Horwood, & Lynskey, 1994; Frick et al., 1993; Martel, Gremillion, Roberts, von Eye, & Nigg, 2010).

1.2 Subtypes within DBD

In addition to the primary diagnostic criteria, multiple subtypes of CD can be specified to account for the phenotypic heterogeneity among children and adolescents who fulfill diagnostic criteria of CD. First, the age of onset defines either the childhood-onset type (with individuals showing at least one symptom characteristic of CD prior to age 10 years) or the adolescent-onset type (with individuals show no symptom characteristic of CD prior to age 10 years). Although the most appropriate age for the cutoff between these subtypes is continually debated (Moffitt et al., 2008), there is evidence indicating that the earlier the onset of symptoms, the more severe and persistent are the resulting detrimental behaviors (Frick & Viding, 2009). Currently, there is no age of onset specification for ODD.

Next, the severity of CD and ODD symptoms can be specified. A *mild* form of CD is diagnosed when few, if any, CP in excess of the minimum required to make the diagnosis are present (e.g. lying, truancy, staying out after dark without permission, or other rule breaking). A *moderate* form of CD is diagnosed when the number of CP intermediate between those specified in the mild and the severe type of CD (e.g. stealing without confronting a victim, vandalism) and a *severe* form of CD is diagnosed when many CP are present, or when CP cause considerable harm to others (e.g. forced sex, physical cruelty, use of a weapon, stealing while confronting a victim, breaking and entering). Regarding ODD, symptom severity again can be either a mild (symptoms are confined to only one setting, e.g. at home, at school, at work or with peers), moderate (some symptoms are present in at least two settings) or severe (some symptoms are present in three or more settings) form of ODD.

1.2.1 Psychopathic or callous-unemotional traits

Importantly, psychopathic traits, including CU traits, represent a meaningful specifier for severe antisocial, respectively less prosocial, and aggressive behaviors in adult psychopathology and have been suggested as a relevant factor in subtyping CD in youth (Frick, Barry, Bodin, & Gacono, 2000). The current concept of psychopathy describes a pattern of personality characterized by low levels of empathy and sense of guilt, arrogance, superficial charm, irresponsible and

resulting antisocial behaviors (Cleckley, 1951). Research further disentangled this concept in three inter-correlated domains: *The CU traits* consist of lack of empathy and remorse, with short-lived emotions, whereas the *manipulative domain* is characterized by verbal and manipulative abilities, superficial charm, egocentricity and eloquence (also named narcissism) and the *daring-impulsive domain* (also named impulsivity or psychopathy-related impulsivity) traits include irresponsibility, proneness to boredom, novelty seeking and low prosocial behavior (Brazil & Forth, 2016). Previous research pointed out that these domains are not exclusive of adult psychopathology, but they can also be found in children and adolescents (Frick & White, 2008), leading to the concept of childhood psychopathy, firstly conceptualized by Forth and colleagues (Forth, Hart, & Hare, 1990), and further supported by Frick (Frick, O'Brien, Wootton, & McBurnett, 1994) and Lynam (Lynam, 1997). Subsequent studies (Frick et al., 2000; Kotler & McMahon, 2005) confirmed that the multidimensional structure of adult psychopathy is detectable also in the adolescent populations. Moreover, these studies on children and adolescents strongly suggested the association between psychopathic personality traits and CP (Asscher et al., 2011; López-Romero, Romero, & Luengo, 2012; Lynam et al., 2009).

In addition to the diagnostic specification of age of onset and symptom severity, psychopathic or CU traits now can be assessed in children and adolescents and qualify for the LPE specifier, which has been introduced with the DSM-5. However, CU traits are also debated as a more broad personality construct, in isolation from other facets of psychopathy, and they are also associated to altered emotional reactivity and brain structural alterations within normative populations (Frick & Ray, 2015; Hyde, Shaw, & Hariri, 2013; Raschle et al., 2018). Thus, CU traits might be considered a trait-like dimensional construct applicable in healthy and clinical populations. In turn, prosocial behavior, as reduced in psychopathic traits and associated with higher empathy and less anger and aggression in children (Roberts, 1997), can serve as an inverse proxy to the measure of CU traits (Truedsson, Fawcett, Wesevich, Gredeback, & Wahlstedt, 2019).

To fulfill criteria of the LPE specifier, an individual must have persistently displayed at least two out of four characteristics over at least 12 months in multiple relationships and settings (see

table 3). These characteristics need to reflect the individual's typical pattern of interpersonal and emotional functioning over this period and not just occasional occurrences in some situations. Therefore, multiple information sources need to be considered in addition to the individual's self-report, e.g. parents, teachers, co-workers, extended family members and peers, to validate the diagnosis of this subtype. However, in the DSM-5 and ICD-10 the LPE specifier is provided only for the diagnosis of CD, but in the upcoming ICD-11, the LPE specifier will be also applicable to the diagnoses of ODD. Interestingly, the definition of the LPE specifier in the ICD-11 will include an additional symptom that is related to *indifference to punishment*, which is not present in current diagnostic manuals.

Table 3. Diagnostic criteria for the LPE specifier

Lack of remorse or guilt:

Does not feel bad or guilty when he or she does something wrong (exclude remorse when expressed only when caught and/or facing punishment).

The individual shows a general lack of concern about the negative consequences of his or her actions. For example, the individual is not remorseful after hurting someone or does not care about the consequences of breaking rules.

Callous—lack of empathy:

Disregards and is unconcerned about the feelings of others.

The individual is described as cold and uncaring. The person appears more concerned about the effects of his or her actions on himself or herself, rather than their effects on others, even when they result in substantial harm to others.

Unconcerned about performance:

Does not show concern about poor/problematic performance at school, at work, or in other important activities.

The individual does not put forth the effort necessary to perform well, even when expectations are clear, and typically blames others for his or her poor performance.

Shallow or deficient affect:

Does not express feelings or show emotions to others, except in ways that seem shallow, insincere, or superficial (e.g., actions contradict the emotion displayed; can turn emotions "on" or "off" quickly) or when emotional expressions are used for gain (e.g., emotions displayed to manipulate or intimidate others).

1.2.2 Reactive and proactive aggression

Research on subtypes of aggressive behavior also established the differentiation between *reactive* and *proactive* aggression (Smeets et al., 2017) as well as the differentiation between *impulsive* and *instrumental* aggression (Berkowitz, 1993). Both concepts are closely interlinked and can be considered equivalent for the sake of simplicity. Reactive/impulsive aggression are defined by defensive responses to a perceived threat, provocation or frustration whereas proactive/instrumental aggression describe the more unprovoked, premeditated, manipulative and selfish behaviors (Dodge & Coie, 1987). This terminology has not been transferred into diagnostic specifiers yet, but may still be relevant for characterizing DBD, especially with regard to decisions on specific treatment-strategies. Additionally, these distinctions have been related to CU traits. Although proactive aggression was found to be more prevalent in individuals with high CU traits than in those with low CU traits (Helseth, Waschbusch, King, & Willoughby, 2015), individuals with high CU traits were also more likely to exhibit combined proactive and reactive aggression (Fanti, Frick, & Georgiou, 2009). Moreover, a recent study reported that proactive but not reactive aggression was negatively associated with cognitive and affective empathy, with a combined proactive–reactive aggression cluster showing significantly lower scores on cognitive and affective empathy compared to a reactive and low aggression cluster (Euler, Steinlin, & Stadler, 2017). These findings match the assumption of a more severe subtype among DBD, displaying high CU traits and combined reactive-proactive aggression.

1.3 Comorbidities of DBD

DBD (CD and ODD) can be diagnosed concurrently within children and adolescents since the introduction of the DSM-5. Children with diagnosis of ODD have a 15-fold higher risk to also develop CD throughout childhood or adolescence (Copeland, Shanahan, Erkanli, Costello, & Angold, 2013). The most frequent comorbid condition in CD/ODD is Attention Deficit Hyperactivity Disorder (ADHD) with a comorbidity prevalence rate estimated up to 50% (Greene et al., 2002) and, along the developmental trajectory, symptoms of ADHD often precede symptoms of DBD (Martel et al., 2010). Instead, there is more evidence for a life-course

continuity from DBD to adult antisocial personality disorder (ASPD), especially for those exhibiting high CU traits (Copeland, Shanahan, Costello, & Angold, 2009; Herpers, Scheepers, Bons, Buitelaar, & Rommelse, 2014; Rowe, Costello, Angold, Copeland, & Maughan, 2010). Among DBD and ADHD, co-occurrences with other emotional and behavioral problems are very common. Internalizing disorders also occur frequently within DBD, with around 50% being reported to have comorbid major depressive disorder, bipolar disorder (around 40%) and anxiety disorders (around 35%) (Choi, Kim, Kim, & Kim, 2017; Greene et al., 2002). Further, in a clinical sample of adolescents with CD (aged 10-17 years) up to 56% reported having experienced at least one traumatic event such as physical or sexual abuse, vehicle accident, or being witness of death, suicide or abuse of a loved one, and post-traumatic stress disorder (PTSD) was reported in up to 39% of these cases (Reebye, Moretti, Wiebe, & Lessard, 2000). Finally, substance abuse disorders (SADs) and DBD are associated. Children and adolescents with SADs are approximately four times more likely to have a DBD, and, psychiatric history of ADHD, CD or ODD has been shown to increase the risk of subsequent substance abuse (Groenman, Janssen, & Oosterlaan, 2017; Ryan, Stanger, Thostenson, Whitmore, & Budney, 2013).

1.4 Psychopathology of DBD

The pathophysiology underlying DBDs has been extensively investigated. When tested with neurocognitive tasks, children and adolescents with CD/ODD compared with typically developing individuals show deficits in facial and vocal emotion recognition (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009; Stevens, Charman, & Blair, 2001), affective empathy (Martin-Key, Brown, & Fairchild, 2017), decision-making and reinforcement learning (Fanti, Kimonis, Hadjicharalambous, & Steinberg, 2016). This current work investigates adolescents with conduct problems or severe disruptive behavior disorders and focusses on potential neural correlates of cognitive control and possible neurocognitive changes in affective processing as a measure of treatment outcome. Decision-related studies will be described just briefly for the sake of completeness.

1.4.1 Affective processing

Affective processing has been studied extensively using a variety of tasks including the presentation of emotional images, facial expressions of emotions or empathy-eliciting stimuli, such as observing the pain in others.

1.4.1.1 Affective arousal versus emotional control

Affective arousal occurs when humans are emotionally engaged and feel passionate about something, for example angry, excited or fearful, and is paralleled by an increased sympatheticotonus (Thornton, 2016). Studies found that the activity of some brain regions is associated more strongly with the intensity of affective arousal (or emotional experiencing), whereas other regions are more strongly associated with the execution of cognitive emotion regulatory strategies (Cardinal, Parkinson, Hall, & Everitt, 2002; Ochsner, Silvers, & Buhle, 2012; Okon-Singer, Hendler, Pessoa, & Shackman, 2015). In the healthy population, the amygdala and insula have been repeatedly found to be involved in emotional experiencing, regardless of the emotional valence (positive or negative), so their activity levels can be generally considered as correlates of *affective arousal* (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Although emotional valence may not play a role, different emotional categories, such as anger and fear, are associated with diverging neural reactivity (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Particularly, the amygdala reactivity to affective stimuli has been associated with the perception of fearful facial expressions more strongly than with any other emotional category (Lindquist et al., 2012). Interestingly, psychopathic traits and APD scores (using facet scales of the NEO Personality Inventory-Revised) have also been associated with altered affective processing in a healthy community sample, with higher psychopathy scores were associated with lower amygdala reactivity, whereas higher APD scores were related to greater amygdala reactivity (Hyde et al., 2014). Prosocial behavior, however, is associated with higher affective arousal (as measured by pupil dilation) in healthy individuals (Hepach, Vaish, Müller, & Tomasello, 2017).

In contrast, medial and lateral prefrontal regions, such as the dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) have been repeatedly found to be involved in *cognitive emotion regulation* (Kurth et al., 2010). A recent meta-analysis on emotion regulation in the healthy population identified the superior temporal gyrus, angular gyrus and (pre)supplementary motor area to be involved in the execution of emotion regulatory strategies, initiated by prefrontal areas (Kohn et al., 2014). According to that analysis, the dlPFC could be related to regulation of cognitive processes such as attention, while the OFC and ventral-medial prefrontal cortex (vmPFC) may not necessarily reflect the regulatory process per se, but signals salience and therefore the need to initiate emotional regulation. Additionally, a cluster in the ACC, as a region that is anatomically and functionally in a central position to influence behavior and subcortical structures, has been related to affect generation (Kohn et al., 2014). Furthermore, children's emotional self-regulation appears to operate through orbitofrontal and dorsolateral prefrontal inhibition of striatal and amygdala reactivity (Davidson, 2002; Heatherton, 2011).

In individuals with DBD, a recent meta-analysis revealed lower activation of the dorsal and rostral ACC, medial PFC and ventral striatum compared to controls across emotion processing and executive function tasks, with the most consistent under-activation during affective processing found in the dlPFC and temporal pole (Alegria, Radua, & Rubia, 2016). In individuals with DBD and additional psychopathic traits, decreased activation in the hypothalamus and thalamus (extending into vmPFC and ventral striatum) and increased activation in the dlPFC was also observed during affective processing (Alegria et al., 2016). Additionally, another meta-analytic review revealed amygdala and striatal under-activation in individuals with DBD during emotion processing and reinforcement-related tasks (Noordermeer, Luman, & Oosterlaan, 2016). Importantly, in clinical studies comparing individuals with a diagnosis of DBD and high versus low CU traits often differ in amygdala reactivity in the processing of facial expressions of fear, with low CU individuals showing *hyperactivity*, but high CU individuals showing *hypoactivity* in this region (Jones, Laurens, Herba, Barker, & Viding, 2009; Sebastian et al., 2014;

Viding et al., 2012). Additionally, in dimensional analyses, decreasing activation in AI and the ACC was associated with increasing levels of CU traits in the across affective and empathy-eliciting tasks (Viding & McCrory, 2018). Moreover, reduced amygdala and insula reactivity were also found in adolescents with psychopathic traits compared to controls during the observation of pain in others (Marsh et al., 2013) and, in dimensional analyses in children with CP, the reactivity of the AI was found inversely correlated with the level of CU traits in response to others' pain (Lockwood et al., 2013). However, other studies show no link between specific neural responses and CU traits (Dotterer, Hyde, Swartz, Hariri, & Williamson, 2017; Passamonti et al., 2010).

Additionally, as reduced amygdala responses to emotional distress cues were found to mediate the relationship between CU traits and proactive aggression among children with CP, a potential association between CU traits and proactive aggression was suggested (Lozier, Cardinale, VanMeter, & Marsh, 2014). It is assumed that hypoactivity of the amygdala, the AI and ACC may disrupt empathic responses that are usually responsible for the inhibition of aggression-related behaviors and therefore may increase the risk of proactive aggression (Viding & McCrory, 2018). In contrast, heightened responses to distress cues in the amygdala in individuals with DBD and low CU traits (compared to those with high CU traits) could be related to increased risk of reactive aggression (White, Van Tieghem, et al., 2016). Moreover, the AI has been suggested to play an overarching role across different modalities of self-control and could therefore also be crucial for the inhibition of reactive aggression (Dambacher et al., 2015). Further, it has been commonly demonstrated that the AI and ACC are often co-activated across various paradigms of empathy processing, so both, AI and ACC, are considered significant structures in emotional awareness (Gu, Hof, Friston, & Fan, 2013).

Concerning emotional regulation in individuals with DBD, researchers have measured deficient self-regulation processes on the overt behavioral level that appear to be driving disruptive behavior, such as poor inhibitory control and feedback processing (Martel et al., 2010; Willoughby, Kupersmidt, Voegler-Lee, & Bryant, 2011). fMRI work has shown that school-age

children and adolescents with high disruptive behavior show a broad variety of structural and functional abnormalities related to affective processing, error-monitoring, problem-solving and self-regulation, including the amygdala, insula and left prefrontal cortex (Noordermeer et al., 2016). Interestingly, atypical ACC-amygdala coupling was associated with psychopathic traits in individuals with CD, and atypical OFC-amygdala coupling was also reported in individuals with CD and high CU traits during facial emotion processing (Ewbank et al., 2018; Finger et al., 2012; Marsh et al., 2008). Additionally, dysfunctional OFC-amygdala coupling in response to ecologically-valid social threat signals (processing of angry faces) was reported in individuals with a history of impulsive aggressive behavior.

1.4.2 Decision making

Poor decision-making in children and adolescents with DBDs is thought to result from deficits in reward- and punishment processing and avoidance learning (Blair, Veroude, & Buitelaar, 2018). During reward-processing, decreased striatal and ventromedial prefrontal cortex (vmPFC) responses to rewarding stimuli have been reported in individuals with DBD (White et al., 2013), whereas in punishment-processing children with psychopathic traits showed increased striatal and ventromedial responses compared to controls (Finger et al., 2008). Regarding avoidance-learning, reduced AI, dorsomedial prefrontal cortex (dmPFC) and caudate responses to stimuli that should be avoided have been observed in children and adolescents with DBD compared to controls (White et al., 2013). Biases in decision-making have been also reported, such that individuals with DBD are more influenced by potential rewards and less influenced by punishment (Fairchild, van Goozen, Stollery, et al., 2009). Moreover, dysfunctions in decision-related processes in individuals with DBD are hypothesized to increase the risk of frustration-based reactive aggression and antisocial behavior more generally (Blair et al., 2018).

1.4.3 Summary on affective processing in DBD

Summarizing, the research on affective processing in children and adolescents with DBD and CU traits indicates disrupted emotional and empathy-related neural processing involving

subcortical regions and their prefrontal regulation. However, whether adolescents with DBD are more (or less) emotionally reactive than their peers or less able to control their negative emotions, or a combination of the two, is hard to determine.

In healthy adolescents with CP but not meeting clinical criteria for DBD, however, prefrontal control may be more prominent than subcortical dysfunction, which might be associated with less susceptibility to negative emotions in these individuals. In turn, strengthening cognitive emotional regulation through specific treatment-strategies in adolescents with diagnosis of DBD may improve their disruptive behavior and may also increase adaptive emotional reactivity to affective stimuli in the social context.

2. Interventions

Behavioral and pharmacological interventions are the current recommended therapies for DBD (Gadow, Nolan, Sverd, Sprafkin, & Schneider, 2008). The most effective therapies for DBD focus on improving the quality of parenting in early and middle childhood. Such early treatments can reach large effect sizes with relatively brief interventions, e.g. duration of 10 weeks, and manageable effort (Sampaio et al., 2018). Given that outcomes of childhood-onset DBD are usually more detrimental than those of adolescent onset, interventions in this period are preferable (Comer, Chow, Chan, Cooper-Vince, & Wilson, 2013). However, behavioral treatment as usual (TAU) differs with the social welfare systems of countries. Standard-services are often limited to psychoeducation for parents and, in serious cases, removal of the child from the family into youth welfare institutions remains the only practical option.

2.1 Behavioral therapy in adolescence

In late childhood and adolescence multicomponent and multi-dimensional interventions such as multisystemic therapy (MST) (Henggeler, Schoenwald, Borduin, Rowland, & Cunningham, 2009) or treatment foster care oregon (TFCO) (Chamberlain, 2003), which are basically founded on social learning theory, seem to be effective (Garland, Hawley, Brookman-Frazee, & Hurlburt, 2008). These interventions mainly integrate family strategies, behavioral strategies, and cognitive-behavioral therapy. However, findings regarding the efficacy of these interventions on

symptoms of DBD are mixed, a recent meta-analysis reported generally small effects of MST in reducing delinquency and aggression-related outcomes (Henggeler et al., 2009), whereas another meta-analysis on TFCO reported a higher benefit for the more antisocial compared to less antisocial treatment groups. These results show, that further research on treatment strategies for adolescents with DBD is obliged to develop more subtype-specific treatment strategies and also possibly including novel brain-based techniques such as neurofeedback.

2.1.1 Impact of CU traits on behavioral therapy

The findings on the efficacy of behavioral treatments for patients with DBD and high CU traits suggest that these individuals appear to exhibit a more severe phenotype, benefiting less from current treatment approaches compared to those with low CU traits. On the one hand, CU traits in children with DBD were found to be unrelated to any posttreatment outcomes of a modular behavioral intervention (Kolko & Pardini, 2010) and did not moderate the effects of tailored family centered interventions (Hyde, Shaw, Gardner, et al., 2013). On the other hand, lower rates of treatment engagement, and lower rated quality of participation were reported for juvenile detainees with high CU traits (Colins, Van Damme, Fanti, & Andershed, 2017), and poorer treatment-responses were reported in children and adolescents with DBD and high CU traits receiving a 12-month multimodal intervention (Masi et al., 2013). Further, in a pilot-study a modified behavioral approach for children and adolescents with CU traits seemed to be effective when punishment was de-emphasized in the therapeutic concept (Miller et al., 2014). However, the heterogeneous outcomes among interventions in children and adolescents with DBD and high CU traits further underline the need for more research on subtype-specific and customizable interventions. For example, it has been suggested that treatment effects might be enhanced for individuals with high CU traits by the implementation of specific emotion regulation trainings, which could be applied either alone or in addition with behavioral interventions (Dadds, Cauchi, Wimalaweera, Hawes, & Brennan, 2012).

2.2 Pharmacological therapy

Psychopharmacological therapy should only be considered when behavioral interventions alone are not effective or, in particular, when severe emotional dysregulation and high reactive aggression is present (Bakker et al., 2017; Gorman et al., 2015; Pilling et al., 2013). Additionally, when DBD is comorbid to ADHD, pharmacological therapy can be also indicated in some cases. Stimulants and neuroleptics are the most effective medications in children and adolescents with ADHD and comorbid DBD (Pilling et al., 2013). Stimulants, such as methylphenidate and amphetamines, have shown medium to large effect sizes in children and adolescents with CD, predominantly with comorbid ADHD (Gorman et al., 2015; Pringsheim, Hirsch, Gardner, & Gorman, 2015). Antipsychotics, such as Risperidone, was shown in a recent meta-analyses to have large short-term effects on irritability and reactive aggression in 5-18 year old patients with DBD, but long-term use may lead to adverse effects such as weight gain and metabolic syndrome (Loy, Merry, Hetrick, & Stasiak, 2012, 2017b).

2.3 Neurofeedback

Neurofeedback is a clinical procedure that visualizes specific neurophysiological changes in the brain, enabling the recipient to apply cognitive or mental strategies in order to manipulate his own neurophysiologic activity, e.g. up or down regulation. Neurofeedback is a form of biofeedback, whereas the term biofeedback refers not only to the feedback of signals from the central nervous system but also to signals from the periphery such as skin conductance, heart-rate and muscle contraction (electromyography: EMG). The most commonly used techniques of neurofeedback today are electroencephalography (EEG) and real-time functional magnetic resonance imaging (rtfMRI).

Importantly, performance and the evaluation of performance data in NF-training are highly dependent on a variety of additional variables. One of the most critical decisions is the selection of target and control regions. A single specific target regions is selected, for example because it is assumed to be disrupted in a certain disorder or because it is vastly connected (a hub), assuming that its modulation has large functional impact on its network across the brain. Next, in order to

show specificity of the NF-training, a common practice is to implement so called *sham feedback* as a control condition, which can be NF from another brain region (a priori known to be functionally unrelated to the target region) or NF based on the activity of the same region but from another point in time or from another subject, or feedback from artificially created randomized signals. In case of clinical trials, the efficacy of NF trainings should be evaluated in comparison to a control group receiving an acknowledged form of behavioral therapy or TAU. Third, the kind of instruction is important as NF studies have varied as to whether participants were given explicit strategic instructions or whether they been encouraged to develop their own effective strategies. Since heretofore no explicit strategies for specific up- or downregulation are validated for any psychiatric population (e.g. thinking of positive rather than negative life events), it is sensible to leave instructions on regulation strategies open and at the responsibility of the participant. Additionally, it can be useful to survey the applied strategies after each NF training session.

2.3.1 EEG neurofeedback

EEG neurofeedback (EEG-NF) has been extensively studied as a form of treatment for children and adolescents with ADHD, and the efficacy of EEG-NF on the core symptoms of ADHD (inattention, hyperactivity, and impulsivity) has been the subject of several meta-analyses (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Loo & Barkley, 2005; Micoulaud-Franchi et al., 2014; Sonuga-Barke et al., 2013). However, to date, studies have not reached a consensus on the efficacy of EEG-NF on ADHD symptoms. A recent meta-analysis (including 520 patients with ADHD) found that evidence from well-controlled trials with probably blinded outcomes currently fails to support neurofeedback as an effective treatment for ADHD except for tentative support for standard NF protocols (Cortese et al., 2016). The current debate is on diverging symptom-rating, with significant improvement in randomized controlled trials (RCTs) when ADHD symptoms are rated by parents (non-blind), but not when rated by teachers (probably blind) (Bussalb et al., 2019). Besides these controversies on EEG-NF as an effective treatment for ADHD, EEG-NF may also in principle be

effective on symptoms of DBDs (due to the high comorbidity and overlapping psychophysiology among ADHD and DBD). A recent EEG-NF study in children with ADHD looked at clinical effects on comorbidity measured by the Strengths and Difficulties Questionnaire (SDQ) and showed significant improvement at follow-up compared to pre-test rated by parents for SDQ total score and the subdomains conduct problems, emotional problems and peer problems, but not prosocial behavior (Aggensteiner et al., 2019). Currently only one ongoing trial applies biofeedback of skin conductance specifically in children with DBD and varying levels of CU traits (work in progress, <https://matrices-project.eu/>).

2.3.2 Real-time fMRI neurofeedback

An increasing number of studies using real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF) have demonstrated the technical feasibility and successful self-regulation of brain networks and functions across multiple psychiatric populations (Sulzer et al., 2013; Thibault, Lifshitz, & Raz, 2016). To date, no study applied rtfMRI in children or adolescents diagnosed with DBD. However, one study applied rtfMRI-NF in adolescents (aged 12-17 years) with a diagnosis of ADHD (Alegria et al., 2017). They successfully learned self-regulation of the right inferior prefrontal cortex (an area that is associated with inhibition in ADHD) over a period of 11 rtfMRI-NF training sessions within two weeks and also showed significant reduction of ADHD symptoms even at a 11-months follow up (ibid.).

2.3.3 Physiological principles of rtfMRI-NF

The technique relies on real-time data processing and feedback of the hemodynamic Blood-Oxygen-Level Dependent (BOLD) signal, usually from a specific pre-defined target brain region, during certain tasks of self-regulation, e.g. upregulation, downregulation or no regulation, which can also be combined with additional stimuli (conditions). The BOLD-signal is based on neural activity-dependent changes in the relative concentration of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood, which induce different magnetic susceptibility in the blood and surrounding tissues, allowing the measure of hemodynamic response across the brain (Attwell & Iadecola, 2002). The BOLD-signal is assumed proportional to the local average

neuronal activity such that higher hemodynamic response reflects higher neural activity in the respective region (Heeger & Ress, 2002).

2.3.4 Learning principles of self-regulation

The leading and widely acknowledged learning mechanism of brain self-regulation with NF is the principle of *operant conditioning* (Black, Cott, & Pavloski, 1977; Caria, 2016), which is mediated by reinforcement of action that results in a desired change in brain activation. Further, the participant receives reinforcing feedback (positively connoted signs such as a “shining sun” or a “thumbs up” after successive NF trials) and evaluates it with regard to the regulation goal. Depending on the valuation outcome, the subject improves his mental regulation strategies, which are then changed or maintained (Paret & Hendler, under review). In a recent rtfMRI-NF study in adolescents with ADHD, motivation was enhanced via a score (0–10), reflecting the percentage of distance a rocket travelled through space (which corresponded to successful self-regulation). Additionally, a monetary incentive corresponding to the best performance in the session was given after the scan and, between conditions, researchers briefly acknowledged the effort in not moving the head and congratulated the participants for the score they obtained (Alegria et al., 2017). Interestingly, the OFC was found to be processing neurofeedback value (failure signals), suggesting that learning to self-regulate the brain with NF may involve similar neural networks as the learning of goal-directed action (Paret, Zaehring, Ruf, Ende, & Schmahl, 2019). A detailed overview of NF learning theories and practical implications for treatment can be found elsewhere (Arns et al., 2017; Gaume, Vialatte, Mora-Sanchez, Ramdani, & Vialatte, 2016; Sherlin et al., 2011; Strehl, 2014).

2.3.5 RtfMRI self-regulation in psychopathic populations?

Interestingly, AI upregulation with increasing negative emotions was explored in criminal psychopaths (sexual offenders), but within a limited group of four subjects of which only one managed successful upregulation (Sitaram et al., 2014). Thus, the sample size in this study was too low to draw definite conclusions. However, the study indicates that rtfMRI-NF training can

be possibly more challenging and require more training time and motivation in this clinical group.

Further, successful upregulation of the AI with increasing positive emotions and with increasing negative emotions has been shown in healthy people (Kadosh et al., 2016; Yao et al., 2016). Unspecific AI upregulation in patients with schizophrenia led to improved emotion recognition in a pre-post treatment comparison (Ruiz et al., 2013), whereas successful AI downregulation with decreasing negative emotions was only successfully conducted in one study with patients with spider phobia (Zilverstand, Sorger, Sarkheil, & Goebel, 2015).

Amygdala upregulation with increasing negative emotions was only conducted in two studies with healthy people (Paret et al., 2018; Posse et al., 2003), whereas in one of them negative upregulation of the amygdala could not be achieved. Further, in proof-of-concept studies successful upregulation of the amygdala has been shown in healthy people (Hellrung et al., 2018) as well as clinical populations compared to control groups or control conditions. In the clinical context, symptom improvement of depression, anxiety (Young et al., 2017) and PTSD (Gerin et al., 2016; Zotev et al., 2018) could be gained by upregulation of the amygdala with increasing positive emotions. Downregulation of the amygdala with decreasing negative emotions has been successful in healthy people (Herwig et al., 2019) and patients with Borderline Personality Disorder (BPD) (Paret et al., 2016) and PTSD (Nicholson et al., 2018).

So far, feasibility of rtfMRI-NF training of the amygdala and AI, aiming at improvements in emotion processing and emotion regulation as well as in corresponding behaviors, has been demonstrated across multiple psychiatric populations. However, randomized controlled clinical trials on the efficacy and clinical applicability of such interventions are pending, especially concerning adolescents with DBD and/or high CU (respectively psychopathic) traits.

3. Hypotheses

As discussed above affective processing and emotional self-regulation represent core deficits of DBD. Especially when accompanied with high CU traits impairments in affective processing as well as social-cognitive functioning are hard to treat. Although many children and adolescents

with DBD and CU traits seem to respond to acknowledged forms of treatment, most studies have found that CU traits predict relatively poor treatment outcomes, independent of DBD symptom severity before the treatment (Frick et al., 2014; Hawes et al., 2014). Additionally, parent-focused interventions have had large effect sizes on disruptive behavior symptoms in early- and mid-childhood but not in late childhood and adolescence, where multimodal child- and parent-focused interventions are recommended. Thus, specific, non-pharmacological and customizable treatment strategies are still at their advent to be developed, especially for adolescents with diagnoses of DBD and high CU traits.

The technique of rtfMRI-NF allows addressing specific cortical and subcortical brain structures that have been associated with disrupted affective processing in DBD and CU traits. So far, no one investigated the feasibility or efficacy of rtfMRI-NF from subcortical brain regions as a treatment for adolescents with CD or ODD and high CU traits. Furthermore, prefrontal cortical regions may moderate control mechanisms of cognitive emotion regulation of affective stimuli and therefore could represent possible targets for novel specific NF-trainings or behavioral treatment strategies. However, this needs to be investigated in the healthy population first, including adolescents at varying levels of CP, allowing for variance to indicate specificity and sensitivity of such new, putative NF target regions for the treatment of DBD. Thus, the following hypotheses are nominated:

a. Affective processing in healthy adolescents

Coherently to findings in clinical groups, altered subcortical responsivity has been reported in healthy individuals during affective processing with regard to measures of psychopathy and aggression. Therefore, it is expected to detect diverging neural reactivity during affective processing in group-comparison between adolescents with low and high levels of CP, and in dimensional analyses in the range from low to high CP. Presumably, less susceptibility to negative emotions in healthy adolescents with increased CP (but without diagnosis of DBD) could be related to heightened activity in prefrontal areas related to the self-regulation of

emotion. These specific areas may serve as candidates for future innovative neurofeedback applications.

b. Learning of self-regulation in adolescents with diagnosis of DBD

The amygdala and insula are currently promising candidates for the learning of cognitive self-regulation of affective arousal. Therefore, it is expected that rtfMRI-NF training of the amygdala or insula enables adolescents with DBD and high CU traits to establish mental self-regulation strategies, which can be transferred into daily life. Successful learning of self-regulation is determined by increasing differential activity in the target regions along the course of training sessions. The characteristic learning curve should show significantly diverging BOLD-signals over time between active regulation conditions and no regulation or baseline conditions of the NF-training.

c. Neurophysiological changes in affective processing

Since both, activity of both amygdala and insula were found negatively associated with CU traits in affective processing in individuals with DBD, successful learning of upregulation of these areas may also improve affective processing. However, behavioral treatment may also improve affective processing. Thus, in a pre-post treatment comparison of an fMRI affective processing task, higher activity in subcortical structures is expected after treatment in clinical groups receiving both NF and TAU. Due to the brain-based NF intervention, even higher activity is expected after the treatment in the NF compared to the TAU group.

d. Clinical improvement

In addition to the learning of self-regulation and neurophysiological changes in affective processing throughout the NF-training, improvements in clinically relevant behaviors are expected. This refers to the pre-post treatment comparison of behavioral core-symptoms of DBDs, such as defiant, rule-breaking and aggressive behaviors, which are assessed by questionnaires rated by multiple informants. To evaluate the clinical efficacy of the rtfMRI-NF training, a clinical group receiving TAU is implemented in the design. It is expected that the

clinical effects of the rtfMRI-NF training are not inferior to the clinical effects of TAU (non-inferiority trial).

4. Empirical Studies

4.1 Study 1: Orbitofrontal Control of Conduct Problems? Evidence from Healthy Adolescents Processing Negative Facial Affect

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fMRI

4.1.1 Abstract

Background: Conduct problems (CP) develop during childhood and adolescence, with an involvement of prefrontal regions. Clinical levels of CP have been linked to altered prefrontal processing of negative facial affect when comparing patients with disruptive behavior disorders to control samples. However, it is unknown how problems along the conduct dimension extending from low to clinically relevant levels are linked to prefrontal activity during affective face processing in a healthy epidemiological sample.

Methods: We measured functional brain responses during negative affective face processing (angry versus neutral faces) in 364 healthy adolescents (M=14.44 years, n=174 female) from the European IMAGEN multicenter study. To determine the effects of CP, we applied a two-step approach a) testing groups of low CP versus high levels, that extend into the clinical range (measured with the Strength and Difficulties questionnaire; N=182 in each group) using analysis of variance, and b) considering linear and nonlinear effects along the CP dimension using multiple regression.

Results: We observed no significant differences in brain responses to negative facial affect in adolescents with high versus low CP. Regression analyses along the CP dimension across the groups revealed a significant nonlinear effect: left orbitofrontal cortex (OFC) responses increased with increasing CP up to the clinical range, and, decreased again only for the highest CP range.

Conclusions: Increasing left OFC activity found during affective processing in an epidemiological adolescent sample with low to clinically relevant levels of CP, might represent frontal control mechanisms preventing the outbreak of disruptive or conduct disorder despite conduct problems.

4.1.2 Introduction

Conduct problems (CP) refer to a persistent pattern of antisocial behavior including aggressive, disobedient, rule-violating, deceptive and destructive behaviors, which develop during childhood and adolescence and predict a variety of negative outcomes in life (Odgers et al., 2007). Understanding how CP from low to clinically relevant levels affect healthy adolescents might increase our understanding of the development of disruptive behavior disorders (DBD) such as conduct disorder (CD) or oppositional defiant disorder (ODD) (Loeber et al., 2000). Investigations of affective processing and its neurophysiological correlates may be fruitful in this context, as alterations in affective processing have often been reported in individuals with severe CP or DBD. On a behavioral level, CP and DBD have been associated with impaired recognition of fearful, sad and happy facial expressions, while the recognition of angry and disgusted faces is not consistently reported to be impaired (Blair et al., 2018; Fairchild, van Goozen, Calder, & Goodyer, 2013). Further, CP have been shown to moderate the relationship between callous-unemotional (CU) traits and affective picture processing (Szabo, Halasz, Morgan, Demetrovics, & Kokonyei, 2019).

On a neural level, affective processing is mediated by regions like the insula, hippocampus and amygdala, but also ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex (OFC), including the anterior cingulate cortex (ACC) (Davidson, Jackson, & Kalin, 2000; Davidson, Putnam, & Larson, 2000), which has also been corroborated by lesion studies (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Bechara, Damasio, Damasio, & Anderson, 1994; Damasio, 1994; Hornak et al., 2003; Tolomeo et al., 2016). These brain regions have also been associated with CP and DBD in both structural and functional imaging studies in adults and children. A meta-analysis by Yang and Raine (2009) has shown a reduction of volume and activation in frontal brain regions such as the OFC, ACC and dorsolateral PFC (dlPFC) in individuals with antisocial behavior, which comprised patients with DBD. Dalwani et al. were able to show volume reductions in regions including the OFC and ACC associated with CP in female subjects (Dalwani et al., 2015) and in the dlPFC in males (Dalwani et al., 2011).

Functional brain dysfunctions in DBD have been observed in prefrontal regions as well. In a review Rubia (2011) report orbitofrontal-paralimbic dysfunction during affect regulation in DBD and Sterzer and colleagues (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005) found a stronger reduction in the right dorsal ACC response during negative picture viewing in adolescents with DBD compared to healthy control individuals. Moreover, adolescents diagnosed with DBD showed reduced vmPFC and medial OFC activity compared to healthy controls while viewing pictures of negative facial affect (Fairchild et al., 2014; Passamonti et al., 2010). However, reduced OFC volume and responsivity during affective processing have not been consistently observed across studies in DBD. A study in boys with elevated CP compared to typically developing boys reported increased medial OFC and ACC volumes (De Brito et al., 2009), and increased volume in these regions was associated with increased levels of aggressive symptoms in healthy young adults (Besteher et al., 2017). Increased functional OFC and ACC responsivity was also observed in children with early-onset childhood DBD for pain-related empathic processes (Decety, Skelly, Yoder, & Kiehl, 2014) and some studies found no difference in prefrontal activity between DBD and control in boys (Herpertz et al., 2008; Jones et al., 2009). Further, a critical role of OFC dysfunctions in DBD and affective processing has been discussed in the differentiation of reward and punishment, with a hyposensitive response to positive stimuli (reward, Rubia et al., 2009) and a hypersensitive response to negative stimuli (punishment, Finger et al., 2008). To date, most studies on affective processing and CP have focused on the clinical diagnostic spectrum and it remains unclear whether healthy adolescents with elevated CP, extending up to the clinical range but not meeting diagnostic criteria for DBD, also show altered prefrontal functioning during affective processing. This group may be of particular interest in terms of protective, control mechanisms to keep adolescents, despite high CP scores, from developing DBD. A recently published paper by Spechler and colleagues (Spechler et al., 2019) provided some evidence on an association between lower OFC volume and emotional and behavioral control in a non-clinical sample of dysregulated compared to control adolescents, however, the authors have not examined the involvement of functional brain changes. In this

present research, we focused in the functional brain responses, with a focus on prefrontal areas like the OFC and ACC, to affective facial expressions in adolescents with low versus high CP, and we tested for possible nonlinear effects of the CP dimension. Dynamic stimuli of angry facial expressions, which have been previously shown to robustly elicit prefrontal activity comprising the ACC and OFC (e.g., Quinlan et al., 2017), were used to induce negative facial affect. Prosocial behavior, sex, pubertal development and the intelligence quotient (IQ) were used as covariates due to possible co-effects (Andrade & Tannock, 2013; Girard, Tremblay, Nagin, & Côté, 2019; Prendergast & Zucker, 2018; Smaragdi et al., 2017).

We expect nonlinear effects of CP on the processing of negative facial affect that should particularly be expressed in the OFC and ACC (De Brito et al., 2009; Yang & Raine, 2009). The results may be salient for individuals at high risk for DBD.

4.1.3 Methods and Materials

4.1.3.1 Participants

In the present study, we use data from the European multicenter study IMAGEN (Schumann et al., 2010) where healthy adolescents were assessed at eight European sites across the United Kingdom (London, Nottingham), Ireland (Dublin), France (Paris) and Germany (Mannheim, Berlin, Hamburg, Dresden). For the purpose of the current study, we selected those adolescents, who showed high levels of CP (n=182) at the age of 14-15 years and individuals with low CP levels (n=182), matched for sex, age, IQ and pubertal development (total N=364, M=14.44 years (SD=0.41), n=174 female).

Table 4. Sample description and group characteristics

	CP	Control	Group comparison
	Mean (Std.Dev.)	Mean (Std.Dev.)	p-value
N	182	182	
<i>Matched variables</i>			
PDS	7.37 (1.396)	7.49 (1.394)	0.404
IQ	106.70 (13.987)	106.69 (13.746)	0.994
Age	14.44 (0.412)	14.43 (0.408)	0.846
Sex (% female)	47,3% (87)	47,3% (87)	0.295 (χ^2_{between}) 0.459 (χ^2_{within})
<i>SDQ domains</i>			
Conduct problems	4.84 (1.042)	1.05 (0.763)	**
Prosocial behavior	6.54 (2.059)	8.23 (1.438)	**
Emotional problems	3.31 (2.462)	1.47 (1.569)	**
Hyperactivity	5.25 (2.334)	2.58 (1.958)	**
Peer problems	2.42 (2.071)	1.27 (1.422)	**
Total	15.82 (5.502)	6.38 (3.485)	**

PDS=Pubertal Development Scale, SDQ=Strengths and Difficulties Questionnaire, **p<.001

For the definition of high versus low CP, we followed the clinical cutoff criteria of the Strengths and Difficulties Questionnaire (parent-rated version, cut off score = 4). Prosocial behavior was higher in the control group, and used as a covariate in the analyses (see below; see table 1 for complete sample description). The study protocol was approved by the KCL (King's College

London) College Research Ethics Committee CREC/06/07-71 and by local ethics research committees at each site. Parents and adolescents gave written consent and verbal assent, respectively.

4.1.3.2 Psychometric Assessments

Conduct problems and prosocial behavior were assessed using the Strengths and Difficulties Questionnaire (SDQ), which is a brief behavioral screening questionnaire for individuals of 3 to 16 years and provides a dimensional measure of CP as well as emotional problems, peer problems, hyperkinetic symptoms, and prosocial behavior (Goodman, 1997). The status of pubertal development was assessed using the Pubertal Development Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988) and IQ was estimated by averaging the sum scores of the Wechsler Intelligence Scale for Children (WISC-IV) subscales Matrix Reasoning (fluid IQ marker) and Vocabulary (crystalized IQ marker) (Petermann, 2011).

4.1.3.3 Experimental paradigm

Affective processing was assessed using a faces task from Grosbras and Paus (2006). In this task, participants were asked to passively view 18-second blocks comprising black-and-white video clips of faces and contracting or expanding concentric circles, which served as control stimuli. The faces clips comprised five blocks of angry and neutral expressions each and were interleaved with nine blocks of the control stimuli (duration of each clip: 200–500 ms). In the angry face clips, faces with neutral expressions morphed into angry expressions, while in the neutral face clips, emotionally neutral expressions such as nose-twitching were presented. Each 18-second faces block contained 4-7 video clips.

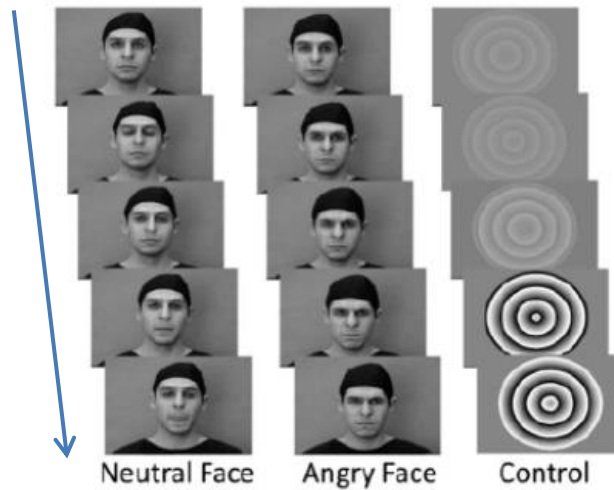


Figure 1. Faces task. Dynamic video clips of neutral faces, angry faces and control stimuli conditions. Neutral faces either morphed into angry faces or displayed emotionally neutral movements.

4.1.3.4 fMRI data acquisition

Magnetic resonance images were observed on 3 Tesla imaging systems (Siemens, Philips, GE, and Bruker). Four sites (using GE and Philips scanners) used an eight-channel coil, and four sites (using Siemens scanners) used a 12-channel coil. All sites used the same scanning protocol and image-acquisition techniques using a set of parameters compatible with all scanners were implemented to ensure a comparison of MRI (cf., Schumann et al., 2010)).

A total of 160 volumes per subject were observed, each containing 40 slices of 2.4 mm (1 mm gap), with a repetition time of 2.2 s and an echo time of 30 ms. Additionally, high-resolution T1-weighted three-dimensional structural images were acquired for anatomical localization and registration with the functional time series.

4.1.3.5 fMRI data preprocessing and first level analysis

Data preprocessing and first level analysis were performed centrally at the Neurospin centre (at NeuroSpin-CEA, Gif-sur-Yvette, France) using the SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>). Time series data were first corrected for slice-timing and then for movement (spatial realignment) relative to the first volume and non-linearly warped on the Montreal Neurological Institute (MNI) space, using a custom EPI template. Finally, images were smoothed with a Gaussian Kernel of 5 mm full-width half maximum. Individuals with

anatomical abnormalities or excessive head movement (> 3 mm in at least one of the translations) did not pass quality control and were not included in the analyses ($n=20$ of complete sample).

The single subject activation maps were computed within a general linear model (GLM) framework including 11 regressors modeling the experimental conditions (1 for each of the 5 angry and 5 neutral face video blocks, 1 concatenating all control stimuli) and convolved using SPM's default hemodynamic response function. Estimated movement was added to the design matrix in the form of 18 additional columns (3 translations, 3 rotations, 3 quadratic and 3 cubic translations, 3 translations shifted 1 TR before and 3 translations shifted 1 TR later). The estimated model parameters were then linearly-combined in first level analyses to yield significance maps and contrast maps between the conditions. The contrast of interest for the present study was angry vs. neutral faces.

4.1.3.6 fMRI data analyses of task and CP effects

To verify expected task activation in the subsample drawn for the purpose of the present study, contrast images were subjected to a one sample t-test across all subjects. To additionally illustrate the whole pattern of neural activity from the angry vs. neutral faces contrast in the current subsample, the group-level contrast estimates were plotted using dual-coded design, which allows visualizing task-related threshold and sub-threshold activity (Allen, Erhardt, & Calhoun, 2012; Zandbelt, 2017).

To determine effects of CP on brain responses during affective processing, we followed a two-step approach. Based on the previous findings from clinical versus control samples, we first tested for group effects of high versus low CP individuals using analysis of variance with the factor group and the angry faces vs. neutral faces contrasts. Second, and along assumptions on curvilinear relationships of CP and brain responses during affective processing in the general population, we performed multiple regression analyses.

Effects were tested on the whole brain level using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) and, as we specifically hypothesized associations with prefrontal regions of interest (ROIs). ROI

analyses were performed by extracting the individual mean contrast estimates of the OFC and the ACC (using masks from the Wake Forest University School of medicine (wfu) Human PickAtlas) for the angry faces vs. neutral faces contrasts. Extracted contrast estimates were then subjected to linear and non-linear regression analyses using SPSS software (Version 25, IBM Corp., Armonk, NY, USA), testing the dimensional effect of CP on neural activity in the ROIs, across all participants and in the high CP group separately. Where possible, prosocial behavior, sex, age, PDS, IQ and site were included as control variables (covariates of no interest). Critical α was set to .05. Family-wise error (FWE) correction for multiple testing was applied for whole brain analyses and Bonferroni correction was applied for ROI analyses, such that critical α was adjusted to 0.0167.

4.1.4 Results

4.1.4.1 Task effect

The angry faces vs. neutral faces contrast revealed activation in prefrontal areas comprising the medial frontal gyrus, OFC and anterior and mid cingulate cortex, as well as the anterior insula and posterior regions including posterior cingulate cortex, and inferior parietal regions and the occipital fusiform gyrus. (For a complete list see supplemental Table A).

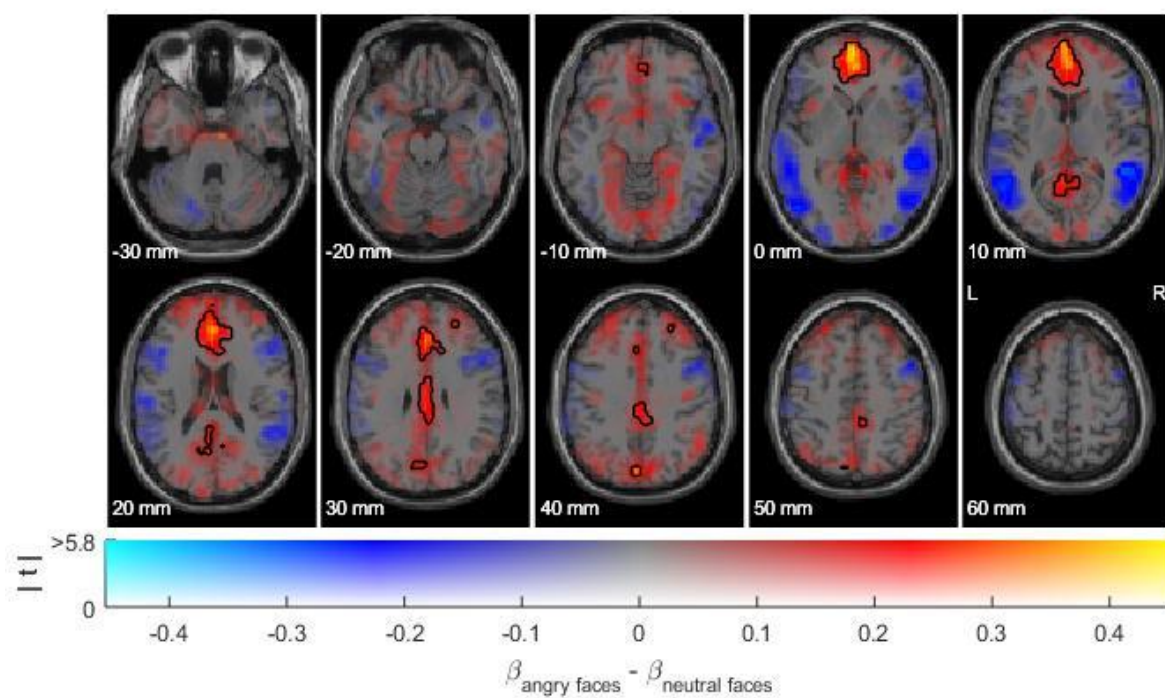


Figure 2. Task activation of the angry vs. neutral faces contrast. Simultaneous display of effect size (color-coded) and unthresholded t-statistics (opacity-coded). Black contours distinguish statistically significant and non-significant voxels at threshold $p < .05$.

4.1.4.2 Between group effects of high versus low CP

Whole brain analyses as well as ROI analyses of the OFC and ACC yielded no significant effect of CP group on brain responses during negative affective face processing.

4.1.4.3 Dimensional effects of CP

Across all adolescents, we found a significant linear relationship between CP and left OFC (L.OFC) activity ($R^2=.047$, $p=.015$) where higher levels of CP were associated with higher L.OFC activity ($\beta=.023$, $p<.001$). There were no significant effects on the whole brain level or in ROI analyses of the right OFC or ACC. We found a significant quadratic association between CP and L.OFC activity ($R^2=.031$, $\beta_1=-.008$, $\beta_2=.004$, $p=.004$). This quadratic association remained significant, but inverted, in the subgroup of participants with high CP ($R^2=.044$, $\beta_1=.170$, $\beta_2=-.011$, $p=.018$), with the slope turning negative again when CP were high (approximately around an SDQ score of 7). After removal of three participants with exceptionally high CP scores (>7) the inverted u-shaped relation in the group of adolescents with elevated CP remained significant ($R^2=.048$, $\beta_1=.062$, $\beta_2=-.001$, $p=.013$). Neither whole brain analyses nor the ROI analyses of the ACC and right OFC yielded significant effects (see supplemental Tables B1-B3 and C1-C2).

Table 5. Coefficients of multiple regression on left OFC across both groups

	Unstandardized Coefficients		Standardized	t	Sig.
	B	Std. Error	Coefficients		
(Constant)	-.416	.471		-.882	.378
Conduct problems	.023	.007	.210	3.516	.000
Prosocial behavior	.013	.007	.113	1.869	.062
Sex	.039	.025	.083	1.547	.123
Age	.008	.032	.014	.254	.799
PDS	.005	.009	.032	.576	.565
IQ	.001	.001	.035	.656	.512
Site	.004	.005	.044	.822	.412

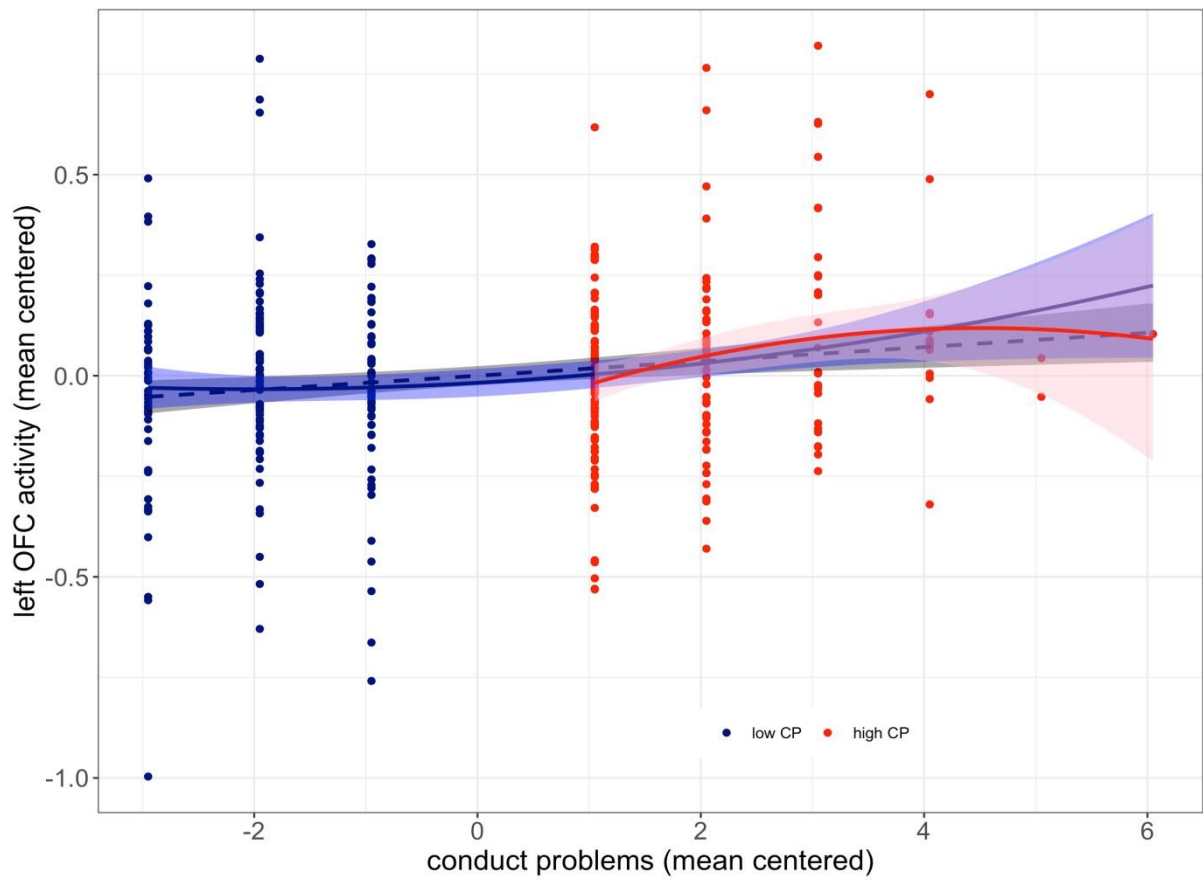


Figure 3 Dimensional effects of conduct problems on left OFC activity. Blue dashed line: Linear regression across both groups. Purple curve: Quadratic regression across both groups (u-shaped). Red curve: Quadratic regression within the high CP group (inverted u-shaped). Shaded areas represent 95% confidence intervals.

4.1.5 Discussion

In the present study, we focused on the relationship between negative affective processing and CP in an epidemiological adolescent sample. We were able to show linear and quadratic relationships between the level of CP and brain activation in the left OFC during negative affective face processing. However, there was no group difference between healthy participants with high compared to low levels of CP.

This non-significant group comparison is in contrast to some studies in clinical samples reporting decreased OFC activity during negative affective face processing in adolescents diagnosed with DBD compared to healthy participants (Fairchild et al., 2014; Passamonti et al., 2010), and observations of reduced orbitofrontal activation in relation to negative emotional stimuli in patients with impulsive aggression (Coccaro, McCloskey, Fitzgerald, & Phan, 2007) or psychopathy (Decety et al., 2014). However, similar to our findings, others have also failed to show prefrontal dysfunction in DBD compared to control participants (Herpertz et al., 2008; Jones et al., 2009). This might depend on the variance of CP levels and their linear composition within the healthy control groups. Our dimensional analysis revealed both linear and non-linear associations between negative affective face processing in the left OFC and CP. Across all participants, activity in the left OFC linearly increased with increasing CP. To our knowledge, dimensional analyses of CP have not been applied to investigate prefrontal functional brain changes in response to negative affective face processing. Interestingly, dimensional analyses of prefrontal volumetric data in healthy participants with elevated CP have also yielded increased volumes associated with CP (Besteher et al., 2017; De Brito et al., 2009) which again matches our fMRI findings but is in contrast to meta analytic reports of the group differences in clinical studies (Yang & Raine, 2009).

Furthermore, visual inspection and statistical analysis of the quadratic association across all participants mainly confirmed an increase of left OFC activation with increasing CP except for those subjects with lowest CP levels (SDQ scores of 0 and 1), where left OFC activation decreased with increasing CP. Focusing on only those participants with elevated CP levels (i.e. above 3)

revealed a quadratic association with an initially positive slope and a decrease in left OFC activity for the highest CP levels. This inverted u-shaped association remained significant when excluding subjects with exceptionally high CP levels. One might speculate that the positive association between OFC activity and elevated CP at least up to some high level reflects compensation processes, where increased OFC recruitment successfully counteracts less effective OFC processing and control reflecting negative effects that are often associated with CP. Such negative effects on OFC can reflect educational deficits, increased peer-problems, or negative parenting styles (Holz et al., 2015; A. L. Murray, Eisner, Obsuth, & Ribeaud, 2017; Wertz et al., 2018) as well as higher perceived social uncertainty and irritability in social contexts (Leadbeater & Homel, 2015; Wakschlag et al., 2018). This potential compensation or coping mechanism may be especially important in adolescence, a transition period where many social changes occur, e.g. adolescents form more complex and hierarchical peer relationships and are more sensitive to acceptance and rejection by their peers than children (Brown, 2004; Steinberg & Monahan, 2007). Investigating only the subjects with elevated CP suggests that this compensatory function of the OFC is no longer present in adolescents with severely elevated CP levels, who may no longer be able to compensate impaired OFC function but fail to meet a clinical diagnosis of DBD for other reasons.

Although the ACC has been reported as a possible relevant prefrontal region in affective processing in clinical studies, we did not find significant associations between CP and activity in the ACC, neither for the group comparisons nor the dimensional analyses. While the reasons for the non-significant group comparisons might overlap with those for the failure to detect significant effects in the OFC responsivity, the non-significant effects in the dimensional approach might indicate that ACC functioning is rather a sensitive brain correlate in the clinical domain (e.g., Herpertz et al., 2008), but did not serve as possible coping brain correlate at higher, but still sub-clinical, CP levels in healthy individuals. Moreover, the findings might also reflect a higher relevance of the OFC, compared to other regions, for the processing of anger-related stimuli (e.g., Phan, Wager, Taylor, & Liberzon, 2002).

The lack of group differences in the present study may be owed to the relatively small amount of individuals displaying very high levels of CP, who also likely fulfill diagnostic criteria of DBD. Since the presence of elevated CP levels is not a sufficient criterion for the diagnosis of DBD, lacking information about frequency and persistence of symptoms, individuals with a confirmed clinical diagnosis of DBD likely represent subjects with more severe impairments. The inverted U shape association, if indeed extending into the clinical domain with increasingly reduced OFC activity, might suggest OFC hypoactivation is observed in group differences only when CP are severe enough. It further suggests that if CP levels are low, OFC hyperactivation may be observed. In the case of the present study, CP levels were ranging from low to high, potentially resulting in the lack of observed group difference.

4.1.5.1 Limitations

While the present study provides important insight into the impact of CP on negative affective face processing, a number of limitations need to be considered. Most importantly, while the sample was large it did not specifically include patients with DBD and thus did not sufficiently cover the entire range of the SDQ CP subscale (scores from 0 to 10). Indeed, the number of subjects presenting with very high CP levels was low. Thus, the investigation of non-linear dimensional associations between CP and brain activity during affective processing needs to be urgently replicated in a sample extending well into the clinical range. Further, De Brito and colleagues (De Brito et al., 2009) have demonstrated an age effect on volumetric deviations in participants with elevated CP levels, thus arguing towards a lag in developmental maturation in participants with CP. In the present study, however, all participants were within a narrow age range. Therefore, despite controlling for age to account for subtle age differences, age effects could not be explicitly investigated here.

Moreover, in our sample we detected sex differences regarding prosocial behavior, emotional problems and peer problems as well as in IQ and PDS. However, also to account for previous findings of sex differences in internalizing and externalizing behavior (Bartels, Cacioppo, van Beijsterveldt, & Boomsma, 2013; Eagly & Wood, 2013; Kendler & Gardner, 2014) and the

developmental differences in intelligence performance in boys versus girls (Nyborg, 2005), we further controlled for sex, IQ and PDS when possible. Finally, as the fMRI task did not require subject responses, we had no control on whether the participants were attentive to the stimuli during the presentation.

4.1.5.2 Conclusions

In this study we observed an increase with a nonlinear, u-shaped component in left OFC response to negative affective face processing with increasing CP levels in a healthy adolescent sample. This pattern in the subclinical range stands in contrast to most findings known from clinical groups with DBD, where a decreased response has often been reported (Fairchild et al., 2014; Passamonti et al., 2010; Sterzer et al., 2005). However, we also observed a nonlinear, inverted u-shaped effect of CP in those individuals with elevated CP levels. This indicates that for those individuals with the highest CP levels, OFC responsivity decreases again. This activity pattern might suggest a compensatory mechanism preventing the outbreak of DBD at lower, sub-clinical CP levels but failing to compensate when CP levels are very high and in the clinical range. As the present sample lacks sufficient coverage of very high CP levels, future studies including clinical samples of adolescents with diagnosis of DBD and adequately sized groups of healthy adolescents with exceptionally high CP are urgently needed to validate the suggested frontal compensatory mechanism.

4.1.5.3 Disclosures

Dr. Banaschewski has served as an advisor or consultant to Actelion, Hexal Pharma, Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Lundbeck, Medice, Neurim Pharmaceuticals, Novartis, Pfizer, and Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, and Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire and Viforpharma; he received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships. Dr. Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses and

acts as a consultant for IXICO. The other authors report no biomedical financial interests or potential conflicts of interest.

4.1.5.4 Acknowledgments

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4.2 Study 2: Individualized real-time functional magnetic resonance imaging neurofeedback in adolescents with DBD

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4.2.1 Abstract

Background: Adolescents with increased callous unemotional traits (CU traits) in the context of disruptive behavior disorder (DBD) show a persistent pattern of antisocial behavior with shallow affect and a lack of empathy or remorse. The amygdala and insula are regions commonly associated with emotion processing, empathy and arousal and are implicated in DBD. While conventional therapies for DBD, like family-based interventions and parenting programs, gain significant but small effect-sizes, there is a considerable need for new, individualized treatment strategies.

Methods: In this randomized controlled clinical trial we explored the feasibility and efficacy of individualized real-time functional magnetic resonance neurofeedback (rtfMRI-NF) of either amygdala or insula activity compared to treatment as usual (TAU). Twenty-seven adolescents were randomly assigned to either 10 sessions of rtfMRI-NF or 6 sessions of TAU. Feedback was provided by gauges and included a transfer condition, without continuous feedback, to foster transfer to everyday life. In addition, an emotion matching task was assessed before and after treatment to test for neurophysiological alterations in affective processing.

Results: The NF and the TAU group showed comparable and significant clinical improvement on DBD-related behavioral scales in line with non-inferiority. Within the NF group, successful learning of self-regulation in the target region was found for NF of the amygdala, but not for NF of the insula. However, clinical improvement in NF was not specific to the amygdala group. In the emotion matching task, both treatment groups showed higher activities prior to treatment in emotion-regulation related areas, potentially indicating higher efficiency of processing affective stimuli after treatment.

Conclusions: For the first time feasibility and efficacy of individualized rtfMRI-NF in a clinical sample of adolescents with DBD and increased CU traits were investigated. Results suggest clinical improvement but further studies are needed to clarify underlying mechanisms and cost effectiveness.

4.2.2 Introduction

Disruptive behavior disorder (DBD), comprises conduct disorder (CD) and oppositional defiant disorder (ODD) and is a common condition in children and adolescents with an estimated prevalence rate of 6.1% (O'Connell et al., 2009). DBD is marked by frequent aggression, deceitfulness, and defiance which often persist through the lifespan and individuals who engage in disruptive behavior represent a large population at risk for significant deleterious long-term outcomes, including family disruption, poor educational attainment, unemployment, substance abuse, and suicidal behavior (Colman et al., 2009; David M Fergusson, John Horwood, & Ridder, 2005; Odgers et al., 2008). Additionally, around 40% of the individuals diagnosed with DBD display elevated callous-unemotional (CU) traits (Rowe, Maughan, et al., 2010). CU traits are a facet of the broader concept of adult psychopathy but can also be described in child and adolescent psychiatry to characterize severe patterns of behavior that reflect a disregard for others, and also a lack of empathy and generally deficient affect (Pisano et al., 2017). As highlighted in meta-analytic studies, evidence-based psychological treatments for DBD only yield small to moderate effect sizes (Bakker et al., 2017; Erford, Paul, Oncken, Kress, & Erford, 2014; Fossum, Handegard, Martinussen, & Morch, 2008). Regarding the impact of CU traits on treatment outcome, findings are mixed but suggest that individuals with diagnosis of DBD and elevated CU traits represent a more severe phenotype with more stable behavior problems, more severe aggressive behavior and poorer response to treatment than their counterparts with low CU traits (Frick et al., 2014; Hawes et al., 2014). Importantly, individuals with diagnosis of DBD compared to controls showed deficient emotion recognition and altered neurophysiological responses during affective processing in subcortical and cortical regions, such as the amygdala (AMG) and the insula (INS), with decreasing activity in these regions was also associated with increasing CU traits (Viding & McCrory, 2018). Specifically, AMG hypoactivity during affective processing has been associated with high CU traits (Viding et al., 2012; White et al., 2012) and decreasing activity of the INS with increasing CU traits was observed in empathy-eliciting tasks (Lockwood et al., 2013) across individuals with CP or diagnosis of DBD. Besides these deficits in

core-regions of affective processing, decreasing activity with increasing CU traits has also been observed in the anterior cingulate cortex (ACC) (Viding & McCrory, 2018), and altered activity in the orbitofrontal cortex (OFC), compared to controls, was indicated in adolescents with DBD during affective processing (Fairchild et al., 2014; Passamonti et al., 2010). Consequently, it has been suggested that treatment effects for individuals with high CU traits might be enhanced by the implementation of specific emotion regulation trainings (Dadds et al., 2012). However, subtype-specific and customizable treatment-strategies for adolescents with diagnosis of DBD are still need to be developed and clinical efficacy of alternate, innovative treatment-strategies needs to be evaluated, and targeting specific brain regions implicated in severe DBD subtyped directly in a personalized fashion seems a particular promising approach to this end

Recently, real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF) has become increasingly feasible and popular as a tool for the training of brain self-regulation and has already been used across various psychiatric populations to train emotion regulatory strategies (Paret & Hendler, under review), with one proof-of concept study in adolescent patients published to date (Alegria et al., 2017). However, only one pilot-study addressed empathy and aggression by applying rtfMRI-NF in criminal adult psychopaths, indicating that NF training can be possibly more challenging and require more training time and motivation in this clinical group (Sitaram et al., 2014). Correspondingly, in adolescents with Attention Deficit Hyperactivity Disorder (ADHD) successful learning of brain self-regulation was observed after approximately seven training sessions (over a course of eleven training sessions) and led to lasting significant clinical improvements in ADHD-related behavioral domains (Alegria et al., 2017). So far, no study evaluated feasibility and clinical efficacy of individualized rtfMRI-NF training and the learning of self-regulation in adolescents with severe DBD. In this context, the AMG and INS may represent suitable target regions to induce improvements in affective processing by the learning of specific upregulation of neural activity in these regions. Thus, in this randomized controlled clinical trial, we explored the feasibility and clinical efficacy of

Evaluating neural targets for future interventions for adolescents with disruptive behavior disorder

individualized rtfMRI-NF of either AMG or INS activity compared to treatment as usual (TAU) in adolescents with DBD and elevated CU traits.

4.2.3 Methods and Materials

4.2.3.1 Study design

Before treatment, diagnosis of DBD was confirmed using a battery of diagnostic tools, including self- parent- and teacher-rated questionnaires (*Youth Self Report (YSR)* (Döpfner, 1998), *Modified Overt Aggression Scale (MOAS)* (Kay, Wolkenfeld, & Murrill, 1988), *Inventory of Callous-Unemotional Traits (ICU)* (Frick, 2004), *Reactive-Proactive Aggression Questionnaire (RPQ)* (Raine et al., 2006), *Strengths and Difficulties Questionnaire (SDQ)* (Goodman, 1997), *Pubertal Development Scale (PDS)* (Carskadon & Acebo, 1993), *Child Behavior Checklist (CBCL)* (Achenbach, 2000), *Teacher Report Form (TRF)* (Achenbach, 1991)) and a clinical interview (*Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)* (Delmo, Weiffenbach, Gabriel, & Poustka, 2000)). Elevated CU traits were confirmed by the ICU total score (ICU total score >20 in self-rating and/or >24 in parent-rating). Additionally, affective processing was captured in all participants before treatment using an explicit emotion matching task (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002) at the beginning of the NF-training.. Subsequently, patients were randomly assigned to either 6 sessions of TAU, which consisted of conventional behavioral therapy, or 10 sessions of individualized rtfMRI-NF, in which the NF-target region (AMG or INS) was chosen for each participant based on the individual activation pattern in an implicit emotion matching task (Hariri, Bookheimer, & Mazziotta, 2000) at the beginning of the NF-training. Patients were re-assessed after completion of the treatment phase.

4.2.3.2 Participants

Participants in the current study were part of the EU-MATRICES project. Twenty-seven participants (12-18 years of age, 22% female) who fulfilled diagnostic criteria of CD and/or ODD and displayed moderate to high CU scores were recruited from in- and outpatient facilities of the clinic of child and adolescent psychiatry and psychotherapy, as well as from local youth welfare institutions and via advertisement. In the TAU group, two patients dropped out before treatment (1 started medication, 1 was relocated to psychiatric ward) and one patient broke off after the first session and could not be reassessed. In the NF group, one patient rejected rtfMRI-

measurement at the first NF-training. Thus, a final sample of 23 patients performed both pre- and post treatment assessment (12 in the NF group, 11 in the TAU group). However, two patients in the TAU group and three patients in the NF group aborted treatment early (TAU: 2 after two sessions, 1 after four sessions; NF: 2 after five sessions, 1 after six sessions).

Exclusion criteria were any contraindications for MRI, an IQ<80 measured from four subtests (vocabulary, similarities, block design and picture completion/matrix reasoning) of the *Wechsler Intelligence Scale for Children-IV* (Petermann, 2011) and a primary DSM-5 diagnosis of psychosis, bipolar disorder, major depression and/or an anxiety disorder. Medication use of the participants had to be stable for at least two weeks prior to inclusion. Ethical approval for the study was observed from the local ethics committee. Written informed consent was given by the participants and their parents or legal representatives.

4.2.3.3 Neurofeedback training procedure

Each rtfMRI-NF training session began with a high-resolution structural magnetization-prepared rapid gradient echo (MP-RAGE) scan, which was transformed into Talairach space to allow for intra-individual mapping between the NF-training sessions. An additional implicit emotion-matching task (Hariri et al., 2000) was conducted before the NF-training at every session, and was used as a functional localizer at the first session. To determine the participant's individual activation within the anatomically defined regions of interest (ROIs: bilateral INS and the bilateral AMG, based on Talairach Deamon), the data was compared to the activity levels in these regions from a healthy normative sample at the same task (sample characteristics are described in Holz et al. (2017)). The region which appeared to show the most prominent hypoactivity (under-activation compared to the healthy sample) was selected as NF-target region for all upcoming sessions of the specific participant. At each session, the implicit face-matching task was followed by three NF training conditions (12.41 min. each).

Each NF-training condition comprised 7 up- and 7 no-regulation trials (40s each), which were indicated by arrows, while two gauges (on the left and right side of the screen) were visualizing the mean activity of the individual target ROI. The sequence of up- and down regulation tasks

within each condition was randomized. Baseline activity was assessed during an initial fixation period (30s) and updated during inter-trial fixation (7.5 s). To reinforce performance, successful upregulation trials (neural activity must be above the adapted baseline activity in 60% of the duration of an upregulation trial) were reinforced in each condition with a “thumb up” sign, while unsuccessful trials received no visual reinforcement (reinforcement period 3s). Points could be collected at each training day (1 point equals three collected thumb ups / 80 points theoretically achievable in total) and were rewarded with a voucher of 10€ value at the participants choice once when 40 and once when 80 points were achieved.

In the first condition (*simple feedback*) only the gauges were displayed. In the second condition (*video feedback*) short video-clips (40s each) with either negative-affective or neutral scenes of social interaction were displayed additionally in the center of the screen (for more detail see 4.2.3.3.1). In the third condition (*transfer*) only the gauges were presented, which remained static so that no concurrent feedback of ROI activity was given. The intention of transfer trials within NF-studies is to ease the transfer of the regulation-skills into daily routine, which was additionally fostered in our paradigm by a rewarded token-system (collecting thump ups) based on the principles of operant conditioning. The rtfMRI-NF training protocol was designed in cooperation with the Institute for Medical Psychology and Behavioural Neurobiology (University Tübingen) and implemented in *Presentation* software (Version 18.0, Neurobehavioral Systems Inc., Berkeley, CA). The real-time analysis was performed by *Turbo Brain Voyager* software (Version 3.2, Brain Innovation B.V., Maastricht, Netherlands) supported by *Brain Voyager* software (Version 20.6, Brain Innovation B.V., Maastricht, Netherlands).

4.2.3.3.1 Video clips

Video clips used as stimuli during rtfMRI-NF were selected based on valence and arousal ratings obtained in a prior pilot-study. A sample of 20 children and adolescents (8-17 years, 70% female) rated valence, arousal und social dominance of 120 non-acoustic, monochrome custom-made video-clips containing neutral, positive and negative social interaction scenes and 20 positive or negative video clips from the Emotional Movie Database (Carvalho, Leite, Galdo-

Álvarez, & Gonçalves, 2012), with the *Self-Assessment Manikin-Scale* (Bradley & Lang, 1994). Each scene of the custom-made video-clips was filmed in first- and third-person-perspective. Based on the results, 33 negative and 6 neutral custom video clips, as well 6 negative video clips from the EMDB, all scoring above the mean values on valence (mean: 5.08, SD: 1.50) and arousal (mean: 3.40, SD: 0.68), were selected. The video-clips were pseudorandomized to three different versions of the video condition which were permuted across sessions and subjects.

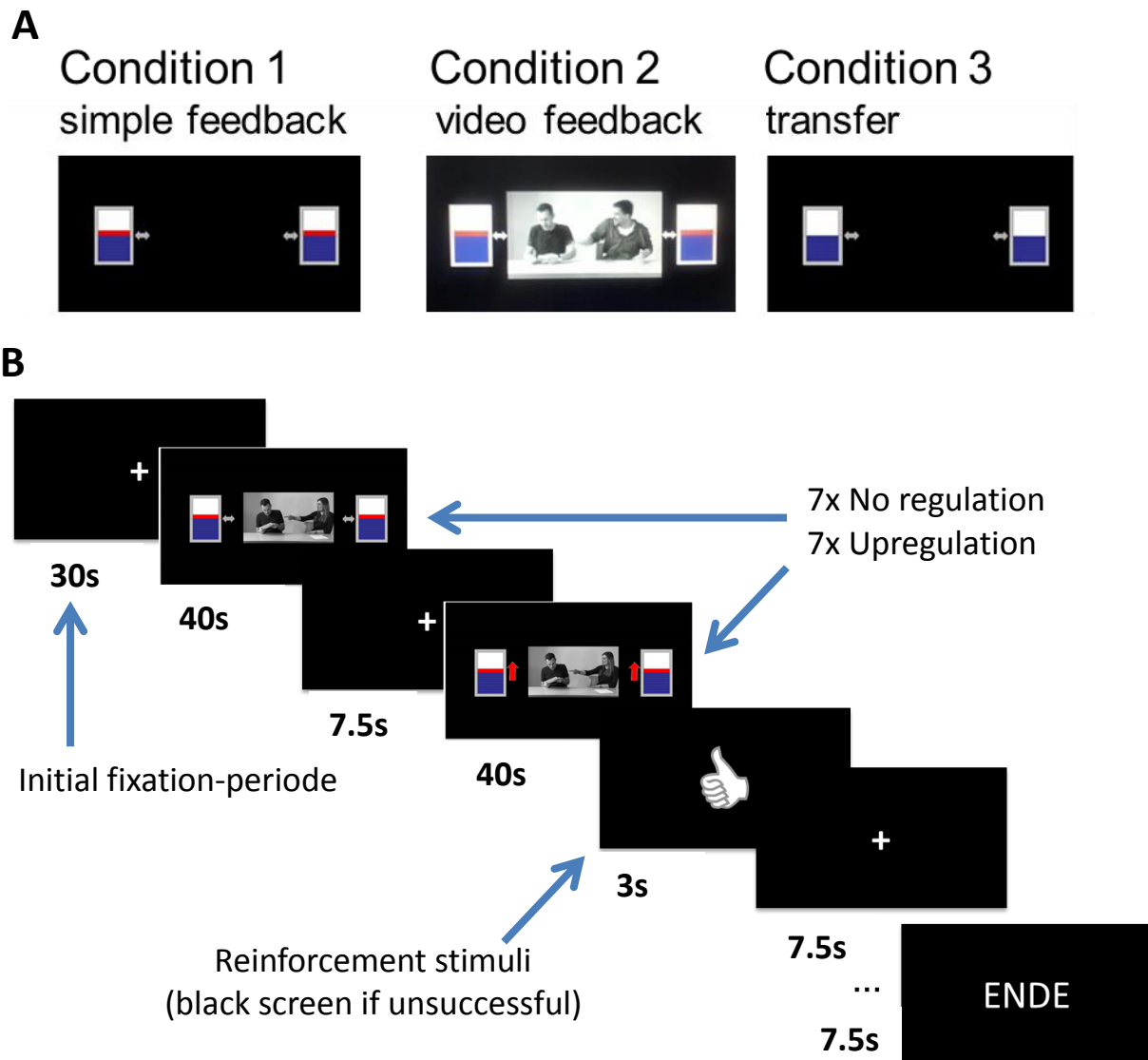


Figure 4. A: The three different conditions of the neurofeedback training. In the simple feedback condition the gauges display activity of the individual target region. In the video feedback condition the gauges display activity of the individual target region and affective video-clips are viewed in addition. In the transfer condition the gauges are fixed at the mid-line, no feedback is provided. **B:** Temporal characteristics of the NF-training conditions exemplified by the video condition. In each condition positive reinforcement appears after successful upregulation trials and a black screen appears if upregulation was not successful. Total time of each condition: 12.41 min.

4.2.3.4 Affective processing

In order to determine neurocognitive changes in affective processing, an explicit perceptual fMRI emotion-matching task (Hariri et al., 2002) was conducted by each participant before and after the treatment. In this task, participants completed four blocks in which they had to match the presented emotional facial expressions (figure 4). Stimuli comprised a trio of faces in which the participants had to select one of two emotions (displayed on the bottom) identical to the target stimulus (displayed on the top). Each faces block consisted of six images derived from a standard set of facial affect with either negative (anger and fear) or positive faces (happy and neutral). At the beginning of the task a fixation cross (10s) was displayed and, interleaved between the faces-blocks, participants completed two blocks of a sensorimotor control task with geometric shapes (horizontal ellipses or vertical ellipses). All images were presented sequentially, with no interstimulus interval, for a period of 5s and in a randomized fashion for all conditions (total time = 190s). The order of the paradigm was counterbalanced across subjects.

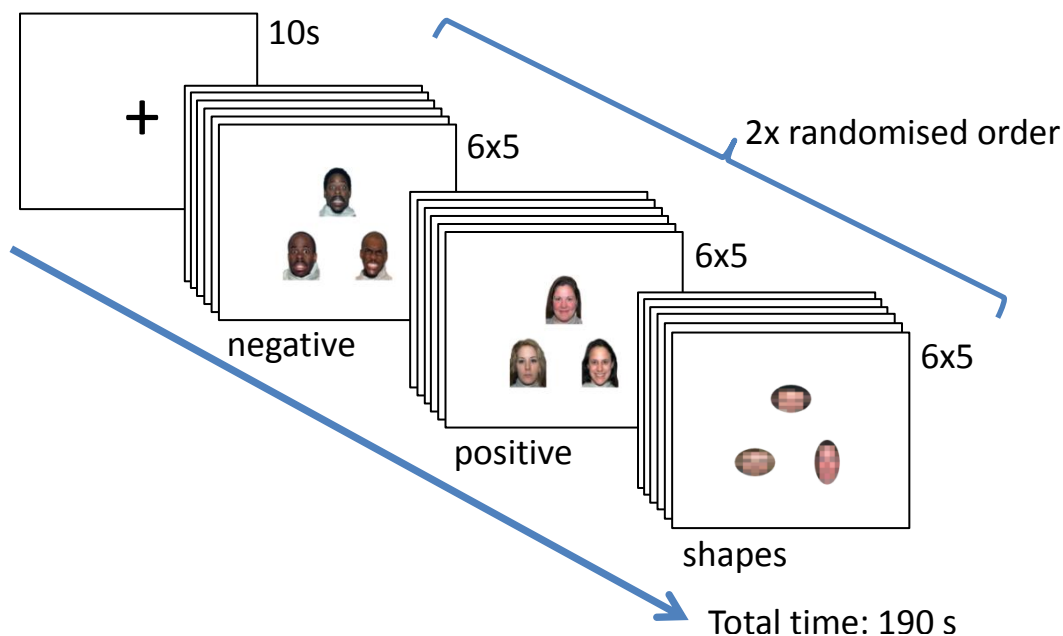


Figure 5. Temporal characteristics of the explicit emotion-matching task performed before and after treatment to determine treatment-related neurocognitive changes in affective processing.

4.2.3.5 Behavioral data

Demographic data between treatment groups were compared by two-sample t-tests and chi square tests. For the pre-post treatment comparison of the behavioral data of the affective processing task and for the evaluation of the clinical outcome of the treatment strategies, 2x2 repeated measures ANOVAs were calculated including a group factor (NF vs TAU) and a time factor (pre vs post).

4.2.3.6 Analysis of learning of self-regulation

A general linear mixed model ANOVA was used with the ROI values of the individual target regions acquired during each session as a dependent variable to compare learning effects between and within the NF groups. Included within-factors were time (sessions), condition (simple, video, transfer), and task (upregulation and no regulation). NF-training group (AMG vs INS) was included as a between-factor. The ROI activity of each task was calculated as task activity minus baseline activity as measured by response to the fixation cross (upregulation-fixation and no regulation-fixation).

4.2.3.7 fMRI data acquisition and preprocessing

RtfMRI-NF training tasks: MRI scans were performed with a Magnetom TRIO (Siemens, Erlangen, Germany). For each self-regulation task, data of the individual NF-target regions were acquired using EPI (498 volumes á 16 axial slices, 5 mm thickness, repetition time 1500 ms, echo time 30 ms, voxel size: 3.3×3.3×5.0 mm, flipangle 70°, FOV=210 mm). The MP-RAGE scan was acquired at a resolution of 1.0×1.0×1.0 mm. Data was analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm/). The first four volumes were discarded to allow longitudinal magnetization to reach equilibrium. EPIs were interpolated in time to correct for slice time differences and realigned to the middle scan to correct for head movements. EPIs were co-registered and normalized to the standard EPI template in MNI space (Montreal Neurological Institute) using linear and non-linear transformations, and smoothed with a full-width-half-maximum gaussian kernel of 8 mm. Realignment parameters were examined to ensure head

movement did not exceed 5 mm (more lenient criteria to consider co-occurring hyperactivity in DBD).

Affective processing tasks: MRI scans were performed with a Magnetom TRIO (Siemens, Erlangen, Germany). Whole brain data were acquired with echo-planar T2*-weighted imaging (EPI), sensitive to the Blood Oxygenation Level Dependent (BOLD) signal contrast (*explicit task*: 176 volumes á 36 axial slices, 3 mm thickness, repetition time 2100 ms, echo time 35 ms, voxel size: 3×3×3 mm, flipangle 74°, FOV=192 mm; *implicit task*: 207 volumes á 36 axial slices, 3 mm thickness, repetition time 2210 ms, echo time 28 ms, voxel size: 3.4×3.4×3.0 mm, flipangle 90°, FOV=220 mm). A MP-RAGE scan was also acquired at a resolution of 1.0×1.0×1.2 mm. Data of the explicit emotion matching task was analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm/). The first five volumes of the EPIs were discarded to allow longitudinal magnetization to reach equilibrium. EPIs were interpolated in time to correct for slice time differences and realigned to the middle scan to correct for head movements and were co-registered and normalized to the standard EPI template in MNI space (Montreal Neurological Institute) using linear and non-linear transformations, and smoothed with a full-width-half-maximum Gaussian kernel of 8 mm. Realignment parameters were examined to ensure head movement did not exceed 5 mm.

4.2.3.8 fMRI analyses

RtfMRI-NF training tasks: For each participant a separate GLM was assessed for each NF-condition (simple feedback, video feedback, transfer) and for each session (10 per subject). Each model included the experimental tasks (upregulation, no regulation, fixation cross and reinforcement delivery) plus six realignment parameters as covariates of no interest, to account for residual motion-related variance (Paret et al., 2014). Low-frequency signal drift was removed using a high-pass filter (cut-off 128 s) and autoregressive correction for serial correlations (AR1) was applied. Contrast images for the comparison of upregulation vs no regulation, upregulation vs fixation, no regulation vs fixation and reinforcement vs fixation were generated. Since successful self-regulation would be characterized by diverging activity (in the

respective target areas) between the upregulation and no regulation tasks, this is the contrast we concentrated on across all NF-conditions.

To test for effects of learning on the group level as a linear increase of this differential neural activity in the respective target region (AMG or INS), multiple regression models were calculated across all participants and in each NF-training group (AMG-NF/INS-NF) and separately for each NF-condition. The model included time as a covariate of interest, coded with increasing distinct values from 1-10 (subsuming all available participant data at each number of training session). Age, sex, IQ, pubertal development and medication status were included as covariates of no interest. To account for the different target regions and drop-out during training, completion and kind of training were also included as dichotomous covariates of no interest in the analyses across the NF groups. Missing sessions were replaced by the last-observation-carried-forward (LOCF) method, which is a common approach of imputing missing data in longitudinal studies (Woolley, Cardoni, & Goethe, 2009). In this analysis, if a person aborted NF-training before completing full amount of sessions, fMRI data of his or her last observed training session was used for all subsequent observation points (total missing data points: 11.7%). The NF target regions AMG and INS were defined as ROIs, thresholded at a familywise error corrected (FWE < .05) level and corrected for each ROI analysis ($0.05/2=0.025$). Additionally, to test for possible involvement of prefrontal areas in affective processing, potentially related to cognitive control of emotions, exploratory ROI-analyses of the medial frontal gyrus, ACC and OFC were also performed in each NF group for each NF-condition.

Pre-post affective processing task: For each participant, a General Linear Model (GLM) assessed regionally specific effects of task parameters on BOLD indices of activation (Friston et al., 1994). The model included onsets and durations of the experimental conditions (negative faces, positive faces and shapes), instructions and task end, plus six realignment parameters as covariates of no interest, to account for residual motion-related variance. Low-frequency signal drift was removed using a high-pass filter (cut-off 128 s) and autoregressive correction (AR1) for serial correlations was applied. Contrast images for the comparisons of negative faces vs

shapes and positive faces vs shapes were generated. The task effect was assessed by means of one-sample T-tests conducted separately for the positive and the negative faces versus shapes contrasts. The pre-post treatment group comparison was calculated in the framework of a 2x2 repeated measures ANOVA separately for the positive and the negative faces versus shapes contrasts, each model including a group-factor (NF vs. TAU) and a time-factor (pre vs. post) and their interaction. Additionally, in these models, each subject received an individual subject-factor to account for inter- and intraindividual variance. For the pre-post treatment comparisons, the NF target regions AMG and INS were defined as ROIs, thresholded at a familywise error corrected ($p_{FWE} < .05$) level and corrected for each ROI analysis ($0.05/2=0.025$).

4.2.4 Results

4.2.4.1 Sample characteristics

Table 6 shows the sample characteristics of the NF and the TAU group. Within in the NF group 6 participants received feedback from the amygdala (AMG-NF) and 6 participants received feedback from the insula (INS-NF). Distribution of male and female participants did not differ between the NF and the TAU group and no significant group differences were observed in demographic and clinical measures before treatment. However, CD and ODD scores as measured by the CBCL were slightly higher before treatment in the NF group.

Table 6. Sample characteristics before treatment

	NF	TAU	p-value
N	12 (6 AMG / 6 INS)	11	
female	25% (n=3)	18,1% (n=2)	.692 (χ^2)
completed treatment	75% (n=9)	72,7% (n=8)	.901 (χ^2)
age	15.15 (1.622)	14.04 (1.527)	.670
CBCL ADHD (T-score)	66.92 (7.585)	67.50 (4.601)	.106
CBCL ODD (T-score)	72.75 (4.413)	68.40 (2.633)	.071
CBCL CD (T-score)	72.58 (4.757)	69.00 (2.944)	.062
ICU (parent)	37.67 (10.421)	36.40 (7.291)	.210
ICU (self)	31.82 (9.745)	30.64 (7.839)	.216
RPQ reactive	11.00 (5.568)	10.18 (4.535)	.443
RPQ proactive	5.09 (5.262)	5.64 (5.025)	.814
MOAS	7.08 (6.999)	7.40 (5.621)	.355

Further, no significant differences in demographic and clinical measures appeared between the AMG-NF and INS-NF group. However, distribution of male and female participants differed significantly between the AMG-NF and the INS-NF group, and the AMG-NF group appeared slightly more severe (table 7).

Table 7. Sample characteristics before treatment within the neurofeedback group

	AMG-NF	INS-NF	p-value
N	6	6	
female	0%	50% (n=3)	.046 (χ^2)
completed treatment	66.6% (n=4)	83,3% (n=5)	.505 (χ^2)
age	14.99 (0.691)	15.30 (2.29)	.754
CBCL ADHD (T-score)	67.33 (6.532)	66.50 (9.138)	.859
CBCL ODD (T-score)	74.67 (4.412)	70.83 (3.817)	.139
CBCL CD (T-score)	74.33 (5.279)	70.83 (3.817)	.218
ICU (parent)	38.83 (7.808)	36.50 (13.217)	.717
ICU (self)	32.83 (8.448)	30.60 (12.033)	.726
RPQ reactive	12.17 (6.178)	9.60 (5.030)	.476
RPQ proactive	6.17 (6.616)	3.80 (3.271)	.487
MOAS	10.83 (8.035)	3.33 (3.077)	.059

4.2.4.2 Learning of self-regulation in the NF groups

4.2.4.2.1 Differences in activity-levels between tasks and sessions

In the general linear mixed model ANOVA a significant main effect of group was observed ($F(1,588)=30.537$, $p<.001$), with higher average activity across tasks and conditions in the AMG-NF group compared to the INS-NF group. A significant main effect of time, indicating differing levels of activity between sessions across groups and conditions ($F(9,588)=2.739$, $p=.004$) and a significant main effect of task, with higher overall activity in the upregulation condition ($F(1,588)=27.515$, $p<.001$) was observed. Further, the interaction of time and task, indicating differing levels of activity between sessions and the upregulation and no-regulation task, was significant ($F(9,588)=2.027$, $p=.034$). Additionally, the interaction of time, task and group ($F(18,588)=1.856$, $p=.017$) was significant, with a marginal significant fixed coefficient of the

upregulation task in the AMG-NF group at session three ($\beta=-2.276$, $t=-1.708$, $p=.088$, $LCI=-4.893$, $UCI=0.342$) and a significant fixed coefficient of the upregulation task at session eight ($\beta=3.033$, $t=2.117$, $p<.05$, $LCI=0.219$, $UCI=5.848$). No significant differences of coefficients within the regulation tasks could be observed in the INS-NF group. No main effects or interactions of condition could be detected.

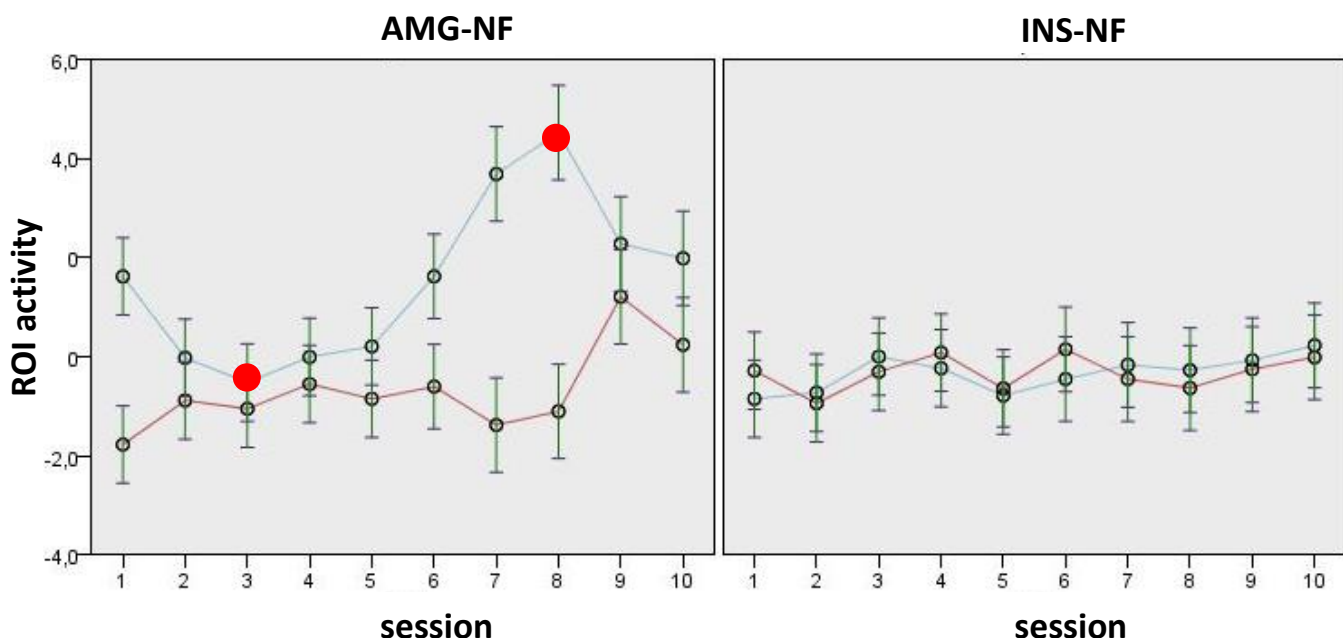


Figure 6. Interaction between time, task and group in the GLMM. In the AMG-NF group, fixed coefficients at each session of the upregulation task differed from the mean-upregulation activity across all sessions marginally significant in the negative direction at session three and significantly in the positive direction at session eight. Blue line = upregulation, red line = no regulation, red dots = (marg.) sig. coefficients.

4.2.4.2.2 Increase of neural activity over time

Simple feedback: In the separate multiple regression model across all participants for each NF group, no specific linear increase in AMG- or INS-activity could be detected.

Video feedback: In the separate multiple regression model across all participants for each NF group, a linear increase over time of the right AMG-activity was observed in the AMG-NF group (ROI-analysis: 11 voxel, MNI: 18, -4, -19; $T=3.54$, $p_{FWE}=.009$ (figure 7A)). No increase in INS-activity could be observed in the INS-NF group.

Transfer feedback: The separate multiple regression models across all participants for each NF group, yielded linear increase over time of bilateral INS-activity in the INS-NF group in five distinct clusters (ROI-analysis: 18 voxel, MNI: 54, -34, 20; $T=4.50$, $p_{FWE}=.020$; 11 voxel, MNI: -54, -40, 20; $T=4.27$, $p_{FWE}=.026$; 52 voxel, MNI: -48, -25, 14; $T=4.27$, $p_{FWE}=.008$; 11 voxel, MNI: -39, -25, 2; $T=3.01$, $p_{FWE}=.026$; 7 voxel, MNI: 45, -16, 17; $T=3.91$, $p_{FWE}=.031$ (figure 7B)). No increase in AMG-activity was observed in the AMG-NF group.

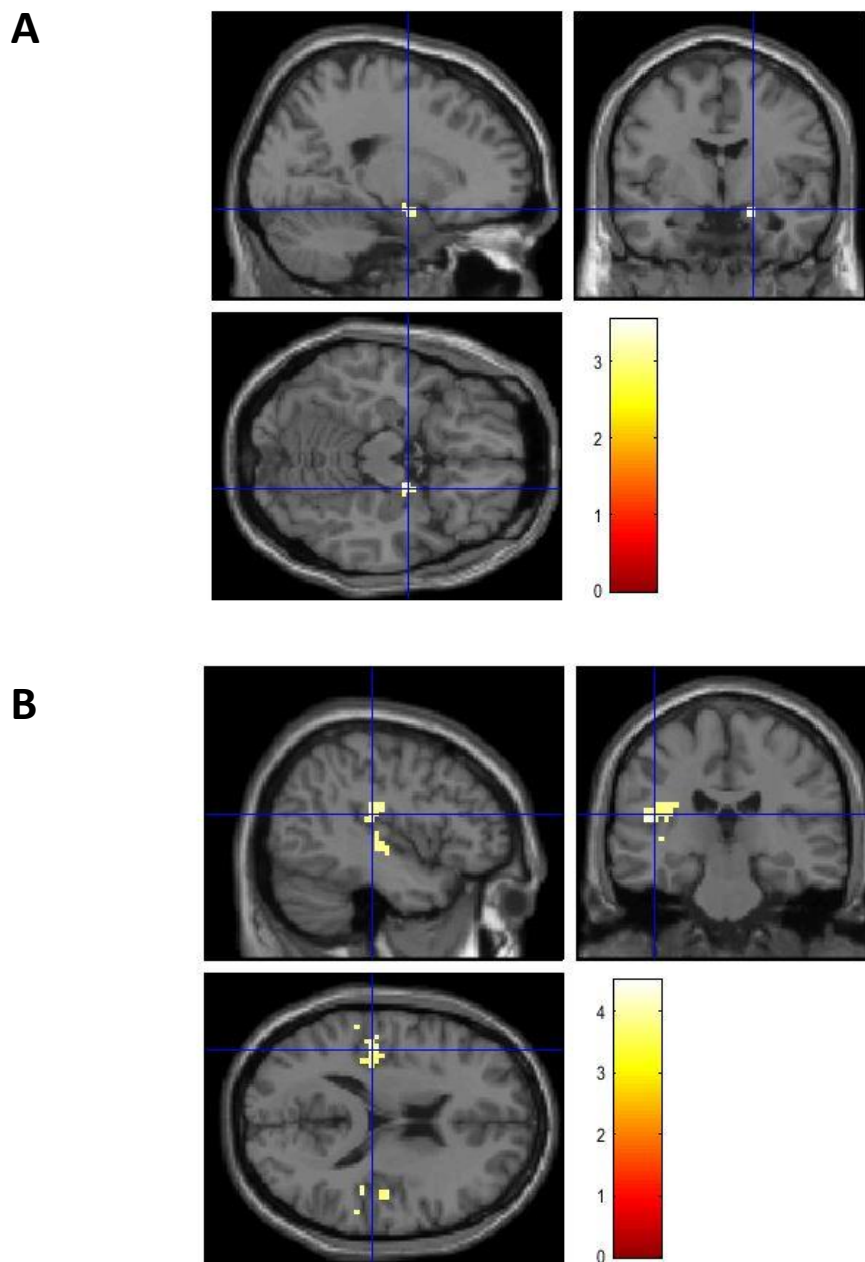


Figure 7. Increase of neural activity in the upregulation vs. no regulation contrast over time within the NF groups. A: Linear increase over time in the video condition in right AMG-activity in the AMG-NF group. B: Linear increase over time in the transfer condition in in bilateral INS-activity in the INS-NF group.

4.2.4.2.3 Additional analysis of linear increase in prefrontal regions

In additional exploratory ROI-analyses of the medial frontal gyrus, ACC and OFC a cluster of two voxels in the left medial frontal gyrus survived FWE-correction (MNI: -6, 65, 11; $T=3.75$, $p_{FWE}=.036$) in the simple feedback condition in the AMG-NF group. However, in the other conditions exploratory ROI-analysis of prefrontal areas revealed no significant activation.

4.2.4.3 Affective processing baseline task effect

Negative faces vs shapes: The affective processing of negative faces before treatment yielded significant activity at conservative FWE-corrected threshold in middle and superior frontal, and middle temporal regions as well as in the precuneus. Explorative analysis using a liberal uncorrected threshold of $p<.001$ yielded activation in several cortical areas, including frontal, temporal and occipital regions across both treatment groups (detailed overview see figures and table 8). Bilateral ROI-analysis of the AMG revealed two voxel in the left (MNI: -24, -4, -25; $T=4.25$, $p_{FWE}=.035$) and one voxel in the right (MNI: 27, -1, -28; $T=3.53$, $p_{FWE}=.040$) AMG, and bilateral ROI analysis of the INS revealed three voxel (MNI: 42, 14, 14; $T=5.35$, $p_{FWE}=.021$) in the right anterior INS.

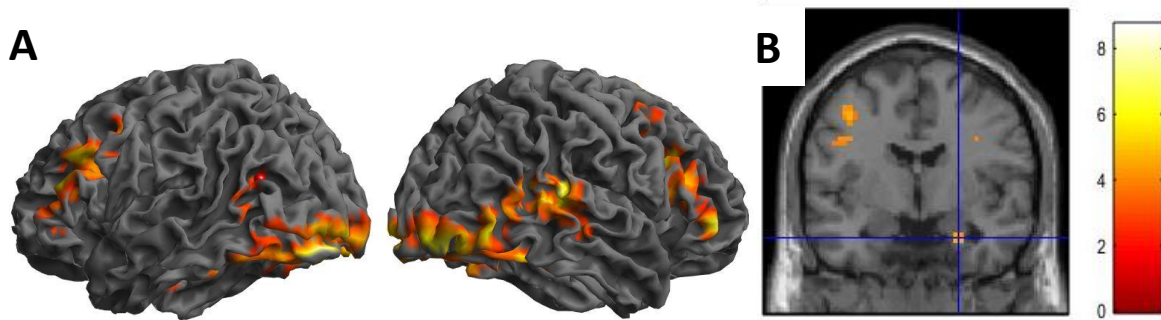


Figure 8. Task activation of the affective processing task before treatment (N=22) in the negative faces versus shapes contrast at $p_{\text{uncor.}} < .001$, $k=10$). A: cortical activity B: subcortical AMG/hippocampus activity.

Table 8. Detailed overview of areas involved in affective processing of negative faces before treatment at $p_{\text{uncor.}} < .001$, $k=10$. FWE-corrected p-values are reported (all $p_{\text{uncor.}} < .001$).

L/R	region	MNI			Cluster	T-value	p (FWE)
		X	Y	Z			
R	middle frontal	39	14	26	672	8.72	.003
R	middle temporal	60	-49	11	1684	8.57	.004
L/R	precuneus	6	-61	35	165	7.51	.020
L/R	superior frontal	0	32	53	125	7.48	.021
L	inferior frontal	-48	23	14	600	6.86	.050
R	cerebellum	9	-76	-37	313	6.78	.055
L	cerebellum	-3	-52	-46	110	5.69	.246
L	middle occipital	-36	-70	20	16	5.61	.275
R	AMG/hippocampus	24	-7	-25	15	4.63	.756
R	posterior cingulate	3	-37	8	22	4.23	.926
R	superior frontal	9	62	32	19	4.20	.935

p (FWE) = whole brain FWE-corrected p-value at peak-level

Positive faces vs shapes: The affective processing of positive faces before treatment yielded significant activity at conservative FWE-corrected threshold in temporal and occipital regions, including the fusiform area. Applying a liberal uncorrected threshold of $p < .001$ yielded activation in several cortical areas, including frontal, temporal and occipital regions. For the purpose of visualization, results of whole brain analysis are reported at $p_{\text{uncor.}} < .001$ (for detailed overview see figures and table 9). Bilateral ROI-analysis of the AMG revealed 22 voxel in the right (MNI: 21, -4, -16; $T=5.11$, $p_{\text{FWE}}=.007$) and eleven voxel in the left (MNI: -27, -1, -28; $T=4.49$, $p_{\text{FWE}}=.016$) AMG. Bilateral ROI analyses of the INS revealed no significant activity.

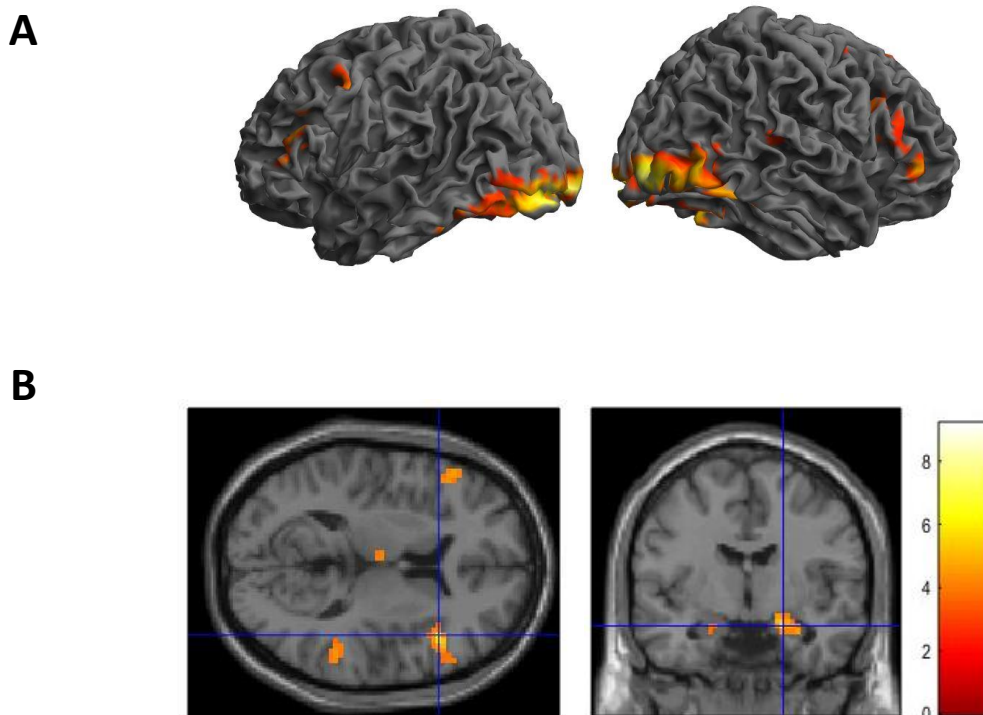


Figure 9. Task activation of the affective processing task before treatment (N=22) in the positive faces versus shapes contrast at $p_{\text{uncor.}} < .001$, $k=10$. A: cortical activity B: right anterior insula (axial view) and subcortical AMG/hippocampus (coronar view) activity.

Table 9. Detailed overview of areas involved in affective processing of positive faces before treatment at $p_{\text{uncor.}} < .001$, $k=10$). FWE-corrected p-values are reported (all $p_{\text{uncor.}} < .001$).

L/R	region	MNI			Cluster	T-value	p (FWE)
		X	Y	Z			
R	occipital/fusiform	12	-100	-7	1178	9.17	.001
R	middle frontal	-57	23	23	136	7.07	.039
L	cerebellum	-3	-52	-43	78	6.29	.116
R	anterior INS	42	20	11	238	6.15	.140
R	AMG/hippocampus	21	-7	-19	63	5.71	.253
L	cerebellum	-6	-76	-28	113	5.07	.541
L/R	thalamus	-3	-13	8	12	5.00	.578
L	middle frontal	-42	-1	44	39	4.99	.581
L	temporal pole	-24	8	-28	25	4.96	.598
	(incl. AMG/ant. INS)						
R	superior frontal	3	38	56	49	4.80	.686
R	precuneus	9	-61	38	20	4.80	.690
R	hippocampus	24	-28	-4	26	4.62	.782
R	middle frontal	42	2	59	34	4.55	.818
R	superior temporal	51	-40	11	29	4.36	.898
L	AMG/hippocampus	-21	-10	-16	11	3.99	.981

p (FWE) = whole brain FWE-corrected p-value at peak-level

4.2.4.4 Pre-post effects on affective processing

Negative faces vs shapes: In the pre-post treatment-group comparison of the processing of negative faces no significant main effect of group could be observed at a conservative whole-brain FWE-corrected threshold. However, applying a liberal uncorrected threshold of $p < .001$, a significant main effect of group could be observed in whole brain analysis in the left fusiform area (14 voxel, MNI: -42, -28, -19; $F=20.39$, $p_{unc} < .001$, $p_{FWE} = .882$) and significant main-effects of time could be observed in middle and lateral frontal and temporal regions at $p_{uncor} < .001$, $k=10$ (for detailed overview see table 10). No significant interaction between group and time was observed in this contrast.

Table 10. Significant main effects of time in the processing of negative affect across groups at $p_{uncor} < .001$, $k=10$. FWE-corrected p-values are reported (all $p_{uncor} < .001$).

L/R	region	MNI			Cluster	F-value	p (FWE)
		X	Y	Z			
L/R	posterior cingulate	0	-37	8	16	30.43	.316
L	middle frontal	-48	29	23	70	29.60	.351
L	superior frontal	-6	23	56	33	27.88	.436
R	superior frontal	12	50	44	19	21.15	.843
L	inferior temporal	-54	-64	-16	15	19.73	.911
L	Precentral	-39	-1	35	21	19.34	.927
L	middle frontal	-24	14	47	11	19.11	.935
R	inferior frontal	45	32	5	10	18.26	.960
R	middle temporal	60	-46	8	30	17.94	.968

P (FWE) = whole brain FWE-corrected p-value at peak-level

Post-hoc comparison of the treatment groups overall higher activity in the TAU group compared to the NF group in the left fusiform area across time (23 voxel, MNI: -42, -28, -19; $T=4.52$, $p_{uncor} < .001$, $p_{FWE} = .657$). The NF group (compared to the TAU group) did not show higher activity in any brain region across time.

Post-hoc comparison of the measurements revealed higher brain activity before treatment (compared to after treatment) across both TAU and NF (for detailed overview see figure 10, table 11). No higher activity in any brain region could be observed across groups after treatment.

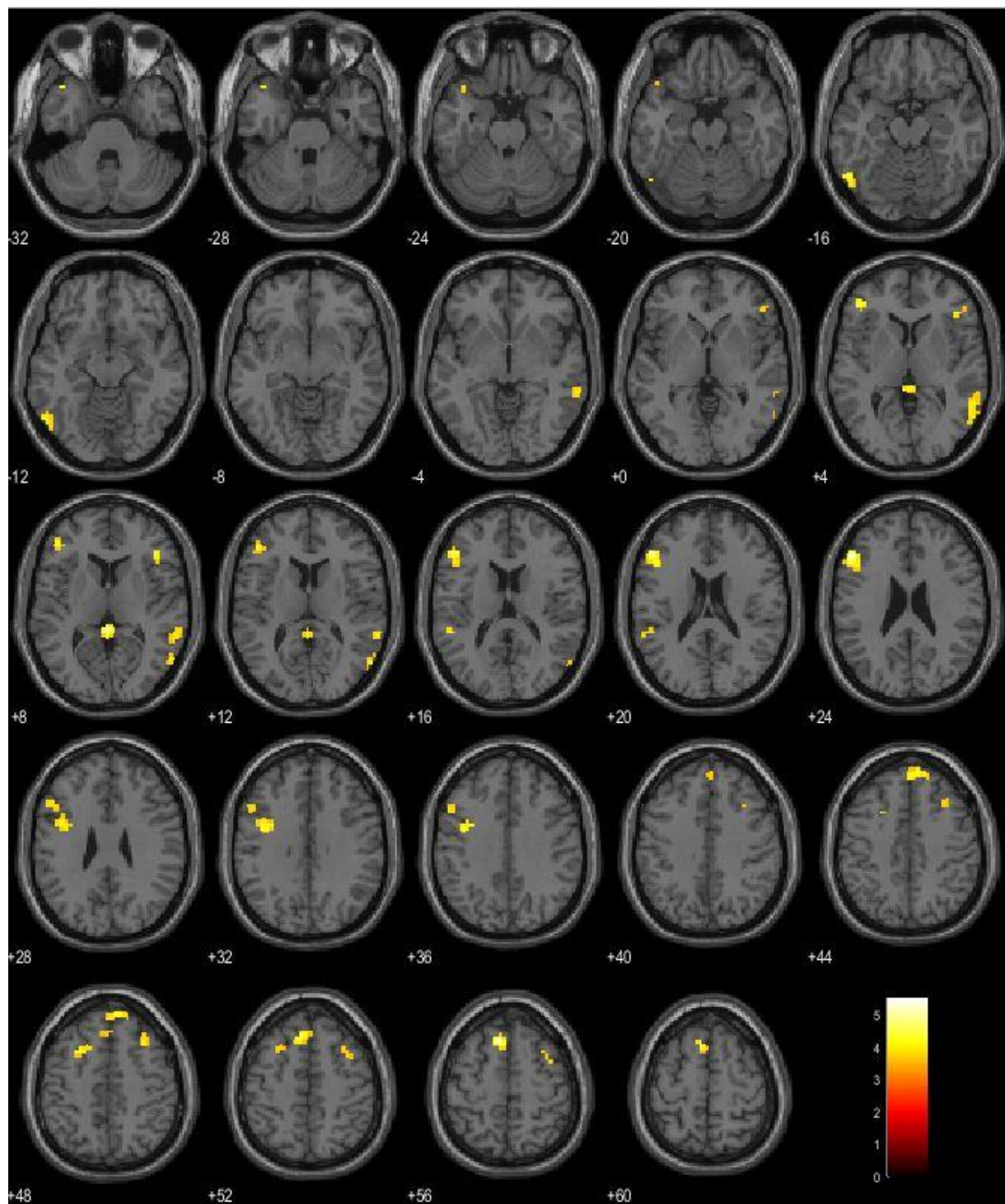


Figure 10. Higher activation in the processing of negative affect before treatment compared to after treatment across groups (N=22) at $p_{\text{uncor.}} < .001$, $k=10$.

Table 11. Higher activation in the processing of negative affect before treatment compared to after treatment across groups as displayed in figure 10. FWE-corrected p-values are reported (all $p_{\text{uncor.}} < .001$).

L/R	region	MNI			Cluster	T-value	p (FWE)
		X	Y	Z			
L/R	posterior cingulate	0	-37	8	33	5.52	.173
L	middle frontal	-48	29	23	140	5.44	.195
L	superior frontal	-6	23	56	59	4.13	.249
R	superior frontal	12	50	44	39	4.60	.604
L	inferior temporal	-54	-64	-16	30	4.44	.702
L	Precentral	-39	-1	35	43	4.40	.730
L	middle frontal	-24	14	47	26	4.37	.745
R	inferior frontal	45	32	5	27	4.27	.800
R	middle temporal	-39	20	-31	11	3.56	.801
R	middle temporal	60	-46	8	93	3.54	.821
L	superior temporal	-51	-40	17	11	3.44	.892
R	middle frontal	33	23	47	30	3.43	.898

p (FWE) = whole brain FWE-corrected p-value at peak-level

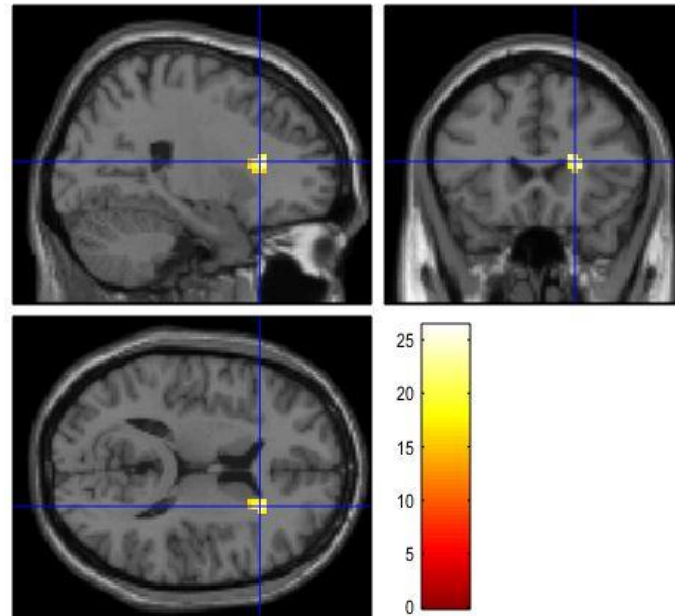


Figure 11. Significant interaction between group and time in the processing of positive affect in the right nucleus caudatus and anterior insula at $p_{\text{uncor.}} < .001$, $k=10$.

Positive faces vs shapes: In the pre-post treatment-group comparison of the processing of positive faces significant activity at conservative FWE-corrected threshold was observed in the right cerebellum (320 voxel, MNI: 30, -55, -31; $F=50.95$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.021$). However, explorative analysis using a liberal uncorrected threshold of $p < .001$ yielded activation in another cluster in the right cerebellum (26 voxel, MNI: 51, -64, -31; $F=32.94$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.201$) and in the right thalamus (36 voxel, MNI: 3, -4, 2; $F=25.33$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.534$) and brain stem (18 voxel, MNI: 9, -31, -31; $F=22.45$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.720$). Significant main-effects of time could be observed in left inferior temporal and fusiform gyrus (36 voxel, MNI: -51, -64, -19; $F=28.37$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.368$ and 17 voxel, MNI: -18, -94, -16; $F=19.20$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.904$), right fusiform gyrus (14 voxel, MNI: 33, -85, -16; $F=21.50$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.780$) and right superior frontal gyrus (35 voxel, MNI: 33, 5, 62; $F=19.60$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}} < .885$) at $p_{\text{uncor.}} < .001$, $k=10$. Further, at a liberal uncorrected threshold of $p < .001$ a significant interaction between group and time could be observed in this contrast (figure 11) in an area comprising the right nucleus caudatus and anterior insula (29 voxel, MNI: 14, 23, 14; $F=26.30$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.476$).

Post-hoc comparison of the treatment groups revealed that the significant main effects of group in this contrast are driven by higher activity the NF group compared to TAU group across time (for detailed overview see table 12). The TAU group (compared to the NF group) did not show higher activity in any brain region across time.

Table 12. Main effects of group across time in the processing of positive affect at $p_{\text{uncor.}} < .001$, $k=10$. FWE-corrected p-values are reported (all $p_{\text{uncor.}} < .001$).

L/R	region	MNI			Cluster	T-value	p (FWE)
		X	Y	Z			
R	cerebellum	30	-55	-31	439	7.14	.010
R	cerebellum	51	-64	-31	34	5.74	.106
R	thalamus	3	-4	2	67	5.03	.317
R	thalamus	9	-31	5	13	4.93	.368
L	brain stem	9	-31	-31	28	4.74	.470
R	superior temporal	42	-40	14	10	4.43	.661
L	middle temporal	60	-46	11	16	4.23	.781
L	precentral	-60	11	26	12	4.10	.846
R	precentral	45	-13	44	12	3.93	.917

p (FWE) = whole brain FWE-corrected p-value at peak-level

Post-hoc comparison of the times of assessment revealed that the significant main effects of time come from higher brain activities at the pre assessment (compared to the post assessment) across groups (for detailed overview see figure 12, table 13). No higher activity in any brain region could be observed across groups after treatment.

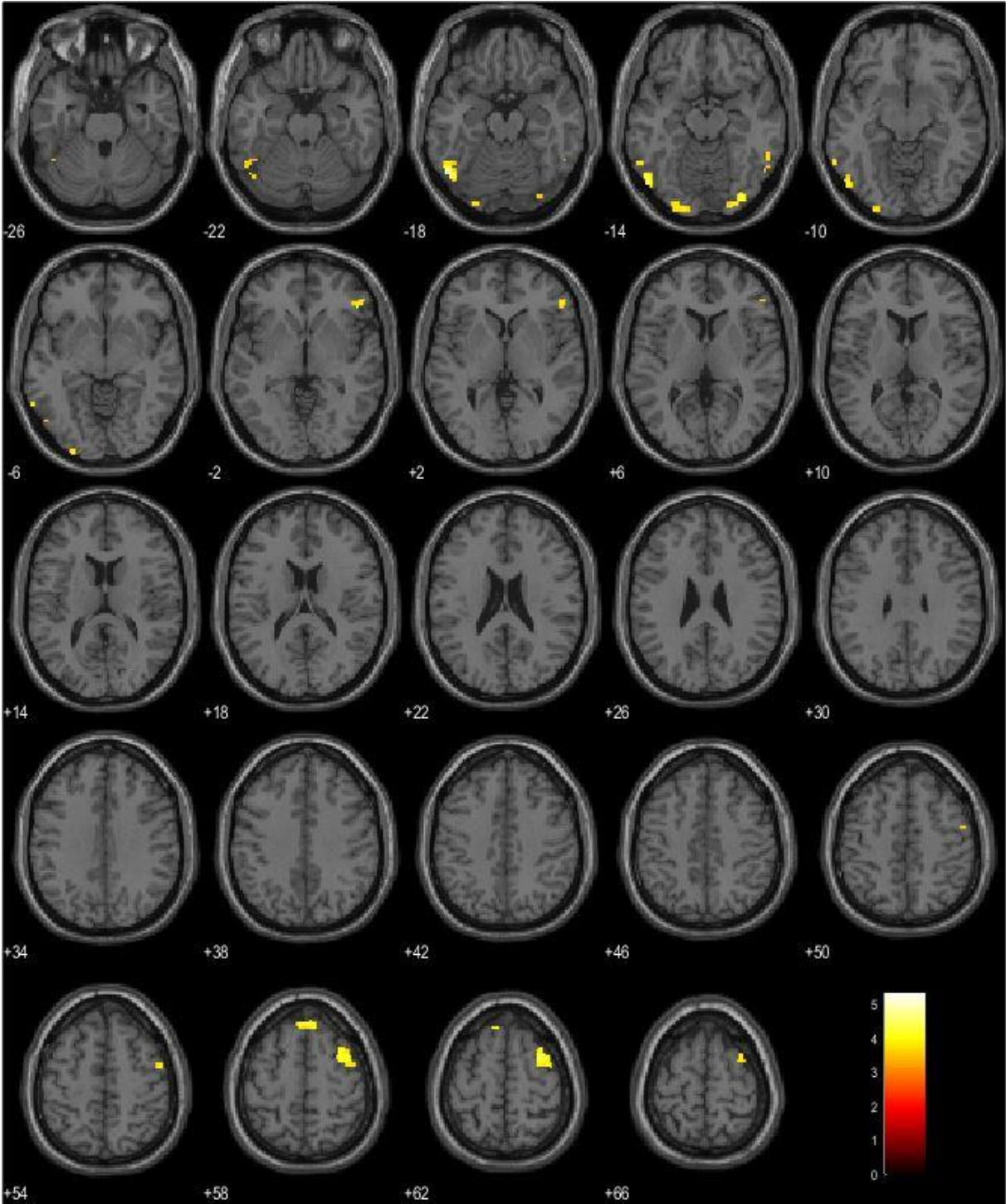


Figure 12. Higher activation in the processing of positive affect before treatment compared to after treatment across groups (N=22) at $p_{\text{uncor.}} < .001$, $k=10$,

Table 13. Higher activation in the processing of positive affect before treatment compared to after treatment across groups as displayed in figure 12. FWE-corrected p-values are reported (all $p_{\text{uncor.}} < .001$).

L/R	region	MNI			Cluster	T-value	p (FWE)
		X	Y	Z			
L	Inferior temporal	-51	-64	-19	71	5.33	.205
R	fusiform	33	-85	-16	25	4.64	.531
R	middle frontal	33	5	62	62	3.65	.661
L	fusiform	-18	-94	-16	42	3.63	.690
R	inferior temporal	57	-49	-16	15	4.25	.767
R	superior frontal	6	35	59	19	4.22	.785
R	inferior frontal	54	38	2	17	3.92	.920

p (FWE) = whole brain FWE-corrected p-value at peak-level

In the post-hoc comparisons of groups and times, the TAU group (compared to the NF group) showed higher activation before treatment (compared to after treatment) at $p_{\text{uncor.}} < .001$, $k=10$, in two clusters in the right occipital gyrus (13 voxel, MNI: 36, -91, 2; $T=4.78$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.446$, and 10 voxel, MNI: 33, -91, 17; $T=4.38$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.688$). In turn, the NF group (compared to the TAU group) showed higher activation before treatment (compared to after treatment) at $p_{\text{uncor.}} < .001$, $k=10$ in the right cerebellum (44 voxel, MNI: 12, -55, -22; $T=5.98$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.072$) and brain stem (MNI: 6, -31, -31; $T=3.70$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.611$). After treatment, the TAU group showed higher activation at $p_{\text{uncor.}} < .001$, $k=10$, in the left caudatus (43 voxel, MNI: -21, 23, 17; $T=5.90$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.081$), the right caudatus including the anterior INS (107 voxel, MNI: 21, 26, 17; $T=5.56$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.142$), the right cerebellum (260 voxel, MNI: 30, -55, -31; $T=5.67$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.118$) and in the bilateral thalamus (83 voxel, MNI: 0, -4, 5; $T=4.21$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.172$, and 11 voxel, MNI: 9, -31, 2; $T=4.51$, $p_{\text{uncor.}} < .001$, $p_{\text{FWE}}=.612$) (see figure 13). The NF group (compared to the TAU group) did not show higher activities in any brain region after treatment.

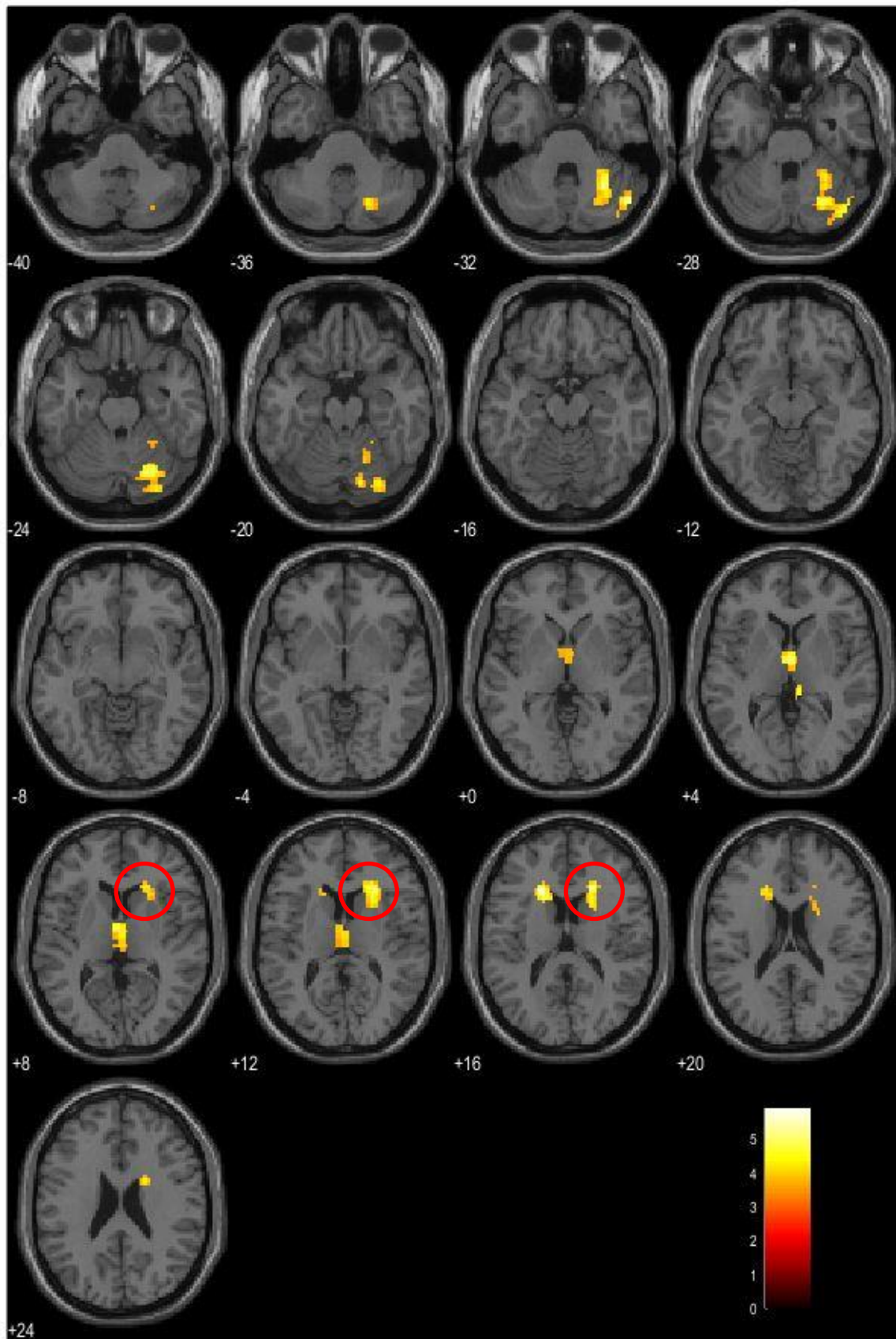


Figure 13. Higher activation in the processing of positive affect after treatment in the TAU group at $p_{\text{uncor.}} < .001$, $k=10$. Red circle indicates overlapping area with the right caudatus and anterior insula significant in the interaction of group and time.

4.2.4.5 Behavioral data of the affective processing task

In the pre post treatment-group comparison of the behavioral data of the affective processing task (see table 14) a significant main effect of time could be observed in reaction-time (RT) with faster responses after treatment across groups for happy faces ($F(1,21)=7.77$, $p=.013$) and a trend for fearful faces ($F(1,21)=3.54$, $p=.078$). Additionally, RT of correct responses improved marginally over time ($F(1,21)=3.75$, $p=.070$). No significant interactions between time of assessment and treatment-group could be observed.

Table 14. Pre-post comparison of responses and reaction-times

Responses/RT	PRE	POST	effect of time (p)
correct response	85.95%	85.05%	.784
incorrect response	11.04%	10%	.660
RT corr. responses	1.79 (0.31)	1.645 (0.36)	.070
RT incorr. responses	1.82 (0.55)	1.875 (0.66)	.838
RT angry faces	2.24 (0.44)	2.13 (0.45)	.495
RT fearful faces	2.07 (0.43)	1.86 (0.42)	.078
RT happy faces	1.97 (0.35)	1.74 (0.35)	.013
RT neutral faces	2.18 (0.59)	2.03 (0.81)	.206
RT forms	1.22 (0.24)	1.12 (0.44)	.402

RT = reaction-time

4.2.4.6 Clinical outcome

In the analysis of treatment effects on clinical outcome, a significant main effect of time was observed for the parent-rated CBCL-ODD ($F(1,19)=8.61$, $p=.008$) and the CBCL-CD ($F(1,18)=7.16$, $p=.015$) using the total scores of each scale, with reduced symptom severity after treatment across both treatment-groups. Interactions between time of assessment and treatment-group were not significant. No clinical improvement was observed in parent-rated ADHD symptoms and CU traits (parent and self-rating). Additionally, the interaction between time of assessment and treatment-group was significant in the reactive aggression domain, as

measured by the RPQ self-rating ($F(1,15)=9.15$, $p=.009$). Post-hoc comparison revealed a significant improvement in the TAU group (mean difference=-2.90 (1.22), $p=.031$) and a marginally significant aggravation in the NF group (mean difference=+2.85 (1.46), $p=.069$) (figure 14). No effects were observed for proactive aggression. In additional repeated measure ANOVA analyses, comparing the clinical outcome between the NF groups (INS-NF vs AMG-NF), interactions between NF group and time were not significant for CBCL-CD ($F(1,9)=0.29$, $p=.600$), CBCL-ODD ($F(1,9)=1.55$, $p=.244$) and RPQ reactive aggression ($F(1,5)=0.90$, $p=.386$).

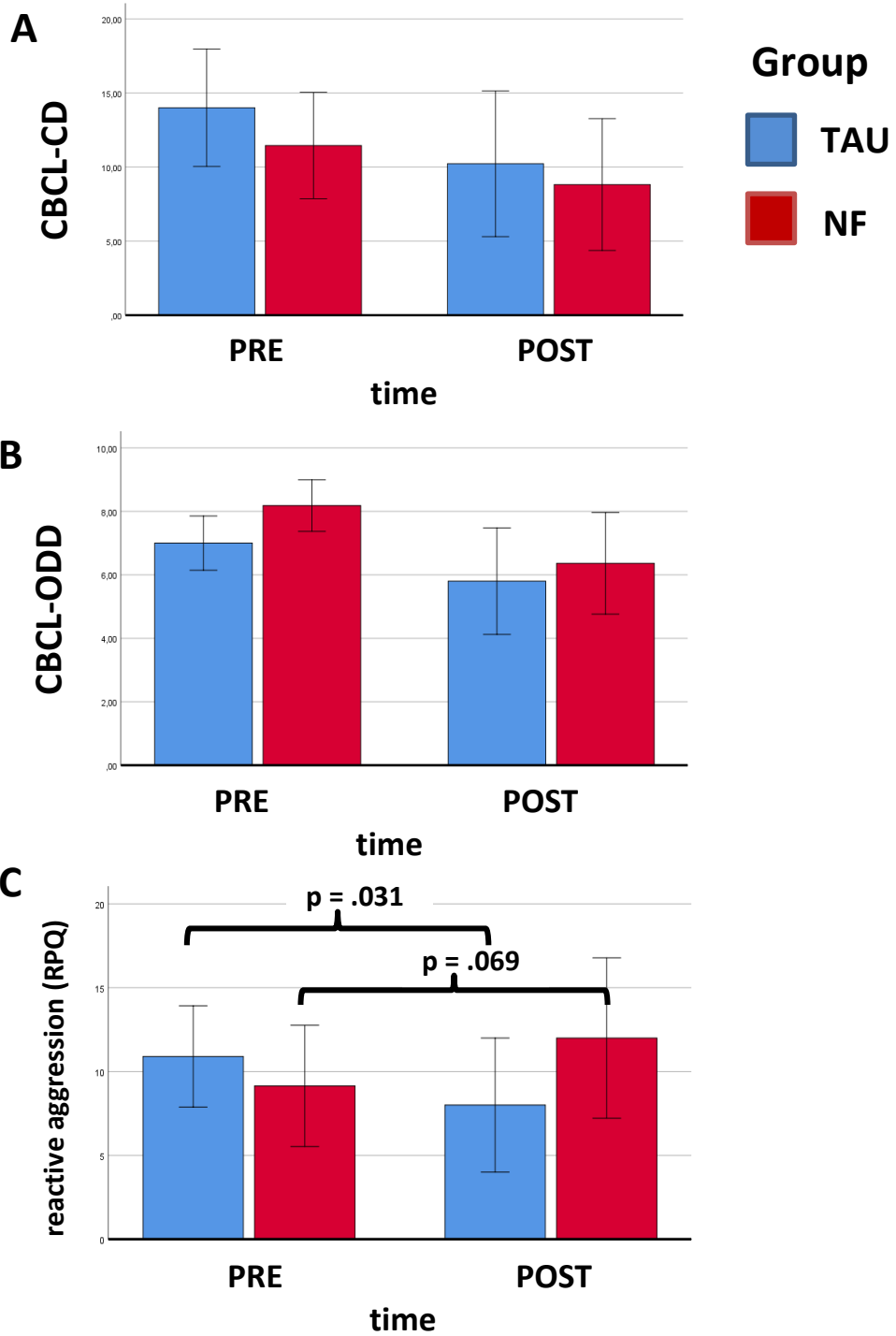


Figure 14. Clinical improvements and aggravations in behavioral scales related to disruptive behavior. Improvement over time across groups was observed for A: CBCL-CD and B: CBCL-ODD. C: Reactive aggression improved in the TAU group, but aggravated marginally in the NF group.

4.2.5 Discussion

For the first time feasibility and efficacy of individualized rtfMRI-NF in adolescents with DBD were investigated. In this randomized controlled clinical trial, we tested rtfMRI-NF as a tool for learning self-regulation of emotional processing regions in adolescents with diagnosis of DBD and increased CU traits. Treatment efficacy was evaluated in comparison to TAU as an active control condition. The NF target-regions were individually selected for each participant in the NF group via a functional localizer, eliciting activity in core-regions of affective processing (AMG and INS), which previously have been reported to be compromised in patients with diagnosis of DBD and elevated CU traits. The TAU treatment also consisted of an intensive and customized treatment, applying individually selected elements from several behavioral intervention manuals (for example from the Anti-Aggression-Training (AAT) (Weidner, 2011) and from the Assertiveness-Training-Program (ATP) (Pfungsten, 2000)).

Regarding the learning of self-regulation as assessed with the GLMM, different levels of activity (mean target-ROI values) along the course of the NF-training were observed in the upregulation condition in the AMG-NF group. Lower levels were obtained in the first five sessions (with a slightly higher value at the first session) and higher levels in session six to ten (with slightly lower values at sessions nine and ten). The activity-level at session three differed marginally significant in the negative direction and, at session eight, significantly in the positive direction from the mean of upregulation activity across conditions. These results suggest a somewhat uneven increase over time in target-ROI activity in the AMG-NF group and across conditions. However, in the INS-NF group no such increase over time was found.

When analyzing each condition separately for each NF group using a multiple regression model, we were able to show a linear increase of differentiation between no- and upregulation over time in the video condition in the AMG-NF group in the right AMG and, in the INS-NF group, a linear increase over time in the transfer condition could be detected in bilateral INS. Results between the GLMM and the multiple regression approach may differ, since the GLMM is less restricted in terms of testing directed hypothesis on linear increase over time. Further, the

GLMM included all conditions and results were assessed using the mean target-ROI values, whereas the multiple regressions were assessed separately for each condition using FWE-corrected peak activity levels within the target-ROIs. However, concerning the AMG-NF group, congruent results of the GLMM and multiple regressions are indicating successful and partly linear learning of AMG-upregulation in this group. Concerning the INS-NF group, potential learning of INS-upregulation was only indicated for the transfer condition. Together, our data suggest that the self-regulation of emotional processing regions might be more promising when receiving feedback from the AMG (as compared to the INS). These differences in learning may be partially explained by the anatomical structures and functional connections of the respective target regions. The AMG is a relatively small and marked out structure and has strong functional connections to prefrontal areas (E. A. Murray & Wise, 2010b), which may ease the addressing of the AMG via cognitive emotion regulation, which is moderated by prefrontal areas (Morawetz, Bode, Baudewig, & Heekeren, 2017). In contrast, the insula is a relatively broad structure and is considered as a multi-modal functional network hub that is widely connected across the brain (Dionisio et al., 2019), which might exacerbate addressing of this structure via cognitive regulation strategies. Additionally, the absolute sizes of the target ROI-masks extremely differed (very large INS-ROI mask in comparison to the AMG-ROI mask). Therefore local learning effects within the INS (for example only in the anterior part) could be underestimated by analyzing mean activity levels of the respective ROI-masks. Further, the insula has been identified by a recent meta-analysis to be consistently activated during self-regulation in rtfMRI-NF independent of the target ROI (Emmert et al., 2016). Thus, when the INS is targeted in NF, care should be given whether activation changes are related to successful regulation or related to the regulation process per se. In our data, increasing differentiation between up- and no regulation of the INS in the transfer condition presumably represents activity which is related to the ongoing search for successful regulation strategies in the INS-NF group (as the GLMM does not indicate successful learning for this group). However, the AMG-NF group did not show such a differentiation in the INS in any condition, which, in the framework of this speculative

explanation, could be because they may have established successful self-regulation-strategies (as the GLMM indicates) faster and more easily via prefrontal control regions and therefore did spend less effort on searching, testing and evaluating different mental strategies. Congruently, in the AMG-group, the medial prefrontal gyrus also showed increasing differentiation between up- and no regulation over time in the simple feedback condition, which is the first in the sequence of the three training-conditions and hence might be associated to the establishment of prefrontal control over AMG-activity, which might be seen as a further support (although a relatively weak) for the assumption of prefrontal control of emotions.

Interestingly, when visually inspecting the learning curve of the AMG-NF group, a steep increase of the slope in the upregulation task can be observed around the sixth session, which resembles the learning-curve that was observed in the study of Alegria et al. (2017). Since NF-studies in adult healthy and clinical populations with fewer number of sessions (from 1 up to 5) already show significant effects of training even after one session (Paret et al., 2018; Posse et al., 2003; Sitaram et al., 2014; Veit et al., 2012), a learning effect around the sixth session appears relatively late. However, the study of Alegria et al. and this current study are the only currently published rtfMRI-NF studies in adolescents. So far, a relatively late onset of learning of self-regulation (around the sixth session) might be attributable to delayed maturation of prefrontal emotion-regulation related areas during adolescence (Nelson & Guyer, 2011). Another explanation might be that both rtfMRI-NF studies in adolescents investigated individuals with high comorbid psychiatric conditions (ADHD, ODD, CD), which are also associated with learning difficulties (Huang et al., 2016). Additionally, the timeframes of the upregulation-conditions were relatively long in both studies (40s in our study and 50s in the study of Alegria et al.) which might also have exacerbated continuous upregulation in each trial.

In the pre-post treatment-group comparison of the affective processing task we could observe higher activity in several brain areas related to emotion regulation, such as the dlPFC, across groups before treatment, which may indicate more efficient affective processing after treatment in both groups (NF and TAU). Additionally, the pre-post comparison of the behavioral data of the

affective processing task supports this assumption, as correct responses were marginally faster across groups in the post assessment. Interestingly, the TAU group showed higher activity for positive faces compared to the NF group after treatment in a cluster comprising the caudatus and the anterior INS. This may be attributed to the fact, that the NF group performed an additional implicit emotion-matching task at each training session, such that effects of habituation may have counteracted a possible increase in anterior INS activity during affective processing as an effect of the learning of self-regulation. In turn, these results indicate that TAU treatment may effectively improve affective processing.

Furthermore, visually inspecting the baseline task effect of the different emotional valences, positive faces elicited larger clusters in the amygdala and anterior INS than negative faces did. Interestingly, reaction times for correct responses to happy faces significantly increased across groups after treatment. Thus, these data may indicate a specific effect of TAU treatment on the improvement of the processing of positive faces. However, no group-difference in improvement of reaction-time to positive faces could be observed, indicating that the NF-group may have also improved in this domain, but, however, do not show potentially associated increased brain-activity after treatment in the anterior INS. This assumption may also be supported by a recent rtfMRI-NF study, showing healthy participants increased activity in the anterior INS better when listening to positive, compared to negative valenced emotional auditory stimuli (Kanel, Al-Wasity, Stefanov, & Pollick, 2019).

Finally, the NF and the TAU group showed comparable and significant clinical improvements on DBD-related behavioral scales. Thus, the results can be interpreted as non-inferiority of the rtfMRI-NF treatment compared to TAU. Within the NF group, clinical improvements were not specific to either target ROI, which, on the one hand, suggests an additional unspecific, “placebo-like” effect, that could be caused by the impressive setting (highly technical, large fMRI machine, etc.) and by the attention and care given by the study-operator to patients with these disorders who often miss such positive interactions. On the other hand, due to differing sizes of the ROI-target masks between the NF-groups (e.g.), potential nonlinear learning effects in the INS-group

may have been underestimated in our analyses of mean ROI-activities, while learning effects in the AMG-group seem overall promising. To validate a specific relation between successful AMG (or INS) self-regulation and improvement in clinical behavioral domains, further investigations with larger treatment groups and possibly implying a sham feedback condition would be needed. However, comparing the technical, financial and human effort of both treatments, conduction of rtfMRI-NF training requires much more resources. Thus, although technical feasibility of rtfMRI-NF in adolescents with diagnosis of DBD has been demonstrated, it still is a very complex and costly setting. The results of our research suggest clinical improvement and non-inferiority compared to other treatment options, but further studies are needed to clarify underlying mechanisms and cost effectiveness.

4.2.5.1 Strengths and Limitations

The strengths of this study include the innovative, non-pharmacological and individualized treatment of adolescents with particularly severe DBD including elevated CU traits, and the comparison to an active behavioral control treatment (TAU) in an RCT. However, there are also limitations worth noting. First, each NF group contained of a relatively small number of adolescents (6 each) and therefore this study must be rather considered a proof-of-concept. Further, as the clinical outcome could not be attributed to the learning of self-regulation in either NF-group, specificity of rtfMRI-NF of the AMG (or INS) could not be validated. Additionally, a marginal aggravation in reactive aggression was observed in the NF group, whereas a significant improvement was observed in the TAU group. However, this result has to be interpreted with caution because the effect is only marginally and not compared with an inactive control group (as TAU explicitly targeted reactive aggression). Further, only seven out of twelve (4 in INS-NF and 3 in AMG-NF) questionnaires were available for the pre-post comparison of reactive aggression. Further, regarding technical feasibility of measuring brain activity from subcortical brain regions, rtfMRI-NF compared to the more traditional EEG-NF approach is superior in spatial resolution (voxel sizes of up to 1mm³) and sensitivity. Thus, neural activity of deep, central brain structures, such as the amygdala or brainstem, can be

precisely targeted. A drawback of fMRI is the hemodynamic response delay of several seconds, and the low temporal resolution (in the range from 0.5 to 1Hz), which is limited to the spin-relaxation time (TR: between 1-2 seconds) of the excited atomic-nuclei in the respective tissue. Contrary, EEG provides high temporal resolution that can range from 256Hz up to 5000Hz (depending on the equipment) but allows only vague spatial resolution, depending on the number of electrodes distributed across the surface of the scalp. Thus, EEG is less applicable to address specific brain structures, especially when it comes to the feedback of neural activity from deep brain areas (there are mathematical approaches that attempt to get around this limitation, but it remains a challenge for EEG research). Therefore, specific feedback from the AMG or INS is more easily acquired and more spatially precise using rtfMRI-NF. In contrast, EEG is generally easier to apply since it is less costly and also portable, whereas fMRI mostly requires extensive funding and is usually not portable.

Summarizing, as long as clinical efficacy is not sufficiently validated for any NF-approach, and as long as financial resources and technical advances limit the application of rtfMRI-NF, customized behavioral treatment will probably remain the most cost-efficient and evidence-based first-line-therapy.

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4 General Discussion

Difficulties with affective processing have been identified as a core feature of psychopathology in DBD involving subcortical structures, such as the amygdala and insula (Beauchaine, 2015; Viding & McCrory, 2018). Additionally, CU traits have been associated with altered affective processing in the healthy population and in children and adolescents diagnosed with DBD and also indicate a more severe subtype within DBD (Hyde et al., 2014; White et al., 2012). To date, rtfMRI-NF is increasingly considered as a promising tool for the training of brain self-regulation. It has already been applied to train self-regulation of compromised inhibitory or emotional brain regions, and of emotion regulation strategies in adult psychopaths (Sitaram et al., 2014) and adolescents diagnosed with ADHD (Alegria et al., 2017). Further, the neural circuitries of cognitive emotion regulation, which might also be relevant for the self-regulation of emotional processing regions and cognitive control over CP, have been mapped to the prefrontal cortex (PFC) (Etkin, Büchel, & Gross, 2015; Johnstone & Walter, 2014).

For the purpose of investigating and evaluating new innovative forms of treatments for adolescents with DBD, this thesis followed a two-way approach. First, a large dataset of healthy young adolescents (mean age: 14.44 (0.41), range 13.08-15.72 years) was analyzed in relation to affective processing with respect to possible neural correlates of control over CP. Second, an individualized rtfMRI-NF training aiming at the learning of self-regulation of emotional processing regions and, as a result, at the improvement of affective processing was conducted with adolescent patients (mean age: 14.62 (1.64), range: 12.04-17.99 years) diagnosed with CD or ODD and high CU traits over a course of 10 weeks and compared with a clinical TAU group.

Regarding the analyses of healthy adolescents, the left OFC was identified as a possible correlate of control over CP, suggesting a compensatory mechanism that may allow adolescents who exhibit CP to remain below symptom threshold of DBD diagnosis. This is in line with the findings on the involvement of prefrontal structures in cognitive emotion regulation during emotion-related rtfMRI-NF (Kohn et al., 2014; Zotev, Phillips, Young, Drevets, & Bodurka, 2013), where the OFC was suggested to play a role in the monitoring of the NF signal (Paret et al., 2019).

Hence, prefrontal areas, especially the OFC, might play a crucial role for the control of emotional self-regulation and processing of affective stimuli that can be relevant for behavioral management in the presence of conduct symptoms. In turn, the inverted u-shaped relation between left OFC activity and CP could be generalizable to other brain regions related to emotional processing and cognitive regulation. Thus, limbic and paralimbic structures and other prefrontal structures could principally also show an inverted u-shaped relation with conduct symptoms ranging from the healthy into the clinical spectrum. Further, a generalizing inverted u-shaped relationship across areas of the brain would indicate a distributed “compensatory” network of emotional control rather than a local mechanism. Interestingly, a recent meta-analysis reviewing the research from fMRI and positron emission tomography on cognitive emotion regulation (23 studies with 479 subjects) identified the superior temporal gyrus, angular gyrus and (pre)supplementary motor area to be involved in the execution of cognitive emotion regulation, initiated by prefrontal areas (Kohn et al., 2014). According to that analysis, the dlPFC may be related to regulation of cognitive processes such as attention, while the vmPFC (which is anatomically overlapping with OFC) may not necessarily reflect the regulatory process per se, but signals salience and therefore the need to regulate (signal monitoring). Further, a cluster in the ACC as a region, which is anatomically and functionally in a central position to influence behavior and subcortical structures was related to affect generation (Kohn et al., 2014). More specifically, children’s cognitive emotional control appears to operate through orbitofrontal and dorsolateral prefrontal inhibition of striatal and amygdala reactivity (Davidson, 2002; Heatherton, 2011). However, elaborate research on inverted u-shaped relationships between reactivity in these areas and symptoms of DBD with regard to affective processing do not exist yet. In the absence of such findings, our finding on the left OFC as a potential compensation site of conduct symptoms is novel and may potentially inspire future research.

The rtfMRI-NF study included a relatively small group of 12 adolescents who received either NF from the amygdala or the insula (6 in each group) and therefore must be considered a proof-of-

concept. However, feasibility of successful learning of self-regulation was indicated for the group who received feedback from the amygdala, but was less clear for the group receiving feedback from the insula. Clinical improvements in behavioral domains of DBD symptoms were significant and comparable across both treatment groups and to control behavioral therapy. However, further research is needed to clarify the specificity of AMG-NF as a treatment that aims at the improvement of affective processing and conduct symptoms. Regarding rtfMRI-NF of the insula, more specific and smaller target-ROIs need to be established, as for example, a recent study demonstrated successful AI upregulation in healthy participants (compared to sham) during an auditory empathy task and found that participants low on empathic traits produced a greater increase in activation of right AI by the end of training (Kanel et al., 2019). Further, customized ROI masks may be established by the use of specific functional localizers or dynamic adaption of individual patterns of activity within a specific target-ROI, e.g. as has been done in amygdala-NF by Nicholson et al. (2017).

In the current investigations, the findings of study 1 suggested that differences in OFC reactivity to affective stimuli are associated to a compensatory function that allows adolescents with increased CP to remain below threshold for clinical diagnosis as long as CP levels are not severe. With regard to self-regulation, such enhanced prefrontal reactivity to the passive viewing of affective stimuli might also represent an aspect of adaptive cognitive emotion regulation. This result indicates that adolescents with increased CP, who do not meet diagnostic criteria of DBD, might be less susceptible to negative affective stimuli and, as a result, show more elaborated cognitive emotion regulation capacities. Interestingly, in study 2, an area in the left medial prefrontal cortex was also found to differentially increase across ten sessions of rtfMRI-NF in the group who received feedback from the amygdala. Since this increasing prefrontal activity appeared only in the first condition (simple feedback) of a sequence of three NF training-conditions, this may also represent a cognitive aspect of emotion regulation, probably related to the learning of successful emotion regulation. Considering these findings on prefrontal involvement in affective processing of study 1 and study 2, they further support the assumption

of a potential prefrontal control over CP. They indicate that prefrontal structures are implicated in the cognitive regulation of emotion and may moderate subcortical reactivity to affective stimuli. Thus, adaptive reactivity of prefrontal structures related to cognitive control over emotions might be also be enhanced in rtfMRI-NF targeting subcortical structures of emotion processing. In turn, this might result in higher adaptive cortical and subcortical reactivity involved in affective processing and behavioral control in the social context.

The results of the pre-post comparison of the affective processing task in study 2 showed lower activity-levels after treatment in adolescents diagnosed with DBD in a variety of areas related to emotion regulation, also comprising prefrontal regions. Additionally, the clinical outcome of this study also implies less CP after treatment across subjects. In study 1, lowering levels of CP were associated with decreasing OFC activity during affective processing in healthy adolescents. Taking together these results, they indicate that decreased activity in prefrontal structures (in comparison to the increased levels in individuals with elevated CP) could be associated with more efficient affective processing. Further, the results underpin the assumption that adolescents with increased CP fail to regulate their emotions efficiently, which could be related to a compensating increase of activity in prefrontal areas relevant to emotion regulation. However, as a restriction, study 1 suggests this may only be true in adolescents with subclinical to moderate levels of CP, as decreased activity in prefrontal regions were also reported in adolescents displaying severe disruptive behaviors (compared to healthy controls) during affective processing (Fairchild et al., 2014; Passamonti et al., 2010). Further, in study 2, moderate to severe clinical cases with elevated CU-traits were included (CBCL-CD T-score range: 62-81, CBCL-ODD T-score range: 62-80; clinical cutoff=70). Thus, some of them may already have shown reduced prefrontal activity (as suggested by previous studies), whereas others might have shown heightened prefrontal activity in affective processing before treatment. However, empiric indications for decreased prefrontal activity in adolescents diagnosed with DBD need to be further validated, and the hypothesis of an inverted u-shaped relation of

prefrontal activity in adolescents in the range from normal to severe CP or diagnosis of DBD during affective processing also need to be further investigated.

Importantly, the interactions of subcortical structures, especially the amygdala, with the prefrontal cortex are pivotal to learning, decision-making, and socio-emotional regulation (Hunt & Hayden, 2017; Rudebeck & Murray, 2014). Recent models increasingly emphasize how the amygdala and the PFC do not support isolated computations but instead have complementary roles in these processes (Munuera, Rigotti, & Salzman, 2018; E. A. Murray & Wise, 2010a; Saez, Rigotti, Ostojic, Fusi, & Salzman, 2015). However, a clear anatomical description of the organization and dissociation of fiber bundles linking amygdala and prefrontal cortex in humans is still lacking (Folloni et al., 2019). As a result and future perspective, further investigation of the role of structural and functional connections between subcortical and prefrontal areas with respect to the cognitive regulation of affective arousal might be fruitful for the development of future specific treatment strategies aiming at the improvement of adaptive reactivity, emotion regulation and social behavior.

4.1 Outlook

On the basis of the current data, rtfMRI-NF cannot be considered a cost-effective treatment strategy for clinical application in adolescents with DBD. However, it was important to evaluate this form of intervention since upregulation of amygdala and insula were promising treatment strategies for rtfMRI-NF in adolescents with DBD and CU traits and feasibility as well as efficacy could be demonstrated. Nevertheless, it is indicated that prefrontal cortical areas related to (effortful) control of emotions represent another possible target for the development of future interventions. Specifically, the OFC could represent a proper target for further NF approaches. The OFC is a region which is distributed across the anterior bottom surface of the forehead-brain and therefore is a horizontally oriented anatomical structure. On the one hand, the anatomic features of the OFC determines it a subject to susceptibility artifacts in fMRI measurement because of its close vicinity to the frontal sinus, which disqualifies the OFC as a reasonable target of rtfMRI-NF, a fortiori when also considered the huge technical, financial and human effort of

this technique. On the other hand, the anatomic features of the OFC make this structure especially accessible to other modalities of psychophysiological real-time data acquisition and feedback techniques, as for example via magnetencephalography (MEG). MEG is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents naturally occurring in the brain, using very sensitive magneto- and gradiometers. However, while EEG measures differences in electric potential at the scalp, MEG measures magnetic flux density outside the head. MEG does not detect radial dipoles but tangential dipoles, which makes MEG more applicable for the measurement of structures like the temporal plane, such as for example the Heschl's gyrus that has been intensively investigated with MEG in psychoacoustics (Schneider et al., 2002). Further, MEG has similar temporal characteristics to EEG (sub-millisecond precision) but in addition provides also good spatial resolution. Moreover, while fMRI measurement requires the complete absence of subject movement during recording, MEG measurement does not fully, so children are allowed moving their heads to certain degrees within the MEG helmet, which is an important issue when working with externalizing, especially hyperactive, patients. Finally, future research should also emphasize the development and implementation of behavioral treatment strategies that foster cognitive prefrontal-control over subcortical affective arousal.

5. Summary

Disruptive behavior is a common phenomenon in human nature and frequently occurs during adolescence. It is associated with conduct problems (CP) in healthy as well as clinical populations. When CP exceed the normal range and disruptive behaviors are severe, Disruptive Behavior Disorder (DBD), including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), is often diagnosed. Individuals who fulfill diagnostic criteria of DBD also frequently display a conspicuous pattern of behavior that is characterized by a callous, uncaring and unemotional interpersonal style, including deficits in empathy, emotional affectivity and conscientiousness. These behaviors have been labeled the affective dimension of psychopathy or callous-unemotional traits (CU traits) in research. Overall, evidence-based psychological treatments for DBD (with and without increased CU traits) only reach small to moderate effect sizes and there is currently not enough evidence to support one specific form of treatment over another. To date, real-time functional magnetic resonance imaging (rtfMRI-NF) is increasingly considered as a promising tool for the training of brain self-regulation in order to treat psychiatric conditions. It has already been applied to train self-regulation of compromised inhibitory or emotional brain regions, and of emotion regulation strategies in adult psychopaths and adolescents diagnosed with ADHD.

For the purpose of investigating and evaluating new innovative forms of treatments for adolescents with DBD, this thesis followed a two-way approach. First (study 1), a large dataset of healthy young adolescents (mean age: 14.44 (0.41), range 13.08-15.72 years) with varying level of CP was analyzed with respect to possible neural correlates of frontal control over CP during affective processing of negative facial emotions. Second (study 2), an individualized rtfMRI-NF training aiming at the learning of self-regulation of emotional processing regions (amygdala or insula) and, as a result, at the improvement of affective processing was conducted with adolescent patients (mean age: 14.62 (1.64), range: 12.04-17.99 years) diagnosed with DBD and elevated CU traits (ICU total score >20 in self-rating and/or >24 in parent-rating) over a course of 10 weeks and compared with a clinical TAU group.

In study 1, we observed no significant differences in brain responses to negative facial affect in adolescents with high versus low CP. However, regression analyses along the CP dimension across the groups revealed a significant nonlinear effect: left orbitofrontal cortex (OFC) responses increased with increasing CP up to the clinical range, and, decreased again only for the highest CP range. This increasing left OFC activity found during affective processing in an epidemiological adolescent sample with low to clinically relevant levels of CP might represent frontal control mechanisms preventing the outbreak of disruptive or conduct disorder despite conduct problems.

In study 2, the NF and the TAU group showed comparable and significant clinical improvement on DBD-related behavioral scales over time, in line with non-inferiority. Within the NF group, successful learning of self-regulation in the target region was found for NF of the amygdala, but not for NF of the insula. The data suggest that the self-regulation of emotional processing regions might be more promising when receiving feedback from the amygdala (as compared to the insula). Additional exploratory analyses also suggested involvement of prefrontal areas in the learning of self-regulation of emotion processing regions. However, clinical improvement in NF was not specific to the amygdala group. In the emotion matching task, both treatment groups showed decreased activities after treatment in prefrontal emotion-regulation related areas, potentially indicating higher efficiency of processing affective stimuli after treatment. The results suggest clinical improvement and non-inferiority of rtfMRI-NF training compared to other treatment options for adolescents with diagnosis of DBD, but further studies are needed to clarify underlying mechanisms and cost effectiveness.

As a future perspective, further investigation of the role of structural and functional connections between subcortical and prefrontal areas with respect to the cognitive regulation of affective arousal might be fruitful for the development of future specific treatment strategies aiming at the improvement of adaptive reactivity, emotion regulation and social behavior. Also, the OFC could form a promising target for further NF approaches aiming at the control of emotions.

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- Zotev, V., Phillips, R., Young, K. D., Drevets, W. C., & Bodurka, J. (2013). Prefrontal control of the amygdala during real-time fMRI neurofeedback training of emotion regulation. *PLoS One*, *8*(11), e79184.

7. Curriculum Vitae

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07/2000 – 08/2001	Stadtranderholung, Lahr, Kinderbetreuung und Erlebnisgestaltung im Ferienlager

IT – Kenntnisse

Microsoft Office	sehr gute Kenntnisse
LaTex	sehr gute Kenntnisse
SPSS	sehr gute Kenntnisse
MatLab/SPM8	sehr gute Kenntnisse
R	gute Kenntnisse

Sprachen

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8. Publication list

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In Preparation (study2):

Boris W. Böttinger, Sarah Baumeister, Nathalie E. Holz, Pascal-M. Aggensteiner, ..., Daniel Brandeis, Tobias Banaschewski (2019), *Individualized real-time functional magnetic resonance imaging neurofeedback in adolescents with DBD.*

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Jilly Naaijen, Leandra M Mulder, Shahrzad Ilbegi, Sanne de Bruijn, Renee Kleine-Deters, Andrea Dietrich, Pieter J Hoekstra, Jan-Bernard C Marsman, Pascal M Aggensteiner, Nathalie E Holz, **Boris W Böttinger**, Sarah Baumeister, Tobias Banaschewski, Melanie C Saam, Ulrike M E Schulze, Paramala J Santosh, Ilyas Sagar-Ouriaghli, Mathilde Mastroianni, Josefina Castro Fornieles, Nuria Bargallo, Mireia Rosa, Celso Arango, Maria J Penzol, Julia E Werhahn, Susanne Walitza, Daniel Brandeis, Jeffrey C Glennon, Barbara Franke, Marcel P Zwiers, Jan K Buitelaar (2018), *Reactive/proactive aggression specific cortical and subcortical alterations in children and adolescents with disruptive behavior.* bioRxiv, 490086.

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