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Neurofeedback Treatment in Attention Deficit Hyperactivity Disorder and Comorbid Aggression

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“*There is no such thing as a disembodied mind. The mind is implanted in the brain, and the brain is implanted in the body”. Antonio Damasio*

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LIST OF ABBREVIATIONS

AAL	Automated Anatomical Labeling
ADHD	Attention-Deficit/Hyperactivity Disorder
ACC	Anterior Cingulate Cortex
AE	Adverse event
Baseline observed carried forward	BOCF
BF	Biofeedback
CD	Conduct Disorder
CU	Callous-Unemotional
DSM	Diagnostic and Statistical Manual of Mental Disorders
DBD	Disruptive behavior disorder
EMG	Electromyography
EOG	Electrooculogram
ERP	Event-related potential
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
FWE	Family-Wise Error Rate
IFG	Inferior Frontal Cortex
IQ	Intelligent quotient
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Aged Children: Present and Lifetime Version
MPH	Methylphenidate
MMRM	Mixed model for repeated measure
MNI	Montreal Neurological Institute
NF	Neurofeedback
ODD	Oppositional defiant disorder
OFC	Orbitofrontal Cortex
ROI	Region of Interest
rtfMRI	Real-Time Functional Magnetic Resonance Imaging
SAE	Serious adverse event
SCP	Slow-cortical potentials
SES	Socioeconomic Status
SMG	Supramarginal Gyrus
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
vmPFC	Ventromedial Prefrontal Cortex
WFU	Wake Forest University

1. INTRODUCTION

Way back in 1845, Heinrich Hoffmann described in his book *Struwwelpeter* typical ADHD-like behavior which is known colloquially in Germany as the *Zappel-Philipp* syndrome. However, it took until 1968 that this was first introduced in the DSM-II as hyperkinetic reaction of childhood, until 1978 in ICD-9 as Hyperkinetic disorder and in 1980 it was introduced in the DSM-III as Attention Deficit Disorder. Nowadays, it is known as Attention-deficit/Hyperactivity and Impulsivity disorder (ADHD), and from a societal point of view, ADHD has a high financial impact on the health care system. A 2013 survey in Europe estimated costs related to ADHD between 9.860 and 14.483 Euros per patient/year (Le et al., 2014). Although common pharmacological treatment strategies provide short-term benefit with good clinical results there are important constraints which should be further investigated (for details see: Cortese, 2018). Additionally, this disorder is characterized by its large comorbidity rate with aggression-related disorders which may limit the efficacy of ADHD treatments and contributes substantially to the global burden of disease. This thesis aims at evaluating new non-pharmacological treatment modalities, such as neurofeedback training for core ADHD symptoms and for aggression-related behavior. In the following sections, we will summarize insights about these externalizing disorders, their neurobiological underpinnings, and possible new efficacious non-pharmacological treatment strategies.

1.1 Externalizing disorders

Externalizing disorders are commonly referred to as disruptive behavior disorders (DBD). These disorders are the most prominent psychiatric referrals during childhood and adolescence and consist of ADHD, oppositional defiant disorder (ODD) and conduct disorder (CD). In the next section, we will provide a concise description of their underlying psychopathology.

1.1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is defined as a developmental disorder, and the core symptoms comprise hyperactivity, impulsivity, and inattention. According to the classification system DSM-5 (American Psychiatric Association, 2013), functional impairment needs to be present for more than 6

months, in more than one environment (e.g. home and school), and six or more symptoms need to be present before the age of 12 years. Symptoms of inattention are described as failing to give closer attention to details, being negligent in schoolwork, or during other activities, showing difficulties sustaining attention in different tasks or play activities and encompass difficulties in organizational skills. Regarding the dimensions of hyperactivity and impulsivity, these symptoms involve excessive energy and acting as if "driven by a motor" (i.e. runs or climbs in inappropriate situations) or interrupting conversations. The latest classification system (DSM-5), distinguishes presentations and severity of the core symptoms instead of subtypes within this disorder. It includes a combined, a predominantly inattentive, or a hyperactive/impulsive presentation, and mild, moderate or severe forms.

1.1.1.1 Prevalence

With regard to the prevalence rate, ADHD is the most frequent externalizing disorder in childhood and adolescence with a worldwide prevalence of 2.6-4.5% (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015), and affecting more boys than girls (ratio 3:1; Wittchen et al., 2011). Further, it is considered a heterogeneous disorder, with high comorbidity up to 75% with ODD/CD, learning disorders, and autism spectrum disorder (Jensen & Steinhausen, 2015).

1.1.1.2 Etiology

ADHD is considered a highly heritable disorder, with 70% to 80% of variance associated with genetic factors. Dysfunctions in dopaminergic, noradrenergic and serotonergic neurotransmitter systems were linked to ADHD (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010; Faraone et al., 2005). Nevertheless, psychosocial factors (i.e. familial context and parenting) may serve as moderators of genetic influences (Nigg, Nikolas, & Burt, 2010; Nikolas, Klump, & Burt, 2015). Additionally, pre- and perinatal environmental factors have been related to ADHD. In particular low birth weight (Franz et al., 2018), smoking during pregnancy (Holz et al., 2014), low income and prematurity, but these findings are correlative in nature due to the lack of experimental studies (for details see: Thapar, Cooper, Eyre, & Langley, 2013). In general, it is likely that due to the complexity of the disorder multiple factors may cause the pathophysiology, possibly resulting in a heterogeneous group of patients (Thapar et al., 2013).

1.1.1.3 Neurobiology and neurophysiology

Recent brain imaging findings showed an association between ADHD and reduced subcortical brain volume (Hoogman et al., 2017). This cross-sectional mega-analysis comprised a sample of 1713 participants with ADHD and 1529 controls. Hoogman and colleagues showed reduced volumes of the accumbens, amygdala, caudate, hippocampus, putamen and intracranial volume in the ADHD population with small, but robust effect sizes. Earlier studies found reduced gray matter volume in frontal and temporal regions, as well as in the caudate and the cerebellum (Castellanos et al., 2002; Frodl & Skokauskas, 2012), highlighting that disease etiology cannot be attributed to single dysfunctional brain regions. In accordance with this, a meta-analysis on functional brain imaging studies (Cortese et al., 2012) highlighted significant distributed deficits in the frontoparietal executive/ventral inhibition-related attention network but also emphasized increased recruitment of the somatomotor system and the putamen, with the latter possibly explaining the observed motor hyperactivity. In addition to the well-known deficient frontostriatal activation, increased activation in other default and visual areas has also been demonstrated, which is in line with the fluctuating attentional focus during cognitive performance in ADHD (Baroni & Castellanos, 2015; Cortese et al., 2012). Interestingly, the structural findings are in line with the brain regions previously identified as being compromised in their function (Cortese et al., 2012).

Electrophysiology findings in ADHD showed that slower oscillations, such as theta, alpha, but as well faster beta frequencies bands to be the most relevant in ADHD research (Loo & Makeig, 2012). A frequent and highly controversial finding is a higher proportion of a frontocentral theta/beta ratio (Snyder, Rugino, Hornig, & Stein, 2015). These authors argue that this electrophysiological parameter can be used as a biomarker which might be useful as a diagnostic aid for ADHD. Nevertheless, this remains controversial, and an additional review concluded that theta/beta ratio as a diagnostic aid for ADHD is unclear in its definitions and does not integrate a good clinical practice of ADHD diagnosis (Loo & Arns, 2015). However, this might be explained by the heterogeneity within ADHD, since a particular subgroup shows larger theta/beta ratio (Clarke et al., 2011). Besides this controversial outcome regarding the electrophysiological spectrum, there are interesting findings concerning event-related potentials (ERPs). Different ERP components showed deviations in ADHD for stimulus discrimination, resource allocation, inhibition, preparation, error detection and conflict processing (Barry, Clarke, & Johnstone, 2003; Barry et al., 2003; Johnstone, Barry, & Clarke, 2013). However, these alterations seem to be non-

specific to ADHD and provide only limited relevance as diagnostic biomarkers (Loo & Makeig, 2012). Nevertheless, a current meta-analysis (Kaiser et al., in prep), found significant and moderate to large effects for specific ERPs associated with attentional preparation and resource allocation.

1.1.2 Oppositional defiant disorder (ODD) and Conduct disorder (CD)

According to the DSM-5 (American Psychiatric Association, 2013), Oppositional defiant disorder (ODD) is characterized by disruptive and impulsive behavior, and conduct problems. Furthermore, essential characteristics of ODD are disobedience, defiance and a negative attitude towards authorities. The persistence and frequency of these behaviors is a crucial factor and should be used to distinguish whether the individual's behavior falls outside the median for the individual's developmental level. A persistent pattern of angry, irritable mood, defiant behavior and vindictiveness should last at least 6 months to meet this diagnostic criterion. The symptoms of ODD can be present only in one setting, and this is frequently the own home. Children and adolescents who show enough symptoms to meet the diagnostic criteria, even only in one setting, may be significantly impaired in their social functioning.

Conduct disorder (CD) is defined as a repetitive and persistent pattern of behavior which violates the rights of others and major age-appropriate societal rules (American Psychiatric Association, 2013). To reach clinical relevance, three out of 15 symptoms have to be met. Symptoms are characterized predominantly by bullying, intimidation, physical fights, cruelty to people or animals, vandalism and serious violations of rules. Aggression-related behavior, mostly present's two different subtypes of externalizing behavior. Recently, the concept of callous-unemotional (CU) traits, possibly implied in instrumental aggression (Frick & Ellis, 1999), has attracted increasing interest (Buitelaar et al., 2013; Viding & McCrory, 2012). In line with this, DSM-5 (American Psychiatric Association, 2013) added a new prosocial specifier, which pertains to patients suffering from the more severe CU behavior. CU traits comprise lack of remorse or guilt, lack of empathy, indifference about performance, and shallow or deficient affect. Additionally, two different phenotype distinctions (reactive and proactive aggression) are often made to subtype aggressive behavior (Raine et al., 2006). Reactive aggression is associated with impulsive, high arousal, hot-blooded or affective aggression whereas proactive aggression refers to goal-directed, planned behavior associated with reduced arousal and higher levels of callous-

unemotional traits, also known as instrumental or cold-blooded aggression (Blair, Peschardt, Budhani, Mitchell, & Pine, 2006).

In section 1.2.4 we will further discuss the heterogeneity of distinct phenotypic behavior of aggression.

1.1.2.1 Prevalence

ODD is a developmental disorder with a similar worldwide prevalence as ADHD, which ranges between 2.8-4.7% (Polanczyk et al., 2015). Further, it is more prevalent in males than in females (ratio 1.4:1) prior to the adolescence, however, this predominance is not consistently found in samples of adolescents or adults (American Psychiatric Association, 2013). Regarding comorbidity, ODD shows a high overlap with ADHD, which ranges between 35% to 50% (Connor, Steeber, & McBurnett, 2010) and could be associated with shared temperamental risk factors (American Psychiatric Association, 2013). Further, there is also an increased risk of comorbid anxiety disorders and mood disorders. Adolescents with ODD also show a higher rate of substance use disorder and conduct disorder (American Psychiatric Association, 2013). With regard to CD, the prevalence rate is lower at about 2% (2.5% in males, 1.5% in females; Rowe et al., 2010) with a median age at onset of 12 years (Nock et al., 2006).

1.1.2.2 Etiology

In general, within these disorders, the etiology is less clear than in ADHD. Overall, numerous factors, including familial, genetic, biological, individual and environmental factors have been identified that may play a role in the etiology of aggression-related behavior (Christophersen & Finney, 1999). Poverty is a well-known risk factor (Costello, Compton, Keeler, & Angold, 2003; Holz et al., 2015; Piotrowska, Stride, Croft, & Rowe, 2015). Almost 60% of families of children with behavioral problems showed lower SES (Alvarez & Ollendick, 2003; Loeber, Green, Keenan, & Lahey, 1995). Regarding genetic factors, Slutske and colleagues (2003) estimated that approximately 13 percent of the variation in the risk for aggression-related behavior symptoms could be explained by non-shared individual-specific environmental factors and heritability of 50% (Gelhorn et al., 2005). Further, it has often been said that the best predictor of future behavior is past behavior, and this may be the case with aggression-related behavior as well (Crowell et al., 2006). In fact, if behavior problems are stable from preschool to school age,

they are more likely to continue into adolescence (Ewing & Campbell, 1995) and, probably, adulthood (Moffitt, 1993). Overall, the link between early aggression and later development of behavioral problems has been well established (Alvarez & Ollendick, 2003; Sanson & Prior, 1999).

1.1.2.3 Neurobiology and neurophysiology

As for ADHD, several studies have focused on structural abnormalities in aggression-related behavior. A recent meta-analysis of thirteen studies analyzed almost 400 participants (aged 9-21 years) with conduct problems showed reduced grey matter volumes in the left amygdala, in the bilateral insula extending to the ventrolateral prefrontal cortex (PFC)/orbitofrontal cortex (OFC) and in the medial superior frontal gyrus extending to the anterior cingulate cortex (ACC) with small to medium effect sizes (Rogers & De Brito, 2016). An additional meta-analysis including ODD/CD and ADHD studies (n=415, age 8-21 years) reported reduced volumes of the amygdala, insula, and frontal regions in participants diagnosed with ODD/CD as well, and with greater reductions in the presence of comorbid ADHD (Noordermeer, Luman, & Oosterlaan, 2016). With regard to functional MRI findings, current neuroimaging studies of aggression-related disorders are in line with the neuropsychological literature implicating deficits in both affective and executive function as well as reward processing (Blair et al., 2006; Nigg & Huang-Pollock, 2003). Specifically, children with ODD/CD show impaired amygdala activity in response to negative face stimuli, suggesting impaired recognition of facial expression (Blair, Leibenluft, & Pine, 2014). However, there are mixed outcomes and subtype-specific differences should be taken into account since evidence for hypo and hyperactivity were found, which are probably moderated by CU traits (Viding, Seara-Cardoso, & McCrory, 2014). The third study of this thesis will specifically investigate this underlying neural heterogeneity within aggression-related subtypes.

With regard to electrophysiological findings, there are very little studies that have investigated electrophysiological deviations in patients with aggression. These studies have found striking similarities to ADHD patients. As such, higher slow-wave activity, such as more theta activity which is normally associated with ADHD, was found in studies of delinquent children (Knyazev, Slobodskaya, Aftanas, & Savina, 2002), in antisocial personality disorder (Lindberg et al., 2005) and teenagers who later committed crimes in adulthood (Raine, Venables, & Williams,

1990). Furthermore, typically decreased beta waves in ADHD has been also found in antisocial participants (Gilmore, Malone, & Iacono, 2010). Taking together the findings for both disorders, there appears to be a link with ADHD and other forms of externalizing disorders. However, in both cases, inconsistent results have been reported. For example, Clarke and colleagues speculated that higher levels of beta activity may define a particular subgroup of children with ADHD, which might be more hyper-aroused and possibly more hyperactive than other children with ADHD (Clarke, Barry, McCarthy, & Selikowitz, 2001). Interestingly, similar results were reported in a sample of homicidal men (Lindberg et al., 2005).

A recent meta-analysis of 62 studies tried to disentangle the literature of ADHD and aggression-related disorders. Externalizing behaviors compared to ADHD showed a negative relationship between alpha power and antisocial behavior and that exclusive slow-waves were particularly sensitive for ADHD, but not for antisocial or mixed samples (Rudo-Hutt, 2015). Nevertheless, there seems to be a large overlap between ADHD and other externalizing disorders, which is not surprising, since there exists a large overlap regarding the clinical phenotype. Additionally, it is worth noting that there is a lack of studies that investigate aggression-related disorders with EEG and in relation to ADHD.

1.2 Treatments in ADHD

The German guidelines for ADHD published in 2018, recommend a multimodal treatment, which includes the following components: parent-oriented counseling, psychoeducation, cognitive-behavioral therapy, and pharmacological treatment. Neurofeedback and dietary restrictions are mentioned as possibly helpful interventions. Neurofeedback applying standard training protocols can be added as a complementary option treating ADHD symptoms, and if they do not interfere with other efficacious treatment. While other guidelines (i.e. NICE) do not address neurofeedback in their ADHD guidelines.

1.2.1 Pharmacological treatment

In severe ADHD patients and older than 5 years, the first-line treatment is pharmacological. Stimulants, such as Methylphenidate (MPH) are the most common and effective used drug to treat the core symptoms of ADHD. The effect sizes are large and ranges between 0.7 and 1 (Banaschewski et al., 2006; Cortese, 2018) and about 70% of patients respond to stimulant treat-

ment (Spence et al., 1996). In particular, stimulants act over the catecholamine neurotransmitters, increasing i.e. dopamine and noradrenaline. Besides the high effect in reducing symptoms, there are important constraints worth mentioning. Adverse events (Graham et al., 2011), unwillingness to take the medication over extended periods (Berger, Dor, Nevo, & Goldzweig, 2008), and the absence of long-term effects (van de Loo-Neus, Rommelse, & Buitelaar, 2011) are important factors which needs to be taken into account when administering pharmacotherapy.

1.2.2 Non-pharmacological treatment

A recent network meta-analysis (Catalá-López et al., 2017) which analyzed 26114 ADHD patients in 190 randomized controlled trials found that behavioral therapy in combination with pharmacological treatment is superior to pharmacological interventions alone, and behavioral therapy particularly with parent and teacher involvement, was the only non-pharmacological intervention associated with significant benefits for ADHD patients. Other non-pharmacological approaches, such as dietary therapy, cognitive training, physical activity, and neurofeedback, could not be recommended. Nevertheless, they concluded that *"there are uncertainties about therapies and the balance between benefits, costs and potential harms, which should be considered before starting treatment and that there is an urgent need for high-quality RCTs"*. An earlier meta-analysis focusing only on non-pharmacological ADHD treatments showed that cognitive training and behavioral interventions had a significant impact on ADHD symptoms reduction with medium to large effect sizes when parents rated the behaviors (Sonuga-Barke et al., 2013). Additionally, no significant ADHD symptom reduction was found when probably blind raters evaluated ADHD behavior, however, significant effect emerged for conduct problems (Daley et al., 2014; Sonuga-Barke et al., 2013).

In summary, non-pharmacological treatments are an important part of the multimodal treatment of children with ADHD, however, more research is required to understand how to optimize treatment response (Daley et al., 2017).

1.2.3 Neurofeedback and biofeedback treatment

Neuro- and biofeedback approaches are techniques in which a variety of unconscious psychophysiological signals (i.e. brain waves, ERPs, skin conductance or bold signal) are feedbacked to the patient (Figure 1). The regulation of psychophysiological signals is trained based

on operant conditioning (Sherlin et al., 2011). One of the first studies which demonstrated learning and modulation of unconscious psychophysiological signals was in Cats. Wyrwicka, Sterman, & Clemente (1962) conditioned successfully the sensorimotor rhythm (SMR;12-15Hz). Additionally, Neal E. Miller (1969) promoted the term of Biofeedback with the visceral learning theory. So far, there exist a considerable number of studies showing successful regulation and learning of brain- and body- related activity mainly in healthy adult humans (for review see Frank, Khorshid, Kiffer, Moravec, & McKee, 2010; Thibault, Lifshitz, Birbaumer, & Raz, 2015).

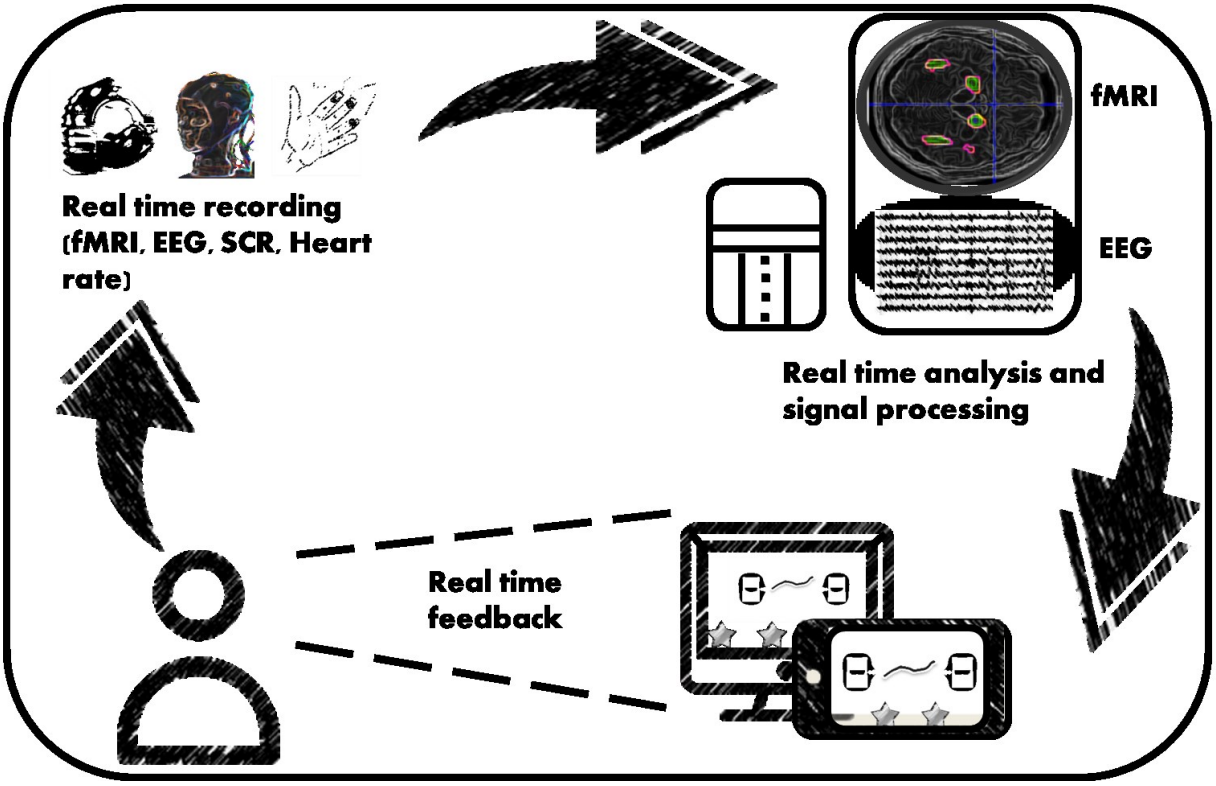

Figure 1. Conceptual diagram of Neuro/Biofeedback. fMRI: functional magnetic resonance imaging; EEG: Electroencephalogram, SCR: Skin conductance response.

With regard to the effectiveness of neurofeedback in reducing ADHD symptoms, there is a comparable large amount of meta-analyses available (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Cortese et al., 2016; Doren et al., 2018; Micoulaud-Franchi et al., 2014; Riesco-Matías, Yela-Bernabé, Crego, & Sánchez-Zaballos, 2019; Sonuga-Barke et al., 2013). A very recent published meta-analysis tried to sum up these findings (Riesco-Matías et al., 2019). The

authors reviewed seven meta-analyses which incorporated 17 RCTs. A significant effect was found for the ADHD core symptoms rated by parents and for inattention subdomain when probably blinded raters (teachers) assessed the symptoms. The effect sizes varied between small and medium for parent ratings and were small for teacher ratings. These significant effects in favor of neurofeedback held only when it was compared to non-active control groups, while pharmacotherapy (active condition) showed to be significantly superior to neurofeedback with large to medium effect sizes.

However, sustained and long-term clinical effects still remain less systematically studied. Only one meta-analysis from Van Dooren and colleagues (2018), on ten studies, showed small to medium effects in favor of neurofeedback when compared to non-active and comparable results as active conditions six months after treatment. So far, there are a few studies which showed interesting long lasting effects which probably might be related to delayed learning effects after neurofeedback. Specifically, Strehl et al., (2006) showed enhanced performance in a specific neurofeedback condition (transfer) which was related to clinical improvement. The transfer condition aims to extrapolate the learned skills into daily live situation. Interestingly, in epilepsy patients, a similar delayed effect was found (Kotchoubey et al., 1999). This might be a promising hint for long-lasting effects after neurofeedback. However, studies assessing longer-term effects are still underrepresented and of particular clinical importance. Therefore, part of this thesis will assess these longer-term effects of neurofeedback treatment on ADHD symptoms, as well as on comorbid aggression disorders.

Furthermore, it is worth mentioning that neurofeedback and biofeedback are umbrella terms. There are a large number of different training protocols which are only limited by the available technology. In the case of EEG neurofeedback, there are many different ways to train and modulate brain-associated patterns (i.e. SMR, Theta/Beta, SCP-NF, Coherence, and asymmetry feedback). Consequently, a recent meta-analysis (Cortese et al., 2016) and the German ADHD guidelines (AWMF, 2018: ADHS bei Kindern, Jugendlichen und Erwachsenen, Registernummer 028 – 045) recommended only three training procedures for ADHD (SMR, Theta/Beta and SCP Neurofeedback). Therefore, this thesis is only based on these ‘standard’ training protocols.

1.2.4 Aggression-related symptoms in ADHD

In general, aggression-related problems in ADHD are treated with modest cost-benefits effects. Stimulant (i.e. MPH), and neuroleptic (i.e. risperidone) treatments showed significant effects on comorbid aggression in ADHD patients. Nevertheless, pharmacotherapy of aggression is limited by quality, the existing literature and serious adverse effects (Pappadopulos et al., 2006), therefore first-line treatment should be psychosocial interventions, which are supported by substantial evidence and have low risks for adverse effects (Wilkes & Nixon, 2015).

With regard to neurofeedback effects on comorbid aggression, only a few studies are available. Gevensleben and colleagues (2009) showed significant reductions in parent-rated oppositional behavior compared to standardized computerized attention training. Additionally, after theta/beta NF training, reduction of ODD symptoms was reported but without group difference compared to standard pharmacological intervention (Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Furthermore, one study investigated SCP-NF in criminal psychopaths showing less aggression and impulsivity (Konicar et al., 2015). Since there is little literature available, part of this thesis will address the effects of neurofeedback on aggression-related symptoms. The potential psychophysiological targets which could be modulated in aggression-related behavior are still unclear. Some less widely available NF treatments, such as real-time NF, showed that up-regulation of the anterior insula had a significant impact on aggression (Sitaram et al., 2014). Nevertheless, there is a gap which tries to address the heterogeneity of aggression-related disorders. In this thesis, we will analyze if the different aggression-related subtypes provide more insight into the underlying neurobiology which might be used for new NF-approaches.

1.3 Hypotheses

The clinical relevance of NF treatment has been supported by previous literature, as reviewed in section 1.2.3. However, evidence so far has been sparse with regard to NF specificity, clinical long-term effects, as well as its relationship with self-regulation and the influence on comorbid aggression.

1.3.1 Specific vs unspecific effects of SCP-NF

Two main approaches can disentangle specific from unspecific effects. First, the comparison with effects of a good control condition, and second the relationship between self-regulation of the trained parameters and clinical improvement (Drechsler et al., 2007; Ros, 2019). With regard to the control condition, this RCT assessed the differential treatment effects between both treatment conditions, while controlling for unspecific effect. We hypothesize that SCP-NF will show superiority in comparison to the control group, and that self-regulation is associated with clinical outcome (Study 1).

1.3.2 Long-term effects

Regarding long-term clinical outcome, in line with the already discussed meta-analysis (Doren et al., 2018), we expect clinical superiority six-month after SCP-NF treatment compared to the control condition (Study 2).

1.3.3 Influence on comorbid aggression

As already discussed in section 1.2.4, there are only a few studies which investigated the effect of NF approaches on aggression with promising results. Thus, we hypothesize that SCP-NF will reduce aggression-related problems (Study 1 & 2).

1.3.4 Putative Neurofeedback targets for aggression-related disorders

To optimize treatment effects for aggression-related disorders we need to disentangle the heterogeneity of these disorders. Distinct subtypes of aggression, and as well CU traits might show divergent and phenotype-specific neural activity. Therefore, in study 3 we hypothesize that patients with more proactive aggression will show blunted activation of core limbic structures, such as the amygdala (Study 3).

2. EMPIRICAL STUDIES

2.1 Study 1: Neurofeedback of Slow Cortical Potentials in Children with Attention-Deficit/Hyperactivity Disorder: A Multicenter Randomized Trial Controlling for Unspecific Effects

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Neurofeedback of Slow Cortical Potentials in Children with Attention-Deficit/Hyperactivity Disorder: A Multicenter Randomized Trial Controlling for Unspecific Effects

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2.1.1 Abstract

Neurofeedback (NF) in children with attention-deficit/hyperactivity disorder (ADHD) has been investigated in a series of studies over the last years. Previous studies did not unanimously support NF as a treatment in ADHD. Most studies did not control for unspecific treatment effects and did not demonstrate that self-regulation took place. The present study examined the efficacy of NF in comparison to electromyographic (EMG) feedback to control for unspecific effects of the treatment, and assessed self-regulation of slow cortical potentials (SCPs).

A total of 150 children aged 7–9 years diagnosed with ADHD (82% male; 43% medicated) were randomized to 25 sessions of feedback of SCPs (NF) or feedback of coordination of the supraspinatus muscles (EMG). The primary endpoint was the change in parents' ratings of ADHD core symptoms 4 weeks after the end of treatment compared to pre-tests.

Children in both groups showed reduced ADHD-core symptoms (NF 0.3, 95% CI −0.42 to −0.18; EMG 0.13, 95% CI −0.26 to −0.01). NF showed a significant superiority over EMG (treatment difference 0.17, 95% CI 0.02–0.3, p = 0.02). This yielded an effect size (ES) of d = 0.57 without and 0.40 with baseline observation carried forward (BOCF). The sensitivity analysis confirmed the primary result. Successful self-regulation of brain activity was observed only in NF. As a secondary result teachers reported no superior improvement from NF compared to EMG, but within-group analysis revealed effects of NF on the global ADHD score, inattention, and impulsivity. In contrast, EMG feedback did not result in changes despite more pronounced self-regulation learning.

Based on the primary parent-rated outcome NF proved to be superior to a semi-active EMG feedback treatment. The study supports the feasibility and efficacy of NF in a large sample of children with ADHD, based on both specific and unspecific effects.

2.1.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder in childhood. According to DSM-IV TR (in effect during this trial), core symptoms include impaired attention, hyperactivity, and impulsivity (American Psychiatric Association, 2000). Stimulant medication represents the most commonly used intervention for children with ADHD, but its use is limited since in some children pharmacotherapy may fail, adverse side effects are common, long-term effects are not yet established and some parents and clinicians have reservations about medication use (Sonuga-Barke et al., 2013).

Among additional or alternative treatments for ADHD neurofeedback (NF) has gained promising empirical support in recent years. Based on the observation of deviant slow event-related potentials in children with ADHD, feedback of slow cortical potentials (SCPs-NF) aims at improving the neurophysiological profile of children with ADHD by self-regulation of cortical excitation thresholds (Albrecht et al., 2010; Banaschewski & Brandeis, 2007; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013) SCPs are slow event-related changes in the EEG, reflecting cognitive and motor preparation (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Studies have demonstrated promising effects on behavior, cognitive, and electrophysiological measures after SCP-NF (Christiansen, Reh, Schmidt, & Rief, 2014; Drechsler et al., 2007; Gevensleben et al., 2009; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Maurizio et al., 2013; Strehl et al., 2006). A recent meta-analysis failed to support NF as an effective treatment for ADHD but this result may reflect methodological weaknesses of the available studies rather than the weakness of NF as such (Cortese et al., 2016). When the analysis was restricted to trials meeting Arns et al.'s (2013) criteria for a standard (established) NF protocol (as related to the target EEG measures, to number and placement of electrodes, trials designed in line with principles of learning theory, involving techniques to promote generalization to everyday life and assessing whether learning took place), significant effects emerged also applying probably blinded ratings. The main drawbacks of previous SCP studies are methodological shortcomings like lack of appropriate control conditions, intent-to-treat analyses, unblinded outcome measures, limited testing for successful self-regulation at the brain level, and failure to control unspecific effects and variables (e.g., amount of reinforcement, time, attention of and interaction with the therapist; sex, age, baseline severity, expectations, and satisfaction with treatment). To disentan-

gle NF-specific and unspecific effects influencing the outcome of any treatment the choice of a control condition is of major importance (Oken, 2008). Active control conditions do not control for unspecific effects as the independent variables causing them differ as regards, e.g., to setting, expectation, interaction, time, and effort. For example, medication cannot control for the unspecific effects of time and attention spent concentrating on the challenging self-regulation task, and for the experience of learning with contingent feedback. Double-blind studies which employ a sham condition may provide strong unbiased evidence regarding efficacy and specificity, and thus have clear merits in NF research (Kerson & Collaborative Neurofeedback Group, 2013) which may involve considerable non-specific effects (Drechsler et al., 2007; Thibault and Raz, 2016). While double-blind controlled placebo studies in general may provide strong evidence regarding efficacy and specificity, the establishment of sham conditions for NF treatments has shown to be at least doubtful if not missing the main aim. Patients and trainer can detect the sham condition and may refuse further participation (Birbaumer et al., 1991). Another outcome was observed by van Dongen-Boomsma et al., (2013). Here the majority of patients in the NF condition assumed that they were assigned to the sham condition. As any acquisition of a new skill, learning to self-regulate brain activity takes time. The lack of success in the first sessions may lead to the impression of being allocated to an ineffective control condition. As a consequence, this may impair motivation and compliance. However, apart from potential ethical and expectancy motivation problems of sham designs, an ideal control condition for NF should also require learning to fully match moderator variables such as motivation, frustration, compliance, and the often stepwise experience of self-efficacy (Gevensleben et al., 2014). Recent neuroimaging research demonstrates specific increases of activity in brain regions supporting inhibitory control following learning of different types of self-regulation in ADHD (Baumeister et al., 2016). Therefore, sham conditions that do not allow learning genuine contingencies also have limitations (Sherlin et al., 2011; Arns et al., 2014). To induce learning of self-regulation but limited to peripheral rather than central nervous targets, we chose a semi-active control condition according to the classification put forward by Arns et al., (2014) in comparing NF with electromyographic (EMG) feedback. Despite not being closely related to the known pathology of ADHD, EMG feedback has been used in several ADHD treatment studies and as a control condition for NF. Some improvements but smaller than those from NF were reported (Arnold, 2001; Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Maurizio et al., 2013). Thus, even participants in the

control condition have the chance to reduce symptoms and learn self-regulation, but not based on a treatment specific to the pathology of the disease. Delivering identical treatment elements in both conditions apart from the specific (NF or EMG) component should allow differentiating specific from unspecific effects of NF. The aim of this investigation was to assess the effectiveness, specificity and feasibility of SCP-NF in comparison to EMG feedback in a prospective, randomized and controlled study, while neurophysiological data and more detailed learning analyses and correlations with clinical outcomes will be published elsewhere (see Materials and Methods).

2.1.3 Materials and Methods

2.1.3.1 Study Design

Study design, methods, and data analysis plan are described in detail in the study protocol published by Holtmann et al., (2014). Patients were recruited and treated in five German university-based outpatient departments for child psychiatry/psychotherapy. All local ethics committees approved the study. Patients' assent was obtained by using age-appropriate information and their parents or guardians gave written informed consent. Figure 2 depicts the design and study flow.

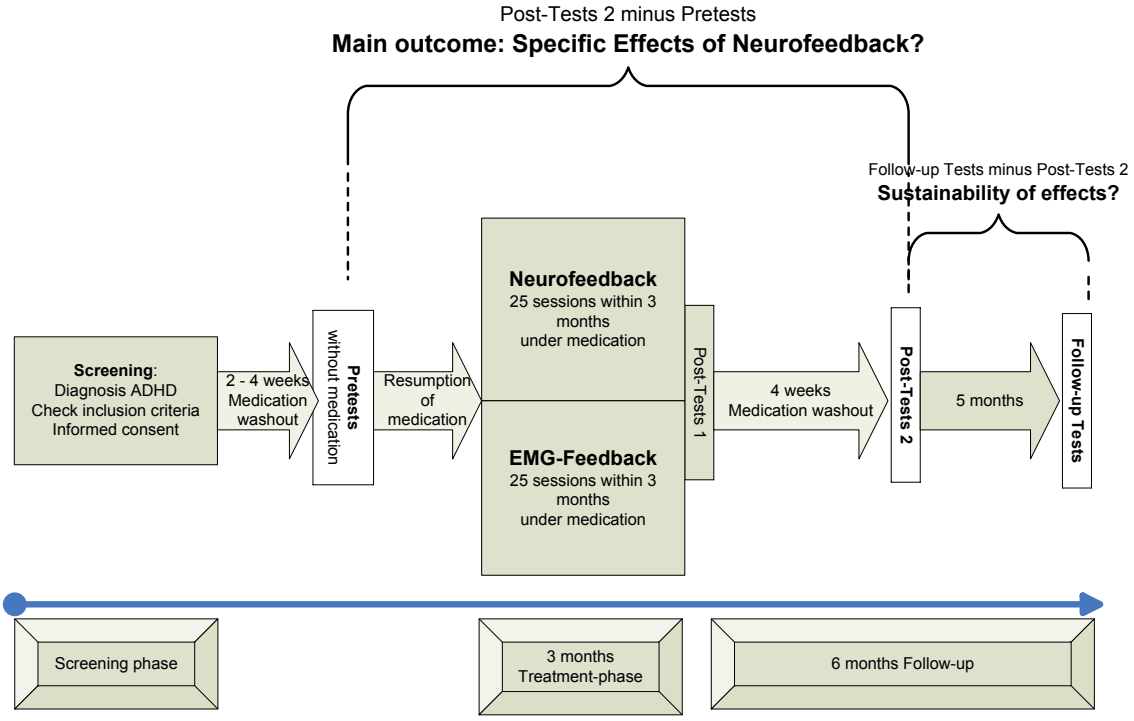

Figure 2. Study flow (modified from Holtmann et al., 2014).

2.1.3.1.1 Study Groups

Inclusion criteria comprised age from 7 to 9 years, and a diagnosis of ADHD combined type according to DSM-IV TR verified in a semi-structured interview under the supervision of clinical psychiatrists/licensed psychologists (Delmo et al., 1998). In the case of positive screenings for comorbid symptoms assessed by the Child Behavior Checklist (CBCL; Arbeitsgruppe Deutsche Child Behavior Checklist, 1998), corresponding parents' rating scales were applied (Döpfner and Lehmkuhl, 2000; Döpfner et al., 2006). Exclusion criteria consisted of a diagnosis of bipolar disorder, psychosis, serious obsessive-compulsive disorder, chronic severe tics or Tourette syndrome, major neurological or physical illness, acute suicidal tendencies, pharmacotherapy for severe anxiety, mood disorders and psychosis, IQ below 80, lack of German-language proficiency in the child or primary caregiver, no telephone, pregnancy and lactation, and current participation in other clinical trials. As the interventions were considered an add-on to treatment as usual pharmacotherapy for ADHD, Oppositional Defiant Disorder and Conduct Disorder were allowed. Patients were randomly assigned in a 1:1 ratio with varying block size to either the experimental or the control group. This assignment was realized by a computer-generated, web-based tool provided by the Interdisciplinary Center for Clinical Trials (IZKS) Mainz. Randomization was stratified per trial site and sex. Medical consultants rating clinical impairments were blinded. Participants were not blinded, because they were instructed according to their group assignment. Parents were not informed about treatment allocation but as the children were given instructions according to their treatment group, parents could infer their child's group assignment.

2.1.3.1.2 Procedures

After screening, there was a washout period of 2 weeks for children with psychostimulants and 4 weeks for participants with atomoxetine. Pre-tests and post-tests 2 were conducted without medication. After the pre-test, children resumed their medication until completion of post-tests 1. The main outcome, therefore, was assessed by changes in post-tests 2 compared to pre-tests (see Figure 2).

Participants received 25 training sessions within 3 months with two to three sessions per week. After session 12, there was a break of 4–6 weeks. Such a break has become standard in clinical NF studies to disburden the patients from the demanding training schedule with two to

three sessions per week and to give him/her the opportunity to practice self-regulation in everyday life (transfer).

2.1.3.1.3 Experimental Group: NF of SCP

SCPs are very slow shifts in the EEG near to 0 Hz, typically generated in an event-related design for several seconds. A negative shift reduces the excitability of the underlying cortical area while a positive shift is understood as inhibition of excitation and/or consummation of energy. As event-related potentials, they prepare adequate cognitive as well as motor responses. In the feedback paradigm, participants were prompted to either produce negative (reducing the excitability threshold of the underlying cortex) or positive shifts (inhibition of excitation) in a randomized order. After session 12, the ratio of negativity to positivity trials was increased from 50 to 80%. The convention in SCP training so far has been to train and reinforce both polarities to improve self- regulation, but particularly toward the end focus on that polarity which is thought to be related to the disease (e.g., Strehl et al., 2006). As the neurophysiological profile of patients with ADHD indicates hypoactivation of cortical excitation thresholds, the training of negative shifts is thought to be more important.

2.1.3.1.4 Control Group: Feedback of electromyographic Coordination of the Supraspinatus Muscles

As a semi-active control condition, EMG feedback of coordination in the supraspinatus muscles was chosen. Participants were instructed either to contract or to relax the left relative to the right supraspinatus muscle. This protocol was chosen to induce differential EMG control corresponding to the "polarities" comparable to the NF condition, without requiring simple relaxation or tension. This allowed us to use the same device and the same representation of the feedback signal on the screen. We did not choose a standard EMG feedback protocol because the control condition should be as unspecific as possible but include the possibility to learn self-regulation, i.e., the unspecific variable of any biofeedback treatment.

2.1.3.1.5 Common components of Behavior Therapy in both Groups

All interventions took place in outpatient clinics. Setting, training devices, electrode montage, feedback and transfer trials, number of sessions, transfer exercises, and the possibility to earn tokens were the same in both groups. The treatment schedule (Figure 3) for each session

comprised four blocks of 40 trials each. Each trial lasted for 10 s (2 s baseline and 8 s feedback and depicting a "sun" after successful trials). In all sessions, the third block operated without continuous feedback; only the sun was shown at the end if the trial had been successful (Figure 3). These trials were part of several measures to carry over self-regulation skills to everyday life: During the break following session 12, patients were asked to practice self-regulation at home using small memo cards depicting the screen during a task. In addition, self-regulation could be trained with the help of a video showing a sequence of both positivity and negativity trials. After each of the 10 final sessions, the children did part of their homework in the lab under the trainer's supervision making use of the memo cards. As a reward for their participation and for good cooperation children could earn tokens. Whenever a certain number was achieved, tokens were swapped for vouchers or small gifts.

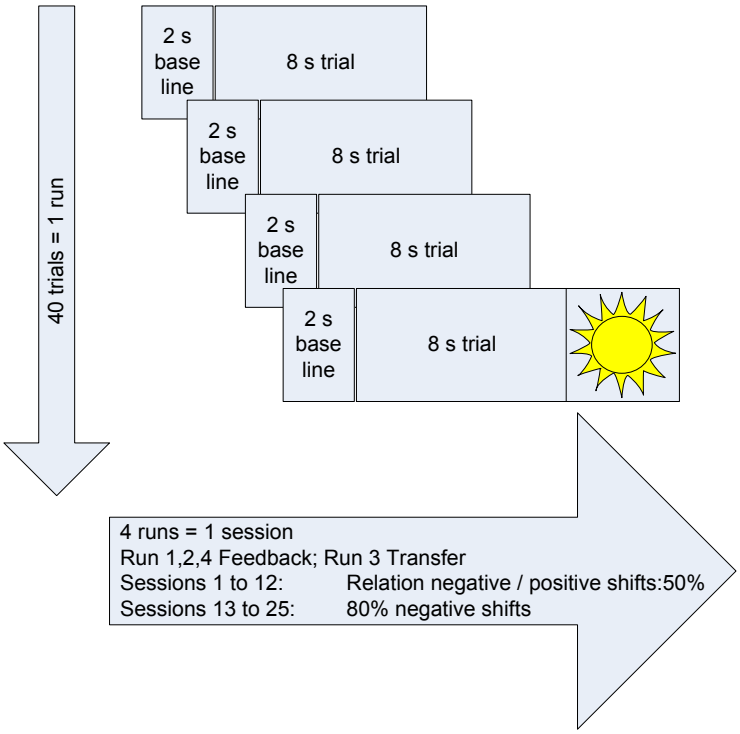

Figure 3. Treatment schedule.

2.1.3.2 Acquisition of EEG- and EMG Signals

EEG and EMG were recorded and fed back with a multichannel amplifier (THERA PRAX R neuroConn GmbH, Ilmenau, Germany). The EEG electrode was placed at Cz, referenced against the mastoid behind the right ear. Four electrodes were used to record the vertical and horizontal electrooculogram (EOG) and one electrode behind the left ear was used as ground. EMG was recorded with one electrode per shoulder placed at the upper area of the right and left supraspinatus muscle. Off-line analyses were performed with the Brain Vision Analyzer (Version 2.0, Brain Products, Gilching, Germany). For training data, EEG was filtered off-line using a 0.01 Hz high cut-off filter (12 dB/octave) plus 50 Hz notch filter, referenced with one mastoid, followed by ocular correction (Gratton, Coles, & Donchin, 1983). Data were segmented for both tasks (positive and negative SCP shifts). Artifacts were rejected semi-automatically if trials were over ±150 µV. Remaining artifact-free trials were averaged. The average was exported using the last 4–8 s of every trial that lasted 8 s. Each center was guided by a detailed manual to ensure equal handling of participants, testing, and treatment. Center representatives met for an initial 2-day training course and on a regular basis thereafter. Supervision visits took place to guarantee compliance with the manual.

2.1.3.3 Outcomes

Psychometric properties of all pre-specified measures are reported in Holtmann et al., (2014). For the present first paper outcomes are reported as changes from pre-test to post-test 2 (after washout of medication, defined a priori as the primary endpoint to avoid residual medication confounds, and to focus on stable or sustained SCP-NF effects). Apart from IQ and cortical self-regulation, a detailed analysis of learning parameters, electrophysiological, neuropsychological outcomes, and 6-month follow-up data will be reported elsewhere. The primary endpoint was the parent-rated ADHD symptom severity assessed using the mean global score of the German ADHD rating scale (24). The scale consists of 20 items assessing the severity of inattention, hyperactivity, and impulsiveness. Each item, corresponding to one of the DSM-IV diagnostic criteria, is rated on a 4-point scale (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). Secondary endpoints were:

- Parents' ratings of ADHD subdomains (inattention, hyperactivity, impulsivity; Döpfner et al., 2006).

– Teachers' ratings of ADHD symptoms (global score and subdomains; Döpfner et al., 2006).
– The Clinical Global Impression-Improvement (CGI-I) responder status assessed by a blinded clinician (Guy, 1976).
– Comorbid symptoms [parents' and teachers' ratings via the Strengths and Difficulties Questionnaire (SDQ); Woerner, Becker, & Rothenberger, 2004].
– Full-scale IQ [indicated by its percent rank; measured with parallel versions of the Coloured Progressive Matrices (CPM) to minimize test-retest effects; Bulheller and Häcker, 1998.
– Quality of life assessed via the global score of the revised German Kid-KINDL(R) (Ravens-Sieberer & Bullinger, 1998).
– Parents' satisfaction with therapy: unpublished questionnaire developed by the Institute of Medical Psychology and Behavioral Neurobiology, Tübingen (2004). Parents submitted these questionnaires directly to the IZKS to guarantee anonymous handling and thereby avoiding responses driven by social desirability.
– Adverse events (AE) and serious adverse events (SAE): at each contact participants were asked to report any AE and their severity using open questions.

As covariates, we assessed parenting style and parents' expectations (Arnold et al., 1993) at screening. Self-regulation of EEG during training sessions was assessed to evaluate the specificity of NF.

2.1.3.4 Statistical Analysis

The methodology for processing and analyzing the data was documented in a Statistical Analysis Plan (SAP) dated and maintained by the IZKS responsible for data management, monitoring, and analysis (for details, see Holtmann et al., 2014). Sample size calculation for the primary endpoint was based on an estimation of effect sizes derived from the SCP-NF study by Heinrich et al., (2004) using the same outcome measure. Expecting a mean ADHD score of 1.2 at post-test 2 in the NF group and of 1.5 in controls with a common SD of 0.55 a sample size of 72 per group was required to achieve a power of 90% ($\alpha = 0.05$, two-sided t-test). Data were analyzed primarily in the modified intention-to-treat (mITT) population, comprising all randomized patients except those who received no treatment due to violation of inclusion criteria. Supportive

analysis was performed in the per-protocol (PP) population, comprising all mITT patients who did not meet any of the following criteria: violation of inclusion or exclusion criteria, major deviations from the visit schedule, and lack of compliance during treatment sessions. Safety parameters were analyzed in the safety population, comprising all participants with at least one feedback session. The primary outcome was tested by an analysis of covariance (ANCOVA) with treatment, trial site, sex, baseline ADHD score, baseline ADHD medication, parenting style, and parents' expectations as covariates. Missing ADHD scores were imputed according to the baseline observation carried forward (BOCF) method. This is usually considered a conservative approach to handle missing data since patients with missing values are treated as treatment failures. This conservative approach is supposed to avoid too positive results when many patients from the NF treatment group dropout who do not improve or even get worse. Therefore, the analysis was repeated with a multiple imputation approaches. Additional covariates were used to create 10 complete datasets. Those datasets were analyzed by the same ANCOVA model as the primary analysis. Afterward, the results were combined by Rubin's rules. Secondary analyses comprised ANCOVAs (analogously to the primary analysis) for differences in ADHD global and subdomain scores (teachers' ratings), t-tests for differences in ADHD global scores (parents' ratings, teachers' ratings), SDQ subscales, IQ, quality of life, and parents' satisfaction with therapy. For the binary variable Clinical Global Impression (CGI) McNemar's tests were used to test for differences between time points within groups, and chi-squared tests were used for differences between groups. Results of all statistical tests except for the primary analysis must be interpreted in an exploratory manner. To assess the magnitude of treatment effects, between-treatment effect sizes were calculated by dividing the treatment-group differences (including the BOCF method if indicated) by the pooled standard deviation at pre-test. Within-treatment effect sizes were calculated by dividing the mean of changes by the standard deviation at pre-test. To assess the extent and specificity of SCP self-regulation, the mean amplitude of SCPs and mean self-regulation performance (percentage of correct trials) were averaged for training sessions 2 + 3, 10 + 11, 14 + 15, and 23 + 24. These session averages were selected in line with previous work (Strehl et al., 2006). This selection provides robust estimates of regulation performance and learning while excluding the undesired influences of novelty or expected completion in the initial and final sessions of each training half. SCP amplitude (μV) was analyzed using group by task × sessions (only the four session averages during training to minimize the number of dropouts) repeated-

measures ANOVAs. Self-regulation performance was analyzed using a group by sessions (the four session averages during training plus post 2 performance) repeated-measures ANOVA. SCP amplitude and self-regulation performance were analyzed separately for thefeedback and transfer condition.

An independent data monitoring and safety board supervised the conduct of the study. The trial was registered under Current Controlled Trials ISRCTN76187185 (5 February 2009).

2.1.4 Results

2.1.4.1 Patients

A total of 174 participants were recruited between September 2009 and January 2013 for screening, 150 of whom were allocated to one of the two treatment groups. In NF 60 and in EMG 51 participants completed treatment and took part in all assessment points. The CONSORT flow diagram is depicted in Figure 4. The mITT population comprised 75 participants in NF and 69 in EMG. Baseline characteristics are depicted in Table 1. There were no diff erences between groups in any of these variables. The safety population comprised 96% of the mITT population for NF and 98.55% for EMG; the PP population consisted of 59% for NF and 58% for EMG. The main reason for violation of the protocol was delay of post-tests 2, which occurred in 41% of NF and in 42% of EMG mITT populations. NF had 16% dropouts, EMG 17%, with most dropouts occurring between pre-test and session 12. A comparison between dropouts and non-dropouts yielded the following differences: lower level of education of fathers ($p = 0.03$—chi-squared test), fewer parents living together ($p = 0.027$—chi-squared test), and more severe oppositional defiant disorder ($p = 0.033$—t-test) in those who did not complete the study.

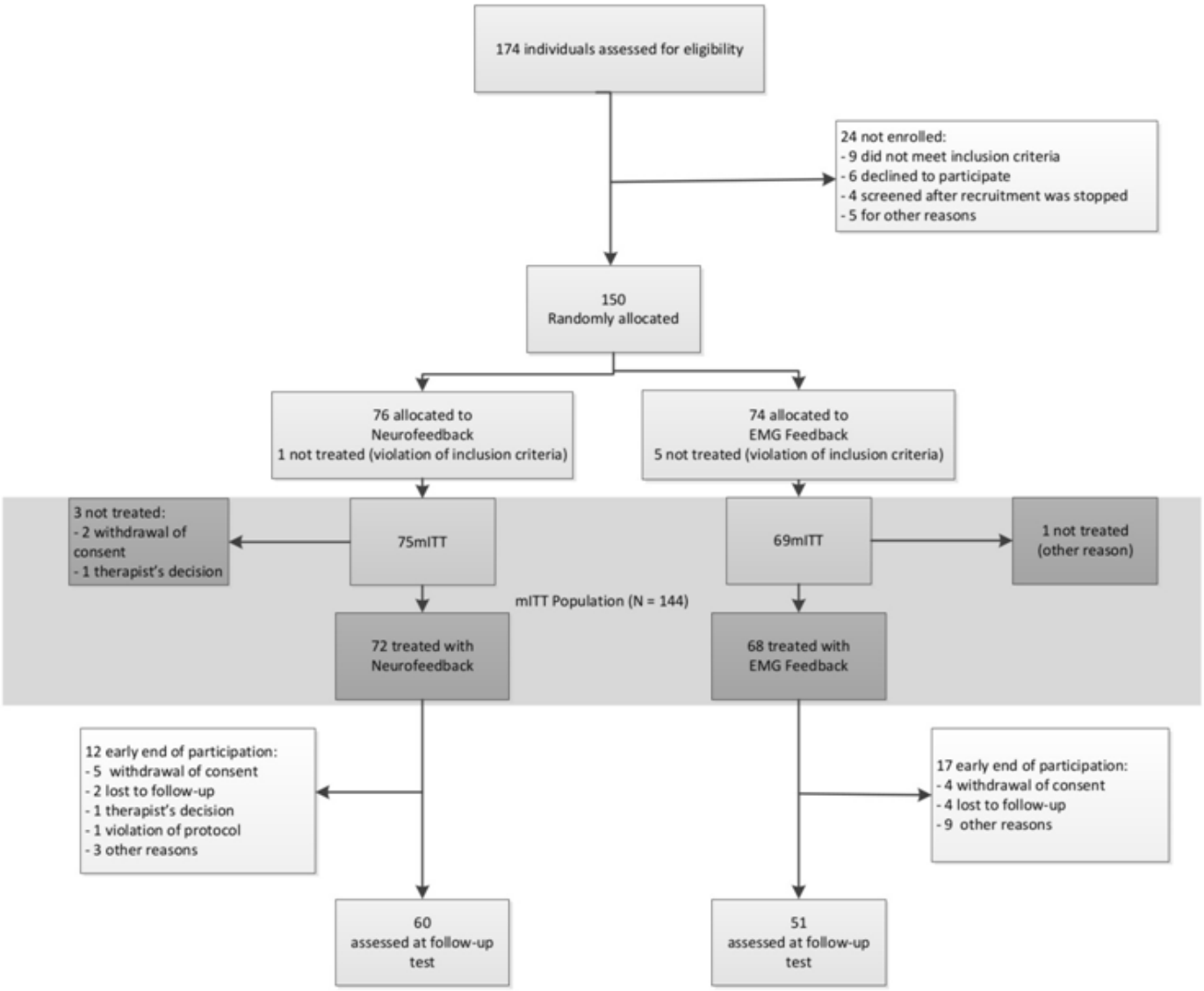

Figure 4. CONSORT flow diagram

Table 1. Baseline characteristics of participants

	Neurofeedback N= 75		EMG feedback N= 69	
Variable	**Mean**	**SD**	**Mean**	**SD**
Age (in years)	8.6	0.92	8.57	0.88
ADHD global score	1.84	0.045	1.78	0.47
KINDL® Quality of Life	67.5	8.9	68.6	9.6
CPM (percentage rank)	63.4	27	65.5	27
CBCL t-value				
Global	63.6	8.4	63.2	7.8
Externalizing problems	66.3	9.4	64.8	9.4
Internalizing problems	62.2	9.5	62.4	9.3
	N	**Percent**	***N***	**Percent**
CBCL Comorbidity*				
Oppositional defiant disor-der	31	41.33	32	46.36
Conduct disorder	0	0.00	1	1.45
Depression	11	14.66	8	11.59
Dysthymia	5	6.67	3	4.35
Separation anxiety	3	4.00	5	7.25
General anxiety disorder	18	24.00	18	27.69
Social phobia	4	5.33	8	11.59
Specific pho-bia	4		6	8.64
Sex				
Femal	14	18.67	11	15.94
Male	61	81.33	61	84.06
CGI-S				
Normal/Bordeline ill	3	5	3	5.36
Mild/Moderately ill	29	48.33	29	45.78
Marked/Severely ill	28	46.67	24	42.86
Missing	15		13	
ADHD medication prior to study	34	45.33	28	40.58

*CGI, Clinical Global Impression-Severity; CBCL, Chiuld Behavior Checklist; *disorder-specific parent ratings*

2.1.4.2 Primary Outcome

NF was significantly superior to EMG in reducing ADHD core symptoms as rated by parents with a difference of 0.17 (95% CI 0.02–0.30, F(1) = 5.30, p = 0.02). ANCOVA yielded no impact on sex, trial site, medication status at baseline, parenting style, and parents' expectations on the reduction of ADHD core symptoms as rated by parents (Table 2). The more pronounced ADHD symptoms were at pre-test the larger was their reduction. The sensitivity analysis with the PP population (N = 84) yielded similar results (Supplementary Table 8). The multiple imputation approaches revealed similar results: the difference between treatments was 0.22 (95% CI 0.03–0.4), p = 0.02. The difference of changes in the ADHD global score between groups, as compared by a t-test, was significant for the mITT population (BOCF), at p = 0.01 (NF mean −0.35, SD 0.42; EMG mean −0.17, SD 0.43), and yielded an ES of d = 0.57 without BOCF and 0.40 with BOCF. Within-group analyses revealed effect sizes of 0.78 for NF and 0.35 for EMG. Global score changes from pre-test to post-test 2 are depicted in Figure 5.

Table 2. Primary analysis: Differences in ADHD global score (parents' ratings; post-test 2 minus pre-test between groups; mITT population, ANCOVA, baseline observation carried forward); df, degree(s) of freedom.

	Adjusted mean (95% CI)	***p***	***F***	***df***
EMG-Feedback	-0.1338 (-0.259 / -0.008)			
Neurofeedback	-0.2987 (-0.416 / -0.181)			
Difference between treatments	0.1649 (0.023 / 0.301)			
Treatment		0.0230	5.30	1
Baseline ADHD global score		0.0008	11.84	1
Sex		0.1879	1.75	1
Trial site		0.5951	0.70	4
Baseline ADHD medication (yes/no)		0.3016	1.08	1
Parenting style		0.8007	0.06	1
Parents' expectations		0.4154	0.67	1

2.1.4.3 Secondary Outcomes

2.1.4.3.1 Parents´Ratings of ADHD Subdomains

Data for all scales at pre-test and post-test 2 are reported in Table 3 (BOCF). For results without BOCF, see Supplementary Table 9.

Table 4 shows the adjusted mean difference of change scores post-test 2 minus pre-test between groups (BOCF). Both groups improved in the subdomain hyperactivity, although no difference between groups was observed. Parents' ratings indicated superior improvements in the NF group for the subscales impulsivity ($p = 0.02$) and inattention ($p = 0.02$) with medium effect sizes. Similar to the primary analysis none of the covariates had an impact on treatment differences.

2.1.4.3.2 Teachers´Ratings of ADHD Core Symptoms

The difference between groups based on teachers' ratings of ADHD global scores (mITT population, ANCOVA, BOCF; Supplementary Table 10) was not significant [treatment difference 0.04, 95% CI −0.12 to 0.21, $F(1) = 0.25$, $p = 0.62$]. ANCOVA yielded a significant within-group difference for NF (mean change of −0.16; 95% CI −0.3 to −0.02) but not for EMG (mean change of −0.11; 95% CI −0.26 to 0.04). Data for all scales at pre-test and post-test 2 are reported in Table 5 (BOCF); for results without BOCF, see Supplementary Table 11. Post hoc t-tests for changes from pre-test to post-test 2 in global score and subscores yielded no differences between groups (see Table 6). According to within-group analyses, improvements in global scale, inattention, and impulsivity were observed for NF only, albeit with small effect sizes.

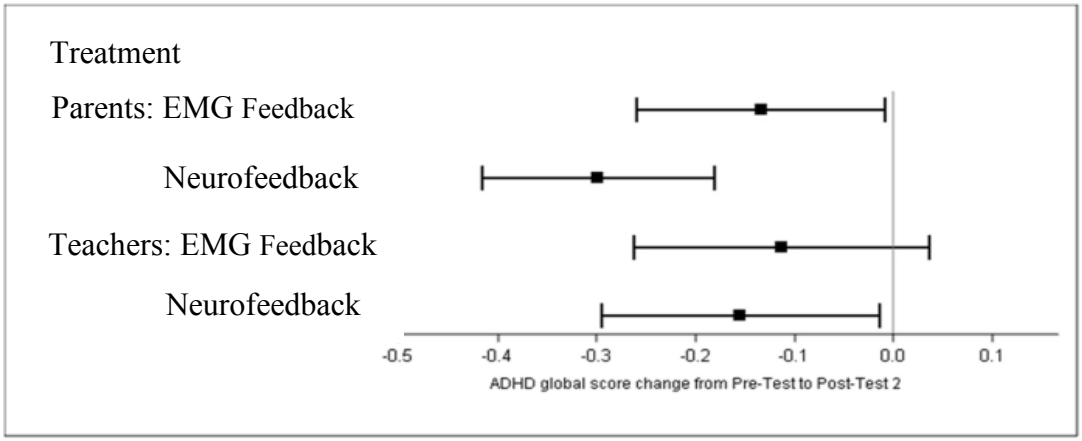

Figure 5. Least square means of ADHD global score changes from pre-test to post-test 2 (parents´ and teachers´ ratings; mITT population, ANCOVA, baseline observation carried forward)

Table 3. Parents´ADHD ratings (mITT population N= 144, BOCF)

	NF				EMG				Total	
	Pre-test		**Post-test 2**		**Pre-test**		**Post-test 2**		**Pre-test**	**Post-test 2**
Hyperactivity										
N	72		73		67		68		139	141
Mean(SD)	1.54	(0.63)	1.22	(0.71)	1.52	(0.67)	1.33 (0.66)		1.53 (0.64)	1.28 (0.68)
Missing	3		2		2		1		5	3
Impulsivity										
N	72		73		67		68		139	141
Mean(SD)	1.93	(0.65)	1.59	(0.65)	1.8	(0.78)	1.71 (0.76)		1.87 (0.73)	1.65 (0.71)
Missing	3		2		2		1		5	3
Inattention										
N	72		73		67		68		139	141
Mean(SD)	2.03	(0.53)	1.64	(0.59)	1.97	(0.51)	1.8 (0.48)		2.00 (0.52)	1.72 (0.54)
Missing	3		2		2		1		5	3
Global score*										
N	72		73		67		68		139	141
Mean(SD)	1.84	(0.49)	1.49	(0.55)	1.78	(0.47)	1.62 (0.5)		1.81 (0.46)	1.55 (0.53)
Missing	3		2		2		1		5	3

**Global score could not be assessed if more than two items in subscales were missing.*

Table 4. Adjusted mean differences in ADHD subdomain scores (parents´ratings; post-test 2 minus pre-test between groups; mITT population, ANCOVA, BOCF)

	Neurofeedback N=75 (23 BOCF)		**EMG feedback N= 69 (20 BOCF)**		**Difference**			
Variables	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*p*	*ES*
Hyperactivity	-0.28	-0.42/-0.13	0.17	-0.33/-0.02	0.11	-0.07/0.28	0.23	0.18
Impulsivity	-0.30	-0.45/-0.15	-0.09	-0.25/0.07	0.21	0.03/0.39	0.05	0.34
Inattention	-0.31	-0.44/-0.18	-0.13	-0.27/0.01	0.18	0.03/0.36	0.02	0.40

2.1.4.3.3 Clinical Global Impression

Clinicians did not observe significant differences between groupsregarding the responder status. At post-test 2 the percentage of responders was 27% (NF) and 26% (EMG). The analysis was limited due to a large proportion of missing values (about 40% of the mITT population in both groups).

2.1.4.3.4 Comorbid Symptoms (SDQ)

No difference between groups was observed regarding changes in comorbid symptoms between pre-test and post-test 1, as assessed with parents' ratings. Children were rated as slightly improved in both groups.

2.1.4.3.5 Full Scale IQ (CPM)

A significant difference between groups was observed regarding the change in full scale IQ from pre-test to post-test 2 ($p = 0.04$, ES = −0.37). While the percentage rank in the EMG group declined from pre- (mean 65.5, SD 25.7) to post-assessment (mean 59.9, SD 31.4) it improved in the NF group from pre- (mean 63.4, SD 28.0) to post-assessment (mean 65.7, SD 28.0).

2.1.4.3.6 Quality of Life [KINDL(R)]

There was no change from pre-test to post-test 2. Scores in both groups ranged from 68 to 72, which is below the standard values of healthy children (Ravens-Sieberer and Bullinger, 1998).

2.1.4.3.7 Parents´Satisfaction with Treatments

There were no differences in parents' ratings regarding their satisfaction with the treatment. Mean values were 4.1 (SD 1.6) for NF and 4.4 (SD 1.4) for EMG on the 6-point Likert scale.

2.1.4.3.8 Adverse Events and Serious Adverse Events

In the safety population (N = 140) 119 AE were reported. At least one AE was reported in 33% of NF participants and 35% of EMG participants. A possible causal relation with the treatment was stated in 4 (6%) of NF participants and 5 (7%) of EMG participants. These children reported headaches (N = 4, both groups), skin reactions (n = 3, NF), myalgia (n = 1, EMG), and nausea (n = 1, EMG). SAE were reported for two children in each group (deterioration of ADHD: n = 2, EMG; n = 1, NF; psychological trauma after traffic accident: n = 1, NF). One of these children (EMG group) was withdrawn from the study because ADHD symptoms deteriorated.

Table 5. Teachers´ADHD ratings (mITT population N= 144, BOCF)

	NF		EMG		Total	
	Pre-test	**Post-test 2**	**Pre-test**	**Post-test 2**	**Pre-test**	**Post-test 2**
Hyperactivity						
N	68	70	63	64	131	134
Mean(SD)	1.15(0.81)	1.05 (0.79)	1.02 (0.85)	1.02 (0.77)	1.09 (0.83)	1.04 (0.78)
Missing	7	5	6	5	13	10
Impulsivity						
N	68	70	63	64	131	134
Mean(SD)	1.41 (0.95)	1.24 (0.94)	1.31 (0.95)	1.27 (0.92)	1.36 (0.95)	1.25 (0.93)
Missing	7	5	6	5	13	10
Inattention						
N	68	70	63	64	131	134
Mean(SD)	1.69 (0.70)	1.59 (0.70)	1.68 (0.72)	1.60 (0.68)	1.69 (0.71)	1.60 (0.69)
Missing	7	5	6	5	13	10
Global score*						
N	65	69	63	61	125	130
Mean(SD)	1.48 (0.64)	1.34 (0.68)	1.38 (0.71)	1.32 (0.71)	1.43 (0.67)	1.3 (0.66)
Missing	10	6	9	8	19	14

**Global score could not be assessed if more than two items in subscales were missing.*

Table 6. Mean differences (SD) in ADHD global and subdomain scores (teachers´ratings; post-test 2 minus pre-test between and within groups; mITT population, BOCF).

	Within group analysis								**Between**	
	Neurofeedback N=75 (23 BOCF)				**EMG feedback N= 69 (20 BOCF)**				**group analysis**	
Variables	*Mean*	*SD*	*p*	*ES*	*Mean*	*95% CI*	*p*	*ES*	*p*	*ES*
Hyperactivity	-0.11	0.7	0.22	0.13	-0.01	0.56	0.86	0.01	0.4	0.11
Impulsivity	-0.2	0.7	0.03	0.21	-0.06	0.62	0.45	0.06	0.24	0.15
Inattention	-0.13	0.53	0.04	0.19	-0.08	0.43	0.16	0.11	0.51	0.08
Global score*	-0.15	0.54	0.03	0.23	-0.07	0.41	0.19	0.1	0.36	0.12

*NF: N=47; EMG; N=39 because global score could not be assessed if more than two items in subscales were missing.

2.1.4.3.9 Self-Regulation of EEG

For the SCP amplitude averaged over all training sessions, a significant interaction was observed between shift direction (trial polarity) and group ($p \leq 0.0001$, $\eta\ 2 = 0.18$). Only the SCP-NF group differentiated between EEG polarities ($p < 0.0001$), achieving negative mean amplitudes in negativity trials and positive amplitudes in positivity trials. These correct polarities were only

achieved in the feedback condition, while the transfer condition did not show significant differences between polarities or groups (see Figure 6). Repeated-measures ANOVA for self-regulation performance during feedback trials revealed a significant main effect of session ($p < 0.001$, $\eta 2 = 0.067$) and a group × session interaction ($p < 0.006$, $\eta 2 = 0.054$). The EMG-NF group achieved higher self-regulation rates compared to the SCP-NF group ($p < 0.0001$). Post hoc comparisons showed that the SCP- NF group improved significantly self-regulation at post 2, and the EMG group improved performance over sessions, however, there the last session was not different from the first one. For the transfer condition, repeated-measures ANOVA showed a significant main effect of session ($p < 0.001$, $\eta 2 = 0.044$) but no group × session interaction. The EMG group achieved higher self-regulation rates compared to the SCP-NF group ($p < 0.0001$). Post hoc comparisons showed that only the EMG group enhanced performance over time (see Figure 7).

2.1.4.3.10 Self-Regulation Performance and its Relation to Clinical Changes

To assess the impact of self-regulation performance on the clinical outcome we grouped participants into learners and non-learners based on the sign of their regression slope for the feedback and the transfer condition separately. For the feedback condition, 67.9% were classified as learners in the SCP-NF group, while 71.1% in the EMG group were classified as learners. For the transfer condition, 53.7% of the SCP-NF group and 73.7% of the EMG group were classified as learners. No significant correlation between performance and clinical outcome was obtained for either group on the primary parent-rated outcome or the corresponding secondary teacher rated total score.

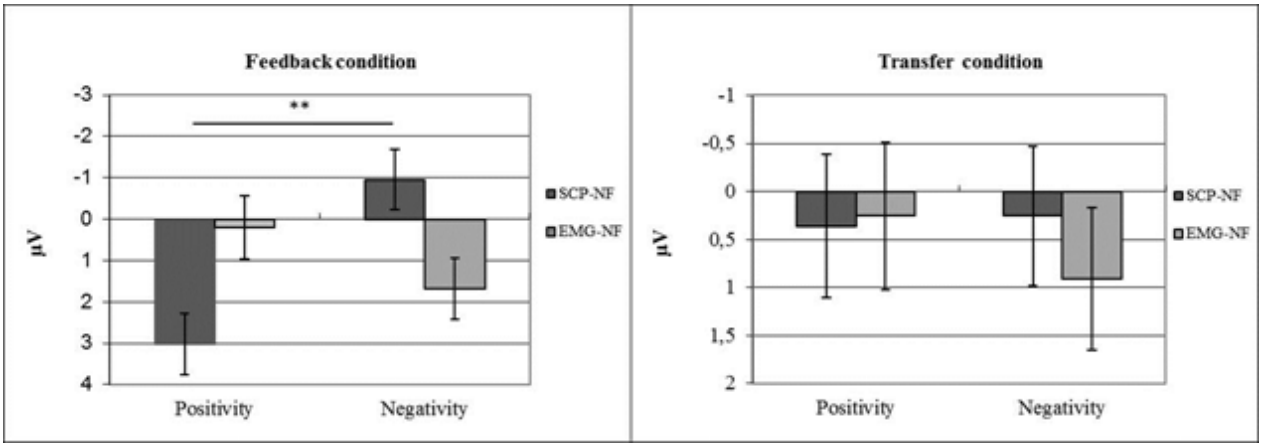

Figure 6. Self-regulation of SCP amplitude by group (NF vs. EMG) and task (polarity; positivity vs. negativity). **p<.05**p<.01.*

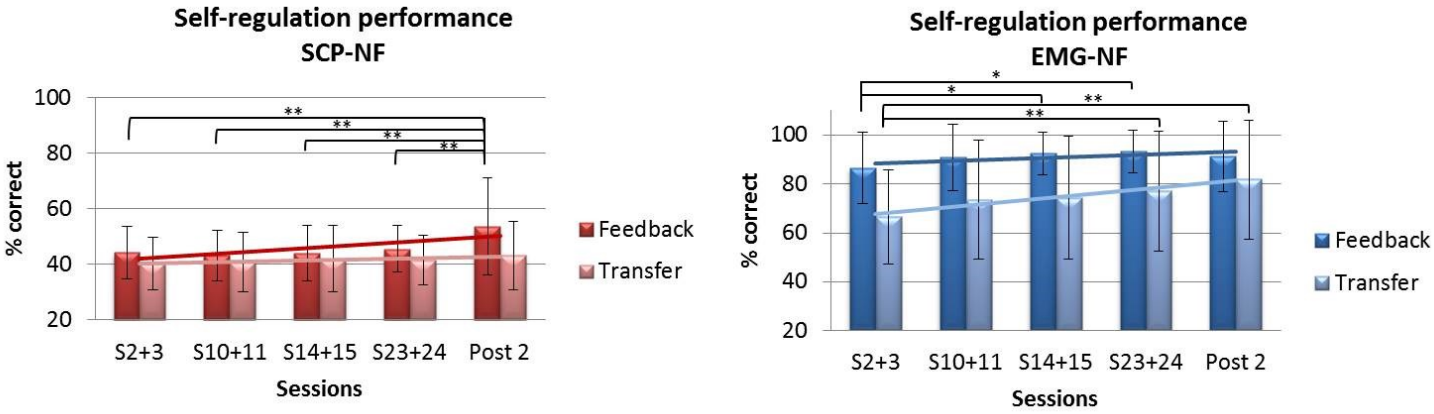

Figure 7. Self-regulation performance during feedback and transfer trials: (A) SCP-NF group and (B) EMG-NF group. **p<.05**p<.01.*

2.1.4.3.11 Post hoc Analyses

Response status was defined based on CGI; however, there were too many missing data for the analysis. We, therefore, assessed the responder rates based on a >25% improvement on the parent-rated ADHD global score from pre-test to post-test 2. As a result, NF yielded a responder rate of 52% and EMG of 35% (mITT population). Based on BOCF analysis we observed 38% responder after NF and 25% after EMG feedback. To explore possible reasons for the difference between parents' and teachers' ratings we computed an independent samples t-test. Teachers rated symptoms as less severe than parents did (see Table 7).

Table 7. Comparison of parents' and teachers' ratings ADHD global

	Parents		**Teachers**		**p**
	Mean	***SD***	***Mean***	***SD***	
NF pre-test	1.84	0.45	1.48	0.64	0.0002
NF post-test 2 minus pre-test	-0.49	0.42	-0.21	0.54	0.01
EMG pre-test	1.78	0.47	1.38	0.71	0.0003
EMG post-test 2 minus pre-test	-0.27	0.5	-0.11	0.51	0.28

2.1.5 Discussion

This is the first randomized controlled clinical trial to investigate the specificity of SCP feedback in children with ADHD, and the largest study on an outpatient ADHD sample treated with NF. We compared two treatments (SCP-NF and EMG feedback) using identical training setups to control for unspecific effects. For the first time in NF research, a BOCF approach was used to handle missing data. This study confirmed specific positive effects of SCP-NF on parent-rated ADHD symptom severity, with a significant greater decrease in symptoms compared to EMG feedback. Sex, trial site, medication, parenting style, and parents' expectation had no impact on the ADHD score change. Sensitivity analyses with multiple imputations and with the PP population generated comparable results. These results are in line with previous findings of trials comparing NF to semi-active control groups (Arns et al., 2014). Symptom severity, comorbidity pattern, and age of our sample match that of the gold-standard MTA-study and can be regarded as

representative for children referred for outpatient ADHD treatment (The MTA Cooperative Group, 1999). Our study set out to assess both specific and unspecific effects of NF. An important hint for specificity is the demonstration of successful SCP self-regulation for children in the SCP-NF group only. The significant symptom improvement in NF may be regarded as a confirmation of specific effects of SCP-NF. The lack of SCP regulation during the transfer condition in the NF group may suggest either limited or delayed transfer and a restricted generalization into everyday life. Here we should wait for follow-up results as it was shown previously for patients with epilepsy (Kotchoubey et al., 1997) and children with ADHD (Strehl et al., 2006) that performance in transfer trials improved substantially 6-month after the end of training. In addition, our results also point to a strong influence of unspecific variables on treatment outcome. We compared two treatments using identical conditions regarding tasks, time schedule, possible amount of reinforcement, and interaction. Children in the semi-active control group underwent the same intense treatment in an identical setting. In feedback treatments, contingent reinforcement of regulation of a physiological parameter improves self-efficacy and coping (Holroyd et al., 1984). Thus, EMG feedback may have an impact on ADHD symptoms (by improving self-regulation skills) even though there is no known direct relation between control of EMG activity and the neurobiological pathology of ADHD. It has to be noted that the type of EMG feedback used in this study is different from the EMG feedback protocols used previously in a couple of studies in the treatment of ADHD (for a review, see Arnold, 2001), showing some effects compared to conditions such as sham feedback, waiting list, keeping children busy by just playing or listening to a storyteller. Bakhshayesh et al., (2011) who used EMG feedback as a control condition for theta/beta feedback report some but smaller effects for EMG feedback compared to frequency band NF. A comparison of tomographic NF with EMG feedback yielded only small differences between treatments with a tendency for EEG feedback with better improvements (Maurizio et al., 2014). While the former study trained relaxation of muscles our participants had to succeed in the simultaneous relaxation and tension of two different muscles similar to the latter study. This differential EMG feedback is far away from standard EMG feedback relaxation protocols aiming to reduce hyperactivity, a core symptom of ADHD. It, therefore, should be of limited specific influence on ADHD symptoms. The finding of similarly reduced hyperactivity according to parents' ratings in both groups fits into this consideration of unspecific effects. The rather small (0.40 with BOCF) or medium (0.57 completer) effect size of the between-group comparisons should be

discussed in several respects. First, due to the considerable unspecific effects in the semi-active control group, the clinical effects of NF (which also include unspecific effects) may have been underestimated. NF-studies in ADHD with waiting list controls tend to yield much higher effect sizes than those with active or semi-active control conditions (see Cortese et al., 2016). In addition, none of the NF studies published so far used the rather conservative BOCF method. Therefore, a comparison with those studies should consider the medium ES for the completers. Furthermore, it must be noted that a meta-analysis of cognitive trainings in ADHD yielded an ES of 0.37 (Cortese et al., 2015). Similarly, for behavioral interventions, the meta-analysis reported an ES of 0.35 (Daley et al., 2014). In addition, we analyzed post hoc within ES for our groups. Here, medium to large effect sizes of 0.78 (BOCF) and 1.09 (completer) for NF were observed, while the effect sizes for EMG were small with 0.35 (BOCF) and 0.48 (completer). According to teachers, who can be regarded as possibly blinded raters, there was no group effect in favor of NF. This is of considerable concern in the light of a recent meta-analysis highlighting smaller effect sizes when applying probably blinded vs. non-blinded ratings (Cortese et al., 2016). Whether NF helps more or faster in the home setting than in school or whether teachers are less sensitive to change than parents are still unresolved questions. Similar to findings from other ADHD studies (e.g., Sollie, Larsson, & Mørch, 2013), teachers compared to parents rated children as being less affected. This may have contributed to the non-significant findings since more pronounced baseline ADHD symptoms were associated with a better response to NF. Within-group analysis of our teachers' results revealed effects of NF on the global ADHD score, inattention, and impulsivity, while EMG feedback did not result in such significant changes. A recent meta-analysis showed similar results of NF based on teacher ratings on inattention (Micoulaud-Franchi et al., 2014). Unfortunately, our study was not powered to detect differences between treatments based on teacher ratings, but the small effect sizes could also suggest that the SCP-NF specific improvements may be of limited significance in school settings. This raises the possibility that more training sessions and transfer trials, or more sensitive blinded ratings may be needed for SCP-NF to produce clinically significant improvement of ADHD symptoms in school settings. However, the observation that teachers judged the children as significantly less affected may put these considerations into a different perspective. If there is less clinical relevance perceived there may be less need for and awareness of change. As discussed by Cortese et al. (2016), teachers may be less attentive to improvements or the instruments used should be complemented, e.g., by behavior

observation. Furthermore, teachers' ratings being probably blind regarding treatment allocation are not necessarily more precise. Blinding does not validate ratings as superior per se. Recently, Janssen et al., (2016) reported reductions in theta power that were predictive of parents' ratings of reduced inattention, whereas no such association was found for (probable blinded) teachers' ratings.

Physicians or clinical psychologists not involved in the study rated about 27% of children in both groups as responders based on CGI ratings. The almost identical response rate in both groups supports the assumption of large unspecific effects of the treatments. Unfortunately, there were about 40% missing values. Furthermore, the validity of the clinicians' ratings is questionable, as some parents reported that the clinicians asked them about their own judgment and gave their ratings accordingly. To supplement the response ratings of clinicians, we determined how many parents described a reduction of ADHD total symptoms of more than 25% for their child. Here, 52% of NF and 35% of EMG children (mITT population) were rated as improved. This result is comparable to response rates reported by Gevensleben et al., (2009) with 52% for NF and 29% for the computer-based attention skills training. The a priori decision to define parents' ratings as "primary" was not only based on methodological requirements. Parents observe many facets of their children's everyday family, social and academic life, and suffer from impairment in all these areas. This may not only explain the more severe ratings compared to those given by teachers but also points to the ecological validity of their judgments. Although parents were not informed about treatment allocation, we cannot rule out that information given to them by their children may have affected their ratings. Parents' ratings were probably not blinded because children were instructed differently according to treatment allocation. Blinding of patients and staff may count as a gold standard of evidence-based medicine in drug research but may interfere in treatments where patients are expected to learn a certain behavior or skill. This holds true for psychotherapy in general and it is of utmost importance in feedback therapy aiming at the acquisition of a self-regulation skill. Without knowing which parameter has to be trained the patient may lose time, motivation and precision (Surwit and Keefe, 1983). An important feature even in blinded designs is the control of expectations influencing the outcome of any treatment (Benedetti et al., 2005; Oken, 2008). In our study, parents' expectations had no effect on outcome. However, their satisfaction was high and did not differ between treatments, again pointing to the impact of unspecific variables acting similarly in both groups. The assessment of expectations is a first step

although the psychometric quality of the questionnaire we used is not yet assessed. We also considered that alternative control conditions where EEG activity unrelated to ADHD must be regulated could have reduced perceptual awareness and allowed blinding. However, we were not aware of any EEG activity that is completely unrelated to ADHD on the one hand and would do no potential harm on the other hand.

In addition to comparing the reduction of symptoms between groups self-regulation, performance and its correlation with clinical outcome was analyzed. This analysis yielded mixed results: in the absence of significant correlations between self- regulation and clinical outcome (global score) the (amount of) specificity remains questionable. On the other hand, more children in the EMG group than in the NF-group learned to improve self-regulation, consistent with the results of Maurizio et al., (2014). Subsequently, better self-regulation and learning resulted in more positive reinforcement (i.e., more frequent reinforcement following successful trials) for children of the EMG group. As learning to self-regulate is acknowledged as an important unspecific variable in biofeedback, one could have expected more clinical improvement and superior outcomes in the EMG group. This was not the case. Therefore, the clinical advantage of NF is unlikely due to unspecific effects only. Given the many ways of analyzing learning (e.g., within sessions learning vs cross sessions as well as pre–post differences in spontaneous as well as event-related brain activity (Gruzelier, 2014; Maurizio et al., 2014; Zuberer et al., 2015) further analyses, including follow-up observations will give more insight in this important matter. For the first time, AE and SAE of SCP-NF were investigated with the help of the WHO Adverse Reaction Terminology, included in the Medical Dictionary for Regulatory Activities for clinical studies (MedDRA R, Version 16). The treatments were feasible and AE related to the treatment were observed in only a few children. While one child of the EMG group had to be withdrawn from the study because his symptoms deteriorated, the other AE in children of both groups remitted quickly. The drop-out rate was similar to previous NF-studies with comparable duration of treatment. Most drop-outs were observed between pre-test and end of first treatment phase. In accordance with evidence on ADHD treatment utilization adherence may have been hampered by personal and family characteristics of dropouts (higher level of oppositional symptoms, lower paternal level of education, more single parents) (Corkum et al., 2015). Such families may require special attention when behavioral interventions are planned. A difference in the change of the full scale IQ was observed between groups. While there was a slight increase in NF,

performance of EMG participants declined. This may be due to EMG children investing less effort in the test, and to SCP-NF releasing attentional resources (Strehl, Kotchoubey, Martinetz, & Birbaumer, 2011). Earlier studies have already reported improvements in children with ADHD after SCP-NF. We have moved a step forward in answering questions regarding specificity, efficacy and feasibility with this study. We included the largest sample treated with NF to date, used a semi-active control condition with an identical setting, a conservative statistical approach (BOCF), and SCPs as target for NF, which has been identified as a stable marker of ADHD. Major limitations of the present study are the lack of power regarding teacher ratings, and only few and questionable clinicians' ratings. Compared with other studies, a possible shortcoming might lie in the fact that for pragmatic reasons, we chose to conduct only 25 training sessions since Arns et al., (2009) observed a correlation of the number of sessions with the reduction of inattention. More sessions and more transfer trials might have improved performance in those trials and clinical effects might have become more robust. Further analysis of electrophysiological and neuropsychological data and long-term outcome will help to understand the mechanisms underlying the reported specific and unspecific effects. A major challenge for future studies will be to identify predictors to decide whether an individual patient would particularly benefit from SCP-NF.

2.1.6 Supplementary Materials

Table 8. Sensitivity Analysis: Differences in FBB-ADHS global score (Parents' ratings; Post-Test 2 minus Pretest between groups; PP Population; ANCOVA, BOCF)

	Adjusted mean (95% CI)	**p-value**
EMG-Feedback	-0.1074 ((-0.2774 / 0.0626)	
Neurofeedback	-0.3287 (-0.4806 / -0.1769)	
Difference between treatments	0.2213 (0.0293 / 0.4133)	
Treatment		0.0245
FBB-ADHS global score		0.0042
Gender		0.1199
Trial site		0.9972
Baseline ADHD medication (yes/no)		0.7604
Parenting style		0.6001
Parents' expectations		0.9069

Table 9. Parents' ADHD Ratings (mITT Population N=144)

	NF		EMG		Total	
	Pre-Test	**Post-Test 2**	**Pre-Test**	**Post-Test 2**	**Pre-Test**	**Post-Test 2**
			Hyperactivity			
N	72	53	67	50	139	103
Mean	1.543	1.086	1.524	1.265	1.534	1.173
(SD)	(0.628)	(0.689)	(0.665)	(0.664)	(0.644)	(0.679)
Missing	3	22	2	19	5	41
			Impulsivity			
N	72	53	67	50	139	103
Mean	1.927	1.453	1.799	1.685	1.865	1.566
(SD)	(0.690)	(0.574)	(0.779)	(0.779)	(0.734)	(0.688)
Missing	3	22	2	19	5	41
			Inattention			
N	72	53	67	50	139	103
Mean	2.033	1.499	1.973	1.705	2.004	1.599
(SD)	(0.527)	(0·534)	(0.509)	(0.448)	(0.518)	(0.502)
Missing	3	22	5	19	5	41
			Global Score*			
N	73	53	67	50	139	103
Mean	1.842	1.346	1.782	1.548	1.813	1.444
(SD)	(0.448)	(0.519)	(0.471)	(0.488)	(0.459)	(0.512)
Missing	3	22	2	19	5	41

*Global score could not be assessed if more than 2 items of subscales were missing

Table 10. Differences in FBB-ADHS global score (Teachers' ratings; Post-Test 2 minus Pretest between groups; mITT population, ANCOVA, BOCF)

	Adjusted mean (95% CI)	**p-value**
EMG-Feedback	-0.1134 (-0.2628 / 0.0360)	
Neurofeedback	-0.1549 (-0.2953 / -0.0145)	
Difference between treatments	0.0415 (-0.1240 /0.2070)	
Treatment		0.6204
Baseline FBB-ADHS global score		**<.0001**
Gender		0.9686
Trial site		0.2200
Baseline ADHD medication (yes/no)		0.8498
Parenting style		0.6290
Parents' expectations		0.5949

Table 11. Teachers' ADHD Ratings (mITT Population N=144)

	NF		EMG		Total	
	Pre-Test	**Post-Test 2**	**Pre-Test**	**Post-Test 2**	**Pre-Test**	**Post-Test 2**
			Hyperactivity			
N	63	51	68	42	131	93
Mean	1.147	1.073	1.024	0.954	1.088	1.019
(SD)	(0.812)	(0.810)	(0.854)	(0.735)	(0.831)	(0.775)
Missing	7	24	6	27	13	51
			Impulsivity			
N	68	51	63	42	131	93
Mean	1.412	1.270	1.310	1.298	1.363	1.282
(SD)	(0.954)	(0.963)	(0.954)	(0.926)	(0.952)	(0.941)
Missing	7	24	6	27	13	51
			Inattention			
N	68	51	63	42	131	93
Mean	1.693	1.595	1.676	1.468	1.685	1.538
(SD)	(0·696)	(0.765)	(0.724)	(0.627)	(0.707)	(0.705)
Missing	7	24	6	27	13	51
			Global Score*			
N	65	51	60	40	125	91
Mean	1.479	1.348	1.381	1.242	1.432	1.302
(SD)	(0.637)	(0.732)	(0.709)	(0.634)	(0.671)	(0.689)
Missing	10	24	9	29	19	53

* Global score could not be assessed if more than 2 items of subscales were missing

2.2 Study 2: Slow cortical potentials neurofeedback in children with ADHD: comorbidity, self-regulation and clinical outcomes six months after treatment in a multicenter randomized controlled trial

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ORIGINAL CONTRIBUTION

Slow cortical potentials neurofeedback in children with ADHD: comorbidity, self-regulation and clinical outcomes 6 months after treatment in a multicenter randomized controlled trial

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2.2.1 Abstract

Despite sizeable short-term effects of neurofeedback (NF) therapy on attention-deficit and hyperactivity disorder (ADHD), longer-term clinical, comorbidity and self-regulation outcomes are less systematically studied. The aim of this largest NF follow-up to date was to evaluate these outcomes six months after NF compared to a semi-active control to disentangle specific from unspecific sustained effects.

We performed a multicentre, randomized, parallel, controlled, clinical, superiority trial in five German university outpatient departments. Participants were eligible if they fulfilled DSM-IV-TR criteria for ADHD and were aged from 7 to 9 years. Participants were randomly assigned (1:1-ratio) to 25 sessions of slow-cortical potential (SCP)-NF or electromyogram biofeedback (EMG-BF). Participants were not blinded, since they received instructions according to each treatment setting. Primary outcome were parent ratings of ADHD. The trial was registered, number ISRCTN761871859.

Both groups showed improvement of ADHD symptoms compared to baseline at six-months follow-up with large effect sizes (ES) for SCP-NF (d=1.04) and EMG-feedback (d=0.85), but without group differences. When analysing all assessments (pre-test, post-test-1, post-test-2 and follow-up), a group-by-time interaction emerged (p=0.0062), with SCP-NF showing stable improvement following treatment but EMG-BF showing a relapse from post-test-1 to post-test- 2, and subsequent remission at follow-up.

Six months after the end of treatment, improvement after SCP-NF remained large and stable. However, the lack of group differences at follow-up suggests shared specific and unspecific effects contributing to this clinical outcome. Our correlational results indicate specificity of SCP-NF for selected subscales after training, but not at follow-up.

2.2.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with high worldwide prevalence of 2.6-4.5% (Polanczyk et al., 2015). It is considered a heterogeneous disorder, with a particularly high comorbidity rate of 40-70% with conduct problems (CP). Stimulant medication is the most common and effective treatment in severe ADHD, and about 70% of patients respond to this pharmacological approach (Spence et al., 1996). However, adverse events (Graham et al., 2011), unwillingness to take medication over extended periods (Berger et al., 2008), and particularly the absence of positive long-term effects (van de Loo-Neus et al., 2011) are serious constraints of this treatment. Thus, there is a demand for alternative treatments with possible long-term effects such as Neurofeedback (NF), which aims to improve self-regulation of certain brain activity patterns (Sherlin et al., 2011). NF has gained encouraging empirical support in recent years. Meta-analysis on the effects of NF on ADHD symptoms showed medium to large effects for all three core domains of ADHD symptoms (Arns et al., 2009). Although effects were substantially reduced for probably blinded raters in RCTs, NF effects remained significant in an exploratory analysis for studies using standard protocols (Cortese et al., 2016). Regarding sustained and long-term effects, a recent meta-analysis of ten studies (Doren et al., 2018) found small to medium effects for NF compared to non-active control conditions at follow-up, and similar effects compared to active control conditions (pharmacotherapy and self-management). Moreover, the effects of NF treatment on CP and the role of this comorbidity on treatment response has not been widely studied in ADHD patients (Saylor & Amann, 2016), although other behavioral ADHD treatments improve CP symptoms (Daley et al., 2014).

Slow cortical potential (SCP)-NF focuses on regulating cortical activation and inhibition. These slow electrical shifts form a phasic mechanism in the regulation of attention (Rockstroh, Elbert, Lutzenberger, & Birbaumer, 1990). A well-studied SCP, the frontocentral contingent negative variation (CNV) reflecting cognitive activation and preparation, is reduced in ADHD children compared with healthy controls (Albrecht et al., 2008). Promising effects of SCP-NF involving upregulation of CNV-like negative SCPs on ADHD have been reported in several studies (Drechsler et al., 2007; Gevensleben et al., 2009; Holtmann et al., 2004; Strehl et al., 2006; Strehl et al., 2017).

The few studies investigating impact of NF on comorbid CP generally found positive effects on CP symptoms. Gevensleben and colleagues (Gevensleben et al., 2009) assessed significant reductions on parent-rated oppositional behavior (ODD) and CP compared to standardized computerized attention training. After theta/beta NF training, reduction of ODD symptoms were reported but without a group difference when compared with standard pharmacological intervention (Meisel et al., 2013). Furthermore, one study investigated SCP-NF in criminal psychopaths showing less aggression and impulsivity (Konicar et al., 2015).

A key question in NF is whether the ability to learn and self-regulate unconscious psychophysiological parameters relates to clinical outcomes and thereby supports the specificity of treatment effects. Two studies (Drechsler et al., 2007; Strehl et al., 2006) linked self-regulation outcome with impulsivity, inattention and hyperactivity subscales when participants were classified as learners. Gevensleben and colleagues (2009) reported that successful initial increases of negativity (until the ninth session) correlated with inattention improvement. However, one recent frequency band NF study (Janssen et al., 2016) could not find any association between self-regulation and symptom reduction. These analyses are important to disentangle specific from unspecific effects provided by NF treatment approaches.

The relation between long-term effects and self-regulation in ADHD participants was analyzed only in one study six months after SCP-NF treatment. Strehl (2006) reported medium to large effect sizes, which were predicted by self-regulation performance during transfer conditions after training, and as a trend at follow-up.

The main aim of this follow-up on our large randomized controlled multicenter trial, which demonstrated a superior primary ADHD outcome for SCP-NF compared to a semi-active control group (Strehl & Aggensteiner et al., 2017), was to evaluate the clinical long-lasting effects on ADHD and CP symptoms and relate them to self-regulation capabilities.

2.2.3 Materials and Methods

2.2.3.1 Study design and participants

We did a multicenter, randomized controlled, parallel, superiority trial. The study was approved by all local ethics committees according to the Declaration of Helsinki. Written consent was obtained from all participants and their persons in charge of primary custody. For more de-

tails see (Holtmann et al., 2014) regarding the study protocol and randomization and (Strehl & Aggensteiner et al., 2017) regarding the primary outcomes 4 weeks after treatment. Participants had to meet the diagnosis of ADHD combined type according to DSM-IV TR and aged 7 to 9 years. Comorbid symptoms at baseline were assessed by the Child behavior Checklist (CBCL). Exclusion criteria consisted of a diagnosis of bipolar disorder, psychosis, obsessive-compulsive disorder, chronic severe tics or Tourette syndrome, major neurological or physical illness, acute suicidal tendencies, pharmacotherapy for severe anxiety, mood disorders and psychosis, IQ below 80, lack of German-language proficiency, no telephone, pregnancy and lactation, and current participation in other clinical trials. Since the interventions were considered an add-on to treatment as usual, pharmacotherapy for ADHD, ODD and CD was allowed.

2.2.3.2 Procedures

After screening, there was a washout period of 2 weeks for children with psychostimulants and 4 weeks for participants with atomoxetine. Assessments were carried out at pre-intervention (pre-test), after treatment (post-test 1), one-month after treatment (post-test 2) and six months later (follow-up). Pre-tests and post-tests 2 were conducted without medication, and six months after treatment end participants underwent a naturalistic follow-up. Participants were trained one to two times per week for a total of 25 sessions within three months. Six months after training, a follow-up and booster session probed the sustainability of acquired self-regulation skills. Each session lasted about one hour.

SCP-NF sessions were conducted with NEUROPRAX systems (neuroCare GmbH, Germany) using a monopolar setting (Cz, referenced to the right mastoid). Each training session consisted of three feedback runs (with visual feedback) and one transfer run (without feedback). A run consisted of 40 trials, each lasting 10 s, with three phases (2 s baseline and 8 s feedback, followed by a “sun” for reinforcement after successful trials). The participants had to differentiate between activation and deactivation of brain activity. During an “activation”-task an electrically negative SCP shift was required, in contrast to the “deactivation”-task, asking for an electrically positive shift. The baseline was set to zero. Trials were randomly distributed with a 50/50% rate for the first phase of the training (Sessions 1-12). Thereafter, participants had a 3-4 weeks break. The second phase of the training (Sessions 13-25) was more focused on “activation” with 80% negative SCP-shifts.

The semi-active control condition EMG-BF required coordinated activity of the supraspinate muscles. Participants were instructed either to contract or to relax the left in relation to the right supraspinate muscle. Setting, training devices, electrode montage, feedback and transfer trials, number of sessions, and follow-up assessments were the same as in the SCP-NF group.

2.2.3.3 Outcomes

The primary outcome was ADHD symptoms rated by parents. The secondary outcomes were teacher-rated ADHD scale, time course of Comorbid symptoms which were rated by parents via the Strengths and Difficulties Questionnaire (SDQ) and NF training self-regulation performance (percentage of correct trials) and its relation to clinical outcomes. Psychometric properties of all pre-specified measures are reported in the protocol (Holtmann et al., 2014).

2.2.3.4 Statistical analysis

Statistical analyses were run using the Statistical Package for Social Sciences version 23.0 (SPSS). Post-intervention (post-test 2) effects have been reported previously (Strehl & Aggensteiner et al., 2017). This study evaluated sustained and long-term effects between treatments. Primary outcomes (ADHD parent ratings) were tested by an analysis of covariance (ANCOVA) to test sustainability of effects (Follow-up minus post-test 2), as predefined in our protocol (Holtmann et al., 2014) and the longitudinal course across all assessments was analyzed using a mixed model for repeated measure (MMRM). ANCOVA analysis included the covariates trial site, sex, age, baseline ADHD score, ADHD medication at pre-test, parenting style and parents´ expectations. The MMRM model included fixed effects for group, site, time and group by time interaction, adding sex, age, baseline ADHD score, ADHD medication at pre-test, parenting style and parents´ expectations as covariates. We also repeated the same MMRM analysis substituting medication status at pre-test with medication at follow-up.

Secondary outcomes (ADHD teacher ratings) were tested by an analysis of covariance (ANCOVA) with trial site, sex, age, baseline ADHD score, ADHD medication at pre-test, parenting style and parents´ expectations as covariates. Differences were calculated between follow-up and post-test 2 assessments to test sustained effects and between follow-up and pre-test to test long-term clinical effects. Paired T-Tests were used for within group analysis. Between-treatment

effect sizes were calculated by dividing the treatment-group differences by the pooled standard deviation at pre-test. Within-treatment effect sizes were calculated by dividing the mean of changes by the standard deviation at pre-test. Influence of baseline comorbid CP on the primary outcome was assessed repeating the main analysis introducing conduct problems as an additional covariate. The course of comorbid conduct problems and other comorbid symptoms over time was assessed via the SDQ measuring CP, emotional problems, and peer problems in addition to total problems and hyperactivity. Non-parametric Wilcoxon signed rank tests were used for this statistical analysis. NF self-regulation was analyzed based on the regression slope of all selected mean training sessions (for details see Strehl & Aggensteiner et al., 2017). Consolidation of performance was compared by paired T-test between follow-up training session and the first mean session using online obtained reinforcement rate. Pearson's or spearman correlations were assessed to link linear regression of self-regulation performance and clinical outcome for ADHD and comorbid symptoms.

For the ANCOVA data were analyzed primarily in the modified intention-to-treat (mITT) population, comprising all patients except those who received no treatment due to violation of inclusion criteria. Baseline observation carried forward (BOCF) was used to replace missing values for analysis of covariance.

2.2.4 Results

A total of 174 participants were recruited between September 2009 and January 2013 for screening, 150 (86%) of whom were allocated to one of the two treatment groups and 144 (82%) participants started the treatment. The CONSORT flow diagram is depicted in Figure 8. Finally, the mITT population comprised 75 (52%) participants in SCP-NF and 69 (48%) in EMG-BF. In SCP-NF 60 (41%) and in EMG 51 (35%) participants completed treatment and took part in all assessment points. Baseline characteristics did not differ between groups and are depicted in Table 12.

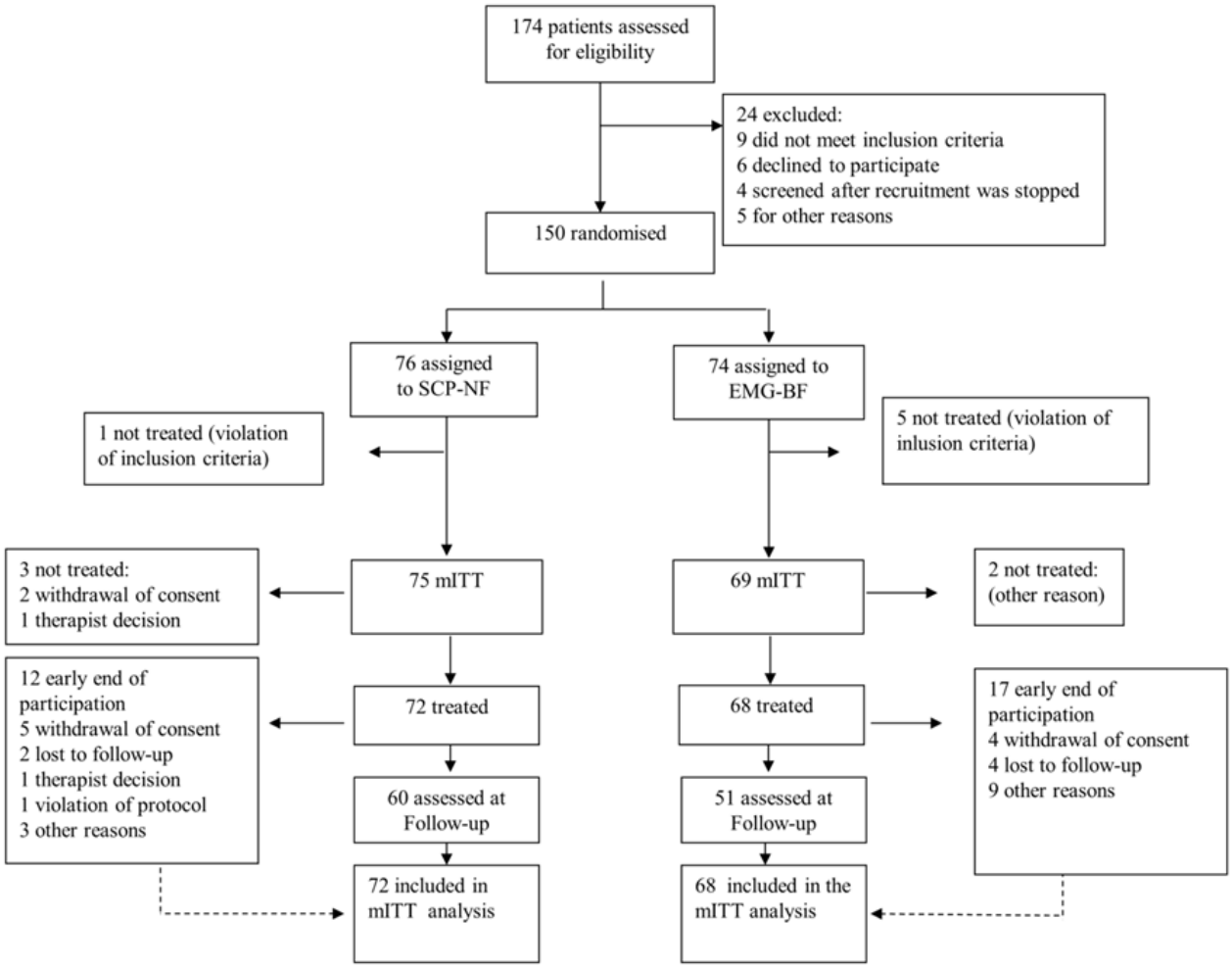

Figure 8. Trial profile. Modified from Strehl et al., (2017). SCP-NF slow cortical potential neurofeedback, EMG-BF electromyographic biofeedback, mITT modified intention to treat.

Table 12. Baseline characteristics of the mITT population

	SCP-NF n=75	**EMG-BF n=69**
	Mean (SD)	**Mean (SD)**
Age (years)	8.6 (0.92)	8.57 (0.88)
Female	14 (18.67%)	11 (15.94%)
Male	61 (81.33%)	58 (84.06%)
ADHD global score	1.842 ± 0.448	1.782 ± 0.471
ADHD medication prior to study	34 (45%)	27 (39.1%)
CBCL t-value		
Global	63.6 (8.4)	63.2 (7.8)
Externalizing problems	66.3 (9.4)	64.8 (9.4)
Internalizing problems	62.2 (9.5)	62.4 (9.3)
SDQ total score	17.49 (6.0)	17.69 (5.5)
CPM (percentage rank)	63.4 (27.0)	65.5 (27.0)
equivalent IQ value	105	106

As predefined in our protocol, we performed an ANCOVA assessing the sustained effects between groups (follow-up minus post-test 2) of the ADHD global score rated by parents revealed a trend for a superior improvement after EMG-BF versus SCP-NF (BOCF: treatment difference: 0.15, p=0.066, ES 0.32), while no effect of sex, trial site, medication, symptom severity at baseline, parenting style, parents´ expectation, and age was observed. Regarding ADHD subdomains, ANCOVA yielded significant group differences for hyperactivity only (BOCF: treatment difference: 0.19, p=0.013, ES 0.44). No effect of sex, trial site, medication, parenting style and parents´ expectation was observed, but age (p=0.044) showed a positive association with improved hyperactivity (Supplementary Table 15).

Analyzing the longitudinal course across all assessments from pre-test to end of six months follow-up together using the MMRM showed large within group improvement on the ADHD global score for both treatments (time difference: 0.43, p<0.0001) with significant group-by-time interaction [F(3,4.376), p=0.006]. Figure 9 shows the clinical trajectories for all assess-

ments for primary outcome rated by parents and in Table 13 results of the MMRM are depicted. Both groups showed large initial improvement immediately after 25 training sessions (post-test 1). However, one month after treatment, following the medication washout, only the SCP-NF group remained stable and the EMG-BF group showed a significant relapse, resulting in significant group differences (group difference: -0.21, p=0.019). However, at follow-up assessment group differences disappeared (group difference: -0.065, p=0.534), indicating that the EMG-BF group significantly recovered (improved) from post-test 2 to follow-up assessment (time difference: 0.16, p=0.035). Regarding the covariates, age (p=0.008), and symptom severity at baseline (p<0.0001) showed significant impact on treatment outcome, reflecting more improvement with increasing age or more severe baseline ADHD (Supplementary Table 16). Further, when repeating the same analysis with medication status at follow-up, a significant interaction for time-by-medication [F(3,2.858), p=0.045], but not for time-by-group-by-medication [F(3,0.365), p=0.778] emerged (Supplementary Table 17). The post-hoc tests indicated that only medicated participants showed a significant recovery from post-test 2 to follow-up (time difference: 0.16, p=0.048), while unmedicated participants showed a stable improvement after post-test 1.

Table 13. Summary of primary outcome: ADHD FBB-HKS rated by parents

		GROUP										Long-term effect size		
		NFB			EMG			Group differences				Between groups	Within groups[a]	
			95% CI			95% CI			95% CI			ES	ES	
	Assessment	Mean			Mean			Difference			p		SCP-NF	EMG-BF
Global scale	Pre-test	1.79	1.79	1.79	1.79	1.79	1.79	0.00	0.00	0.00	0.8760			
	Post-test 1	1.37	1.22	1.51	1.41	1.25	1.56	-0.04	-0.23	0.17	0.7190	0.08	0.97***	0.86***
	Post-test 2	1.34	1.20	1.47	1.55	1.41	1.69	-0.21	-0.40	-0.04	0.0288*	0.57*	1.09***	0.48**
	Follow-up	1.33	1.18	1.49	1.38	1.22	1.54	-0.04	-0.27	0.14	0.6954	0.05	1.04***	0.85***
Inattention	Pre-test	2.03	1.94	2.12	1.98	1.87	2.05	0.05	-0.09	0.16	0.3111			
	Post-test 1	1.52	1.39	1.65	1.56	1.40	1.68	-0.04	-0.20	0.17	0.8053	0.16	0.91***	0.87***
	Post-test 2	1.51	1.38	1.63	1.71	1.57	1.82	-0.20	-0.36	-0.01	0.0348*	0.54*	1.03***	0.52**
	Follow-up	1.53	1.38	1.67	1.60	1.43	1.73	-0.07	-0.27	0.15	0.6321	0.20	1.00***	0.66***
Hyperactivity	Pre-test	1.47	1.38	1.56	1.53	1.44	1.62	-0.05	-0.19	0.73	0.3950			
	Post-test 1	1.16	0.99	1.32	1.10	0.92	1.28	0.06	-0.19	0.31	0.6320	-0.16	0.57**	0.71***
	Post-test 2	1.09	0.94	1.24	1.27	1.10	1.43	-0.18	-0.40	0.05	0.0866°	0.27°	0.70***	0.4**
	Follow-up	1.12	0.96	1.29	1.05	0.87	1.22	0.08	-0.17	0.31	0.5446	-0.20	0.61**	0.80***
Impulsivity	Pre-test	1.89	1.75	2.02	1.81	1.68	1.95	0.07	-0.12	0.26	0.4566			
	Post-test 1	1.54	1.38	1.71	1.63	1.45	1.81	-0.09	-0.33	0.16	0.4829	0.27	0.55***	0.25
	Post-test 2	1.49	1.32	1.66	1.69	1.51	1.87	-0.20	-0.44	0.05	0.1153	0.50	0.64***	0.16
	Follow-up	1.48	1.32	1.65	1.58	1.40	1.76	-0.10	-0.15	0.34	0.4341	0.22	0.64***	0.38*

*Note: Adjusted means. MMRM= Mixed model repeated measure. Bonferroni adjustment for multiple comparisons. [a]Effect sizes for follow-up, post-test 2 and post-test 1 minus pre-tests.°p < 0.1 *p < 0.05 **p < 0.01 ***p < 0.001.*

In exploratory additional medication subgroup analyses, the group by time interaction remained significant for parent ratings in consistently unmedicated patients [N= 25 vs 24; F(3,2.122), p=0.025]. Analysis of the consistently medicated participants showed a significant group effect for the impulsivity subscale [n= 21 vs 19; F(1,8.020), p=0.007]. Post-hoc analysis revealed significant lower impulsivity for the SCP-NF group for post-test 1 (p=.054), post-test 2 (p=.003) and follow-up (p=.008). Changes in medication status during the study were comparable in both groups (see Supplementary Table 18). There was no evidence that more children reduced medication use in the SCP group (n=4) than in the EMG (n=7).

ADHD subscales rated by parents are depicted in Figure 9. Similar results as in the primary outcome were obtained. Inattention [F(3,110.26)= 27.753, p<0.0001] and hyperactivity [F(3,107.28)= 18.316, p<0.0001] achieved a significant effect of time. Hyperactivity subscale showed significant group-by-time interaction [F(3,107.24)=3.476, p=0.018] and inattention a trend [F(3,110.23)= 2.506, p=0.062]. The impulsivity subscale showed as well a significant effect of time [F(3,111.03)=10.767, p<0.0001], however without a group-by-time interaction [F(3,111.00)=1.724, p=0.1661].

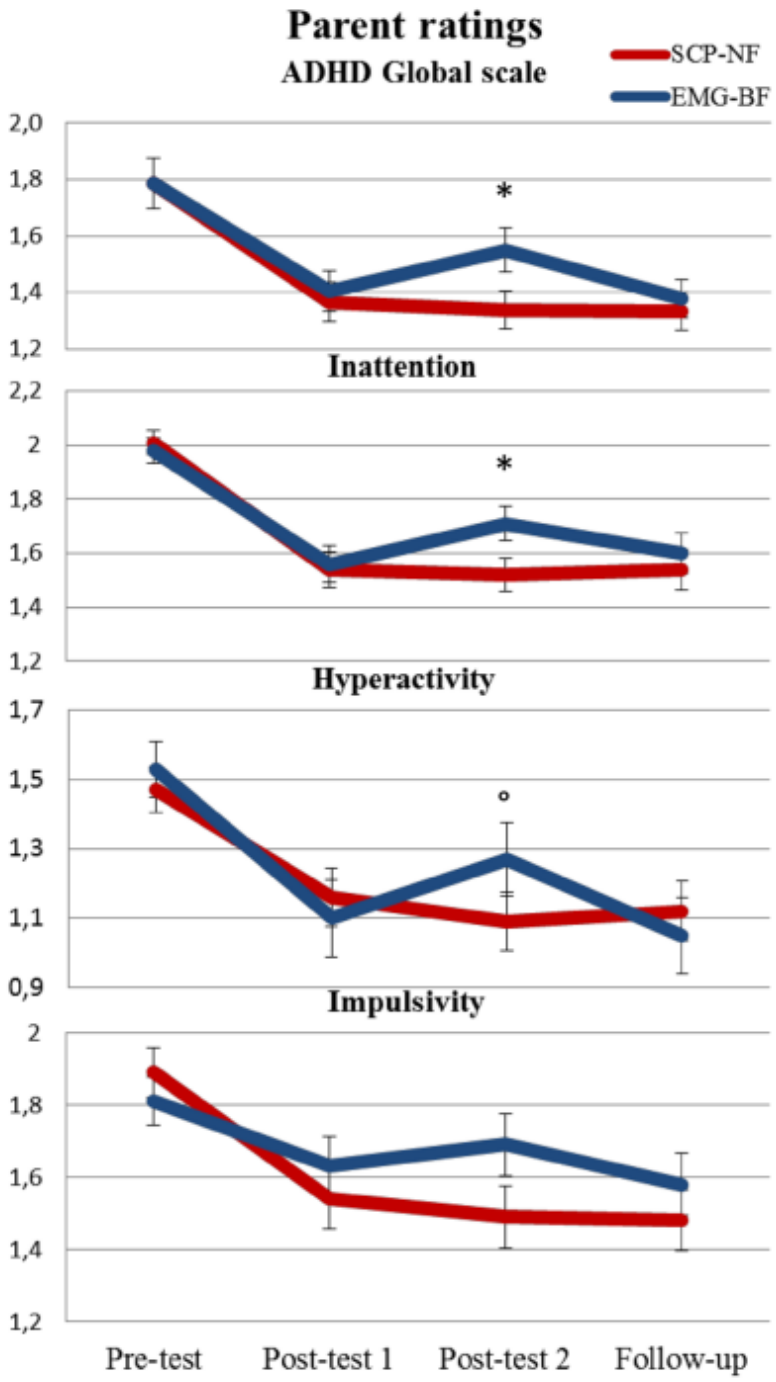

Figure 9. Clinical trajectories of ADHD parent ratings. Pre-test and post-test 2 were conducted without medication. °p<0.1, *p<0.05

ANCOVA between groups assessing the secondary outcome rated by teachers did not show any significant difference between groups neither for sustained effects (follow-up minus post-test 2; BOCF: treatment difference: -0.09, p=0.3559) nor for long-term effects (follow-up minus pre-tests; BOCF: treatment difference: -0.15, p=0.1480) (for details see Supplementary Table 19). Within group analysis are depicted in Table 14. SCP-NF showed significant improvement for ADHD global score t(64)=3.055 p=0.0032 and all subdomains for long-term effects with small to medium effect sizes. For EMG-BF teacher ratings showed only a trend improvement for the impulsivity subdomain t(62)=1.807, p=0.0756.

Table 14. Summary of secondary outcomes: ADHD rating scale rated by teachers (mITT population, N= 144, BOCF).

	Pre-tests			Post-test 2			Follow-up			Follow-up minus Pre-test [a]		Follow-up minus Post-test 2 [a]	
SCP-NF	*Mean*	*n*	*SD*	*Mean*	*n*	*SD*	*Mean*	*n*	*SD*	*ES*	*p*	*ES*	*p*
Global score*	1.48	65	0.64	1.34	69	0.69	1.28	65	0.66	0.34	0.003**	0.09	0.61
Inattention	1.69	68	0.70	1.60	70	0.69	1.52	68	0.68	0.24	0.015*	0.07	0.68
Hyperactivity	1.15	68	0.81	1.05	70	0.79	0.95	68	0.79	0.25	0.033*	0.13	0.43
Impulsivity	1.41	68	0.95	1.23	70	0.93	1.20	68	0.89	0.23	0.012*	0.04	0.82
EMG-BF													
Global score*	1.38	60	0.71	1.32	61	0.65	1.30	60	0.68	0.12	0.205	0.00	0.98
Inattention	1.68	63	0.72	1.60	64	0.68	1.58	63	0.71	0.13	0.230	0.00	1.00
Hyperactivity	1.02	63	0.85	0.99	64	0.77	0.99	63	0.78	0.04	0.557	-0.03	0.82
Impulsivity	1.31	63	0.95	1.26	64	0.90	1.20	63	0.90	0.13	0.075	0.05	0.56

*Note: ∗ Global score could not be assessed if more than two items in subscales were missing. [a] Within group analysis. *p<.05 **p<.01 ***p<.001.*

To assess long-term effects of learning on self-regulation we grouped participants into learners and non-learners based on the sign of their regression slope over sessions including the follow-up session for the feedback and transfer condition separately. For SCP-NF 63.5% of the participants were classified as learners for the feedback condition and 58.3% for the transfer condition. In the semi-active control group, 70.2% were classified as learners during the feedback condition and 80.7% for the transfer condition. Paired T-Tests for showed significant improvement of performance only during transfer trials between follow-up sessions and first training sessions for SCP-NF (t(42)=2.438, p=0.019) and EMG-BF (t(38)=4.650, p<0.0001). For details see Supplementary Figure 11.

Long-term clinical effects (follow-up minus pre) and self-regulation performance did not show any significant correlation for SCP-NF. For the semi-active control group we found significant correlations between linear performance increase and parent rating scale for ADHD global score ($r(48)=0.361$, $p=0.011$), inattention ($r(48)=0.302$, $p=0.0370$), and hyperactivity ($r(48)=0.367$, $p=0.010$) but no significant correlation with teacher ratings. As reported in our previous study (Strehl & Aggensteiner et al., 2017), no significant correlations between training performance and parent-rated ADHD global score were found at post-test 2. However, the analysis of ADHD core symptom subdomains revealed a significant correlation of improvement of performance until post-test 2 for SCP-NF with parent ($r(41)=0.401$, $p<0.009$) and teacher ratings ($r(36)=0.339$, $p=0.043$) for improvement of impulsivity and a trend for hyperactivity ($r(41)=0.256$, $p<0.0976$) rated by parents´. In the EMG-FB group, parent-rated hyperactivity correlated significantly negative ($r(41)= -0.391$, $p=0.036$) with improved performance. For details see Supplementary Table 20.

Conduct problems at baseline did not significantly impact the clinical ADHD symptom change at follow-up on the FBB global scale ($p=0.576$) or any subdomain rated by parents´ and teachers´ (all $p>0.1844$). Regarding the clinical effects on comorbidity measured by the SDQ, Wilcoxon signed rank test showed significant improvement at follow-up compared to pre-test rated by parents for SDQ total score ($U=922.0$, $z= -5.337$,$p<0.0001$), and the subdomain conduct problems ($U=843.5$, $z= 3.792$,$p<0.0001$), with no significant group differences. The other SDQ subdomains also improved (hyperactivity $U=471.0$, $z= -5.727$,$p<0.0001$, emotional problems, ($U=471.0$, $z= 5.727$,$p<0.0001$) and peer problems ($U=1.012$, $z= 3.642$,$p<0.0001$) except prosocial behavior ($U=1.474$, $z= -1.062$, $p=0.288$). Significant group differences emerged only for the subdomain peer-problems (in favor of SCP-NF: $U=1833.5$, $z= 2.617$, $p=0.009$). Significant correlations between self-regulation during the transfer condition and symptom reduction were found only in the SCP-NF group, and only for SDQ total score ($r_s(58)= -0.285$, $p=0.030$), peer problems ($r_s(58)= -.349$, $p=0.007$) and at trend level for CP ($r_s(58)= -0.255$, $p=0.052$) and hyperactivity ($r_s(58)= -0.247$, $p=0.061$).

2.2.5 Discussion

We studied the long-term effects of SCP-NF compared to a semi-active control condition. Our study showed that both treatments showed large improvements on ADHD core symptoms direct after treatment. Superior results for SCP-NF one month after treatment end, became non-significant at follow-up for the primary outcome rated by parents. However, the improvements seen at post-test 1 remained stable six months after treatment end for the SCP-NF, suggesting long-lasting effects. Interestingly, the semi-active control group showed a significant relapse during the medication washout from post-test 1 to post-test 2 with a significant recovery at follow-up, suggesting that these changes are driven by a medication effect. This finding might resemble the observation of Monastra and colleagues (Monastra, Monastra, & George, 2002), where only the control group deteriorated after medication washout. However, in our study, medication did not show such group-specific effects, and the significant time-by-medication interaction at follow-up did not interact with group. Since the clinical trajectories suggested that the medicated SCP-NF subgroup improved more, we also performed subgroup analyses of consistently medicated and unmedicated participants. However, these revealed no new NF-specific improvements, and did not change the finding with the entire sample. Nevertheless, age did significantly impact treatment outcome, suggesting that the long term effect of these intense treatments may benefit from the common symptom reduction with development (Biederman, Mick, & Faraone, 2000). Also, baseline severity remained significantly associated with improvement at follow-up, which may reflect continued regression to the mean or more room for improvement.

Regarding the clinical effects after SCP-NF, our results are in line with a recent meta-analysis (Doren et al., 2018), which analyzed sustained effects after NF in comparison with active and non-active control groups. This meta-analysis showed that superior clinical effects at follow-up for NF only holds true when it was compared with non-active control groups and showed similar effects compared with active conditions. Our study used a semi-active control group which might be considered as a more rigorous control condition compared to non-active control groups. This, together with the developmental effects and the possible influence of additional confounders, may explain the missing superiority of SCP-NF six months after treatment. A recent study from Geladé and colleagues (Geladé et al., 2017) showed that a significant advantage of medication over NF seen at post intervention disappeared at FU. These findings suggest that in other study designs, NF-specific improvements may appear only at FU. Concerning teacher ratings, no

differences between groups were found. However, within group analysis showed significant improvement in the SCP-NF group only, with small to medium effect sizes. Teachers may be less biased but also tend to be less sensitive (Minder, Zuberer, Brandeis, & Drechsler, 2018), although in a recent follow-up study (Geladé et al., 2017) teacher ratings indicated an advantage of NF over a non-active group, comparable to medication. Further, reductions of comorbidity symptoms measured by SDQ were significant and independent of groups, except for peer problems which improved more in the SCP-NF group.

Considering the association between self-regulation and clinical outcome, only very few SCP-NF studies followed this relationship in participants with ADHD after the end of NF treatment (Drechsler et al., 2007; Strehl et al., 2006). They related self-regulation outcome to impulsivity, inattention and hyperactivity at the end of treatment. We reported significant correlations between clinical improvement and self-regulation performance for both groups. The SCP-NF group showed at post-test 2 a significant correlation with self-regulation and symptom improvement for impulsivity and a trend for hyperactivity rated by parents and teachers, whereas the EMG-BF group showed a significant negative correlation for self-regulation and hyperactivity only. These outcomes might be interpreted as a specific effect of SCP-NF. However, at the follow-up six months after treatment, the EMG-BF group showed significant correlations between self-regulation performance and ADHD global score, attention and hyperactivity subdomain, which might be due to unspecific effects, such as the developmental course or regression to the mean. Interestingly, symptom change measured with SDQ at follow-up showed specific correlations between self-regulation and symptom improvement only for the SCP-NF group. Overall, after these unexpected and mixed outcomes, no firm conclusions can be drawn regarding specific and unspecific effects related to self-regulation for the follow-up outcomes after NF.

As limitation we may consider that our follow-up was not powered enough to disentangle specific from unspecific effects between groups six months after treatment. Additionally, our SCP-NF setup could be insufficient regarding the trained parameters (i.e. compared to other studies fewer training and particularly transfer trials) as well as the overall regulation performance during SCP-NF training. Our participants achieved a mean reinforcement rate of 44% for SCP-NF and 82% for EMG-BF. Still, these data are in line with the few published studies. Some SCP-NF studies (Baumeister et al., 2016; J. Takahashi, Yasumura, Nakagawa, & Inagaki, 2014) showed reinforcement rates around 40% or less, and similar good performance for the EMG-BF

(Baumeister et al., 2016; Maurizio et al., 2013), indicating as expected that EMG-regulation is easier to learn. The rather low regulation (percentage of correct trials) of SCP-NF might be an important factor and potentially explain the absence of group differences at follow-up for the primary outcome and teacher ratings, as well as the modest relationship between self-regulation and clinical improvement. Self-regulation is known as an important unspecific variable contributing to the clinical outcome in biofeedback treatments. Therefore, the substantial lower reward rates for SCP-NF compared to EMG-BF as in this study may have interfered with the specific effects. Future studies should ensure enough learning and address the question why participants do show low regulation performance.

In conclusion, the superiority of SCP-NF over the semi-active control group, which was reported in our previous paper, became non-significant six months after treatment end but only the semi-active control group showed a relapse one month after treatment. This study adds important outcomes regarding the specificity of SCP-NF and the possible influence of unspecific variables on long-term treatment outcome.

2.2.6 Supplementary Materials

Table 15. Parent ratings (Hyperactivity); Follow-up minus Post 2 between groups; mITT. BOCF;

	Adjusted mean (95% CI)	**p**	**F**	**df**
EMG-BF	-0.169 (-0.279/-0.059)			
SCP-NF	0.027(-0.079 / 0.134)			
Difference between treatments	0.197 (-0.352 / -0.042)			
Treatment		0.013	6.302	1
Baseline ADHD global score		0.238	1.406	1
Sex		0.229	1.460	1
Trial site		0.484	0.494	4
Age		0.044	4.136	1
ADHD medication at PRE (yes/no)		0.953	0.004	1
Parenting style (mean)		0.886	0.021	1

ANCOVA. df=degree(s) of freedom

Table 16. Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	182.95	70.25	<0.0001
Group	1	182.91	1.12	0.291
Time	3	73.01	24.26	<0.0001
Group * Time	3	73.05	4.20	0.0084
Site	4	182.87	1.28	0.279
Age	1	194.89	6.97	0.0089
Parents´expectation	1	173.73	1.16	0.283
Parenting style	1	186.51	0.23	0.633
Gender	1	174.30	3.35	0.069
Medication at Pre Yes/No	1	184.57	0.00	0.961
Bseline ADHD global score	1	187.22	135.47	<0.0001

a. Dependent Variable: ADHD global score

Table 17. Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	196.281	8.521	0.0046
Group	1	197.030	0.782	0.378
Time	3	58.773	6.257	0.001
Medication at follow-up Yes/No	1	196.981	0.120	0.730
Site	4	149.677	1.811	0.130
Bseline ADHD global score	1	148.437	692.502	<0.0001
Age	1	148.972	13.166	<0.0001
ErwartungenderElternMittelwert	1	148.421	3.390	0.068
Parenting style	1	148.650	0.000	0.9898
Gender	1	147.457	3.490	0.064
Group * Time	3	59.313	4.554	0.006
Group * Medication at follow-up	1	149.740	0.048	0.826
Time * Medication at follow-up	3	59.262	2.801	0.048
Group * Time * Medication at follow-up	3	58.135	0.324	0.808

a. Dependent Variable: ADHD global score

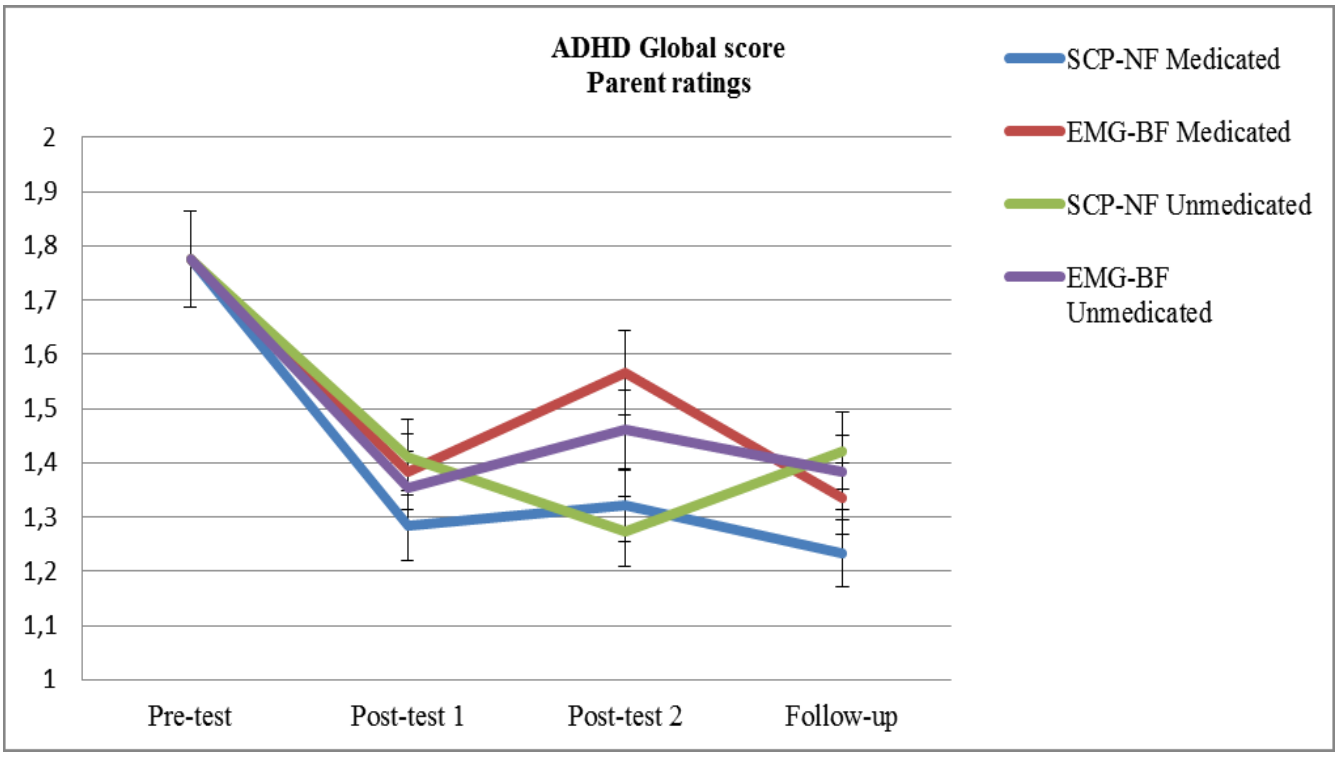

Figure 10**.** ADHD Global score rated by parents. Significant interaction for time-by-medication *(F(3.2.858), p=0.0453*), but not for time-by-group-by-medication (*F(3.0.365), p=0.7785*) emerged. The post hoc tests indicated that only medicated participants showed a significant recovery from post-test 2 to follow-up *(time difference: 0.16 95% CI -0.321 to -0.001, p=0.0482)*, while unmedicated participants showed a stable improvement after post-test 1.

Table 18. Medicated participants at each assessment point

	SCP-NF		EMG-BF		Statistics
	Yes	No	Yes	No	
Pre	34	39	28	41	
	46.6%	53.4%	40.6%	59.4%	X^2 p=.502
Post 1	27	39	23	34	
	40.9%	59.1%	34.8%	51.5%	X^2 p=1.00
Post 2	28	34	23	32	
	45.2%	54.8%	37.1%	51.6%	X^2 p=.712
FU	27	27	22	26	
	50.0%	50.0%	40.7%	48.1%	X^2 p=.694
Medication change	On	Off	On	Off	
On/off Pre - Post 1	1	2	2	1	
	1.4%	2.7%	2.9%	1.4%	
On/off Pre - Post 2	4	2	4	3	
	5.5%	2.7%	5.8%	4.3%	
On/off Pre to FU	5	0	4	3	
	6.8%	0.0%	5.8%	4.3%	
Total	10	4	10	7	

Note: Proportion of medicated participants at each time point where data was available.

Table 19. Teacher ratings; Global score: Follow-up minus Post 2 between groups; mITT. BOCF; ANCOVA. df=degree(s) of freedom

	Adjusted mean (95% CI)	**p**	**F**	**df**
EMG	0.058 (-0.088/0.203)			
SCP-NF	-0.032 (-0.168 / 0.104)			
Difference between treatments	-0.090 (-0.282 / 0.102)			
Treatment		0.3559	0.859	1
Baseline ADHD global score		0.3470	0.892	1
Sex		0.2177	1.536	1
Trial site		0.4931	0.855	4
Age		0.6428	0.0216	1
ADHD medication at PRE (yes/no)		0.8565	0.033	1
Parenting style (mean)		0.9916	0.000	1
Parents' expectations (mean)		0.1430	2.175	1

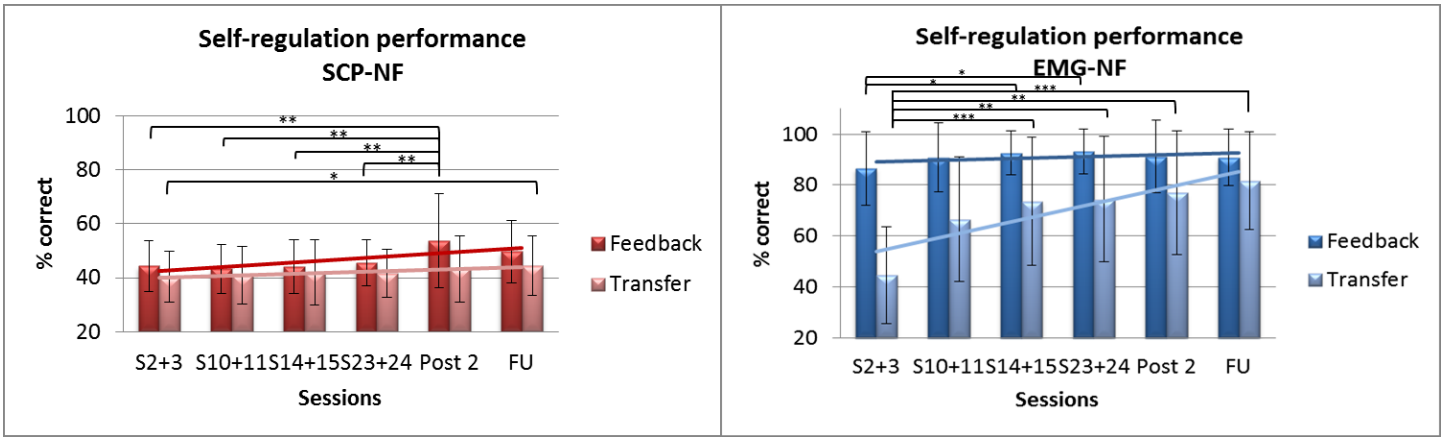

Figure 11. Self-regulation performance

Data partly published in Strehl et al., 2017. ***p<.001 **p<.01 *p<.05.

Table 20. Correlation matrix. Performance and clinical change. Follow-up minus Pre

GROUP			Parent ratings (Follow-up minus Pre)				Teacher ratings (Follow-up minus Pre)			
			FBB Global scale	FBB Inatten-tion	FBB Hyperac-tivity	FBB Impul-sivity	FBB Global scale	FBB Inatten-tion	FBB Hyperac-tivity	FBB Impul-sivity
SCP-NF	FB	Pearson Correlation	0.112	-0.008	0.137	0.207	0.104	-0.016	0.206	0.065
		Sig. (2-tailed)	0.4236	0.9545	0.3285	0.1371	0.5249	0.9218	0.2017	0.6887
		N	53	53	53	53	40	40	40	40
	TF	Pearson Correlation	0.029	-0.067	0.080	0.090	-0.003	0.176	-0.020	-0.290
		Sig. (2-tailed)	0.8394	0.6357	0.5673	0.5223	0.9862	0.2771	0.9022	0.0698
		N	53	53	53	53	40	40	40	40
	FB + TF	Pearson Correlation	0.083	-0.045	0.128	0.175	0.056	0.104	0.102	-0.149
		Sig. (2-tailed)	0.5546	0.7515	0.3592	0.2092	0.7320	0.5244	0.5307	0.3594
		N	53	53	53	53	40	40	40	40
EMG-BF	FB	Pearson Correlation	0.361*	0.302*	0.367*	0.260	0.170	0.301	-0.025	0.056
		Sig. (2-tailed)	0.0117	0.0371	0.0104	0.0740	0.3683	0.1057	0.8973	0.7684
		N	48	48	48	48	30	30	30	30
	TF	Pearson Correlation	-0.246	-0.172	-0.257	-0.234	-0.152	-0.209	-0.101	-0.011
		Sig. (2-tailed)	0.0913	0.2414	0.0774	0.1088	0.4220	0.2666	0.5946	0.9546
		N	48	48	48	48	30	30	30	30
	FB + TF	Pearson Correlation	-0.031	0.003	-0.037	-0.070	-0.033	-0.006	-0.101	0.023
		Sig. (2-tailed)	0.8365	0.9835	0.8027	0.6357	0.8641	0.9729	0.5964	0.9045
		N	48	48	48	48	30	30	30	30

*Note: FB=Slope of feedback run. TF=Slope of transfer run. FB+TF=Mean slope of FB & TF. **p<.01.*p<.05. °p<.01*

Correlation matrix. Performance and clinical change. Post-test 2 minus Pre

GROUP			Parent ratings (Post-test 2 minus Pre) FBB Global scale	FBB Inatten-tion	FBB Hyperac-tivity	FBB Impul-sivity	Teacher ratings (Post-test 2 minus Pre) FBB Global scale	FBB Inatten-tion	FBB Hyperac-tivity	FBB Impul-sivity
SCP-NF	BF	Pearson Correlation	0.144	-0.055	0.256	0.256	-0.084	-0.024	0.024	0.199
		Sig. (2-tailed)	0.356	0.728	0.097	0.098	0.630	0.890	0.891	0.246
		N	41	41	41	41	35	36	36	36
	TF	Pearson Correlation	0.196	-0.016	0.257	.401**	-0.002	-0.013	0.009	-0.102
		Sig. (2-tailed)	0.218	0.919	0.105	0.009	0.990	0.940	0.960	0.561
		N	41	41	41	41	35	36	36	36
	FB + TF	Pearson Correlation	0.090	-0.034	0.155	0.171	-0.140	0.095	-0.023	.339*
		Sig. (2-tailed)	0.567	0.828	0.320	0.274	0.421	0.582	0.895	0.043
		N	41	41	41	41	35	36	36	36
EMG-BF	FB	Pearson Correlation	-0.066	0.087	-0.140	-0.153	-0.167	0.248	0.027	0.132
		Sig. (2-tailed)	0.703	0.614	0.417	0.373	0.378	0.178	0.885	0.481
		N	36	36	36	36	31	31	31	31
	TF	Pearson Correlation	0.178	0.211	0.231	-0.135	0.043	0.137	-0.199	-0.026
		Sig. (2-tailed)	0.300	0.217	0.174	0.432	0.822	0.462	0.284	0.891
		N	36	36	36	36	31	31	31	31
	FB+TF	Pearson Correlation	-0.141	0.067	-.355*	-0.010	-0.185	0.202	0.068	0.224
		Sig. (2-tailed)	0.413	0.699	0.034	0.956	0.328	0.276	0.717	0.225
		N	36	36	36	36	31	31	31	31

*Note: FB=Slope of feedback run. TF=Slope of transfer run. FB+TF=Mean slope of FB & TF. **p<.01.*p<.05. °p<.01*

2.3 Study 3: The role of callous-unemotional traits and aggression subtypes on amygdala activity in response to negative faces

Submitted as: Aggensteiner, Pascal-M., Holz, NE., Böttinger, B., Baumeister, B. Hohmann, S., Werhahn, J.E., Naaijen, J., et al. "The role of callous-unemotional traits and aggression subtypes on amygdala activity in response to negative faces" *(Submitted)*.

2.3.1 Abstract

Background: Brain imaging studies have shown altered amygdala activity during emotion processing in children and adolescents with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) compared to typically developing children and adolescents (TD). Here we aimed to assess whether aggression-related subtypes (reactive and proactive aggression) and callous-unemotional (CU) traits predicted variation in amygdala activity and skin conductance (SC) response during emotion processing.

Methods: We included 177 participants (n=108 cases with disruptive behavior and/or ODD/CD and n= 69 TD), aged 8-18 years, across nine sites in Europe, as part of the EU Aggressotype and MATRICS projects. All participants performed an emotional face-matching fMRI task. Differences between cases and TD in affective processing, as well as specificity of activation patterns for aggression subtypes and CU traits, were assessed. Simultaneous SC recordings were acquired in a subsample (n=63).

Results: Cases compared to TDs showed higher amygdala activity in response to negative faces versus shapes. Subtyping cases according to aggression-related subtypes did not significantly influence on amygdala activity; while stratification based on CU traits was more sensitive and revealed decreased amygdala activity in the high CU group. SC responses were significantly lower in cases and negatively correlated with CU traits and aggression-related subtypes.

Conclusions: Our results showed distinct amygdala activity and SC responses to emotional faces between cases with ODD/CD and TD, while CU traits moderate both central (amygdala) and peripheral (SC) responses. Our insights regarding subtypes and trait specific aggression could be used for personalized diagnostics and treatment.

2.3.2 Introduction

Oppositional defiant disorder (ODD) and conduct disorder (CD) are disruptive behaviour disorders which are, with a prevalence rate ranging from 2 to 4% (Polanczyk et al., 2015), amongst one of the most commonly diagnosed mental health disorders in youth (Loeber, Burke, Lahey, Winters, & Zera, 2000). ODD is characterized by a frequent and persistent pattern of irritable and angry mood, vindictiveness, and inappropriate, negativistic, defiant, and disobedient behavior toward authorities, while CD is defined as a repetitive and persistent pattern of behavior, which violates the rights of others and major age-appropriate societal rules (American Psychiatric Association, 2013). The clinical representation of ODD/CD is heterogeneous, with distinct subtypes of aggression, and high comorbidity rates with ADHD and internalizing symptoms. Moreover, current research suggests that callous-unemotional (CU) traits, which include reduced guilt, callousness, uncaring behavior, and reduced empathy, contribute to this heterogeneity (Blair, Leibenluft, & Pine, 2014; Frick & Viding, 2009). On this basis, CU traits have been added to the fifth edition of the DSM (DSM-5) as a specifier for the diagnosis of CD called "limited prosocial emotions". Additionally, two different distinctions in reactive (RA) and proactive (PA) aggression is often made to subtype aggressive behavior (Raine et al., 2006). RA is associated with impulsive, high arousal or affective aggression whereas PA refers to goal-directed, planned behavior associated with reduced arousal and higher levels of CU traits (Blair et al., 2014).

Recent brain imaging findings have provided insights into the underlying neural mechanisms of these aggression-related disorders. Different neural activity patterns of the amygdala in children with ODD/CD compared to TD children in response to negative (i.e. angry or fearful) face stimuli has been shown (Jones, Laurens, Herba, Barker, & Viding, 2009; Viding, Sebastian, et al., 2012), suggesting impaired recognition of other's facial expressions (Blair, 2013; Veroude et al., 2016). However, previous studies have yielded inconsistent findings showing evidence of both hypo-and hyperactivity of the amygdala to affective stimuli (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Herpertz et al., 2005; Passamonti et al., 2010). This is consistent with the heterogeneity within aggression-related disorders. Two main theories might explain these divergent findings. The threat sensitivity theory which describes an over-activation of limbic areas (i.e. amygdala) and is presumably associated with higher forms of RA, and the deficient empathy theory, which is associated with reduced activity and more PA and higher CU traits (Blair et al., 2014). Nevertheless, the previously mentioned studies did not take subtypes of aggression, and the level of CU traits into account. Studies that have considered the influence of CU traits have revealed hypo-activity in youth

with high CU traits (CU+) and hyper-activity in the amygdala in children with low CU traits (CU-) (Baker, Clanton, Rogers, & Brito, 2015; Blair, Veroude, & Buitelaar, 2016; Viding, Fontaine, & McCrory, 2012). Moreover, altered amygdala responses, particularly to fearful expressions, showed to be independent of comorbidities, such as ADHD (Hyde et al., 2016; Marsh et al., 2008; Posner et al., 2011). Nevertheless, several recent studies did not find any significant influence of CU traits on amygdala activity to negative stimuli (Dotterer, Hyde, Swartz, Hariri, & Williamson, 2017; Ewbank et al., 2018; Hyde et al., 2016).

Heterogeneous findings on the psychophysiological level [i.e. skin conductance response (SCR)] might also be explained by aggression-related subtypes. Physiological hypo-arousal is observed in children with CU+ traits (Fanti, 2016), whereas RA is most commonly associated with hyper-arousal, and increased internalizing symptoms (Gao, Tuvblad, Schell, Baker, & Raine, 2015; Scarpa, Haden, & Tanaka, 2010). Further, reduced SC (i.e. during resting state) has been found in ODD/CD (Lorber, 2004; Van Goozen, Matths, Cohen-Kettenis, Buitelaar, & Van England, 2000).

Our study aimed to evaluate if accounting for aggression-related subtypes or CU traits in children and adolescents with high aggression, can disentangle the heterogeneity of amygdala responses and SCR to negative face stimuli into more consistent patterns, and to compare these responses in participants with ODD/CD to those in a large sample of TD children.

2.3.3 Materials and Methods

2.3.3.1 Participants

Participants in the current study were part of both the EU-Aggressotype and EU-MATRICS projects. In total 208 participants aged 8-18 years were assessed using a functional magnetic resonance imaging (fMRI) across nine sites in Europe. The measures used here were part of a larger test battery including questionnaires, neuropsychological testing, MR scanning and genotyping. Exclusion criteria for all participants 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 (Wechsler, D, 2003) and a primary DSM-5 diagnosis of psychosis, bipolar disorder, major depression and/or an anxiety disorder. Participants who were included as “Cases” were diagnosed with ODD and/or CD based on the structured diagnostic interviews with child and parents using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997) according to DSM-5, or scored above the clinical cut-off for aggressive behavior and/or rule-

breaking behavior as measured with the Child Behavior Checklist completed by parents, teachers or youths (CBCL/TRF/YSR; (Achenbach, Howell, Quay, Conners, & Bates, 1991). In the typically developing comparison group, no DSM axis I disorder, assessed via the K-SADS, and no clinical score in the CBCL, TRF or YSR was allowed. For cases, medication had to be stable for at least two weeks prior to inclusion The parent-rated Inventory of Callous-Unemotional Traits (ICU) (Essau, Sasagawa, & Frick, 2006) and the self-reported Reactive-Proactive Aggression Questionnaire (RPQ) (Raine et al., 2006) were used to subtype aggressive behavior. ADHD symptoms were measured with the parent-rated SNAP-IV questionnaire (Bussing et al., 2008). Ethical approval for the study was obtained for all sites separately by local ethics committees. Written informed consent was given by the participants and their parents or legal representatives.

2.3.3.2 fMRI task

Participants performed a modified version of the emotional face-matching task (Hariri, Bookheimer, & Mazziotta, 2000). In this task, participants completed four blocks of a perceptual face-matching task in which they had to match the presented emotions. 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 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). Interleaved between these blocks, participants completed two blocks of a sensorimotor control task with geometric shapes (horizontal ellipses or vertical ellipses) (for details see Figure 12).

Figure 12. Modified version of the emotional face-matching task.

In this task, participants completed four blocks of a perceptual face-matching task, in which they had to match the presented emotion of the upper face to that of the bottom faces (Fear & Angry and Happy & Neutral). In addition, participants completed two blocks of a sensorimotor control task, during which a set of geometric shapes was presented. Each of the pictures was presented for 4.8s, for a total block length of 28.8s. The total paradigm lasted 231s.

2.3.3.3 Skin conductance recording and pre-processing

Skin conductance response (SCR) was recorded simultaneously with fMRI data in three sites, using a pair of Ag/AGCI electrodes applying an electrode paste with 0.5% saline (TD-246 Skin Resistance–Skin Conductance Electrode Paste, Discount Disposables, Vermont, USA) placed on the distal phalanges of digits I and II on the non-dominant hand. Brain products amplifier and MR-capable sensors were used (Brain Products GmbH Gilching,Germany). Data were downsampled to 10 Hz and analyzed in Ledalab (Version 3.4.9; www.ledalab.de) applying the continuous decomposition analysis (CDA) and we extracted the time integral of the SCR (ISCR) (Benedek & Kaernbach, 2010) for further analysis.

2.3.3.4 Image acquisition and pre-processing

MRI scans were performed in nine different sites across Europe (see Supplemental Table 23 for site and scanner details). Whole-brain data were acquired with echo-planar T2*-weighted imaging (EPI), sensitive to the Blood Oxygenation Level Dependent (BOLD) signal contrast [36 axial slices (except for one site with 39 slices), 3 mm thickness; repetition time 2100 ms; echo time 35 ms; voxel size: 3×3×3 mm, Flipangle 74°; FOV=192mm]. Data were analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm/). The first five volumes were discarded to allow longitudinal magnetization to reach equilibrium. A high-resolution structural magnetization-prepared rapid gradient echo (MP-RAGE) scan was also acquired at a resolution of 1×1×1.2 mm. EPIs were interpolated in time to correct for slice time differences and realigned to the first scan to correct for head movements. EPIs were co-registered and normalized to the T1 standard 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 3 mm.

2.3.3.5 Statistical analysis

2.3.3.5.1 Analysis of demographic and behavioral data

Group differences in demographic variables were analyzed using analysis of variance (ANOVA) or Chi-square tests, when appropriate. Further, behavioral performance data of the face-matching task were assessed by repeated measures ANOVA with experimental condition (negative faces vs. shapes) as the within-subject factor and a between factor of group. Behavioral data were corrected using age, IQ, medication, sex as covariates of non-interest.

2.3.3.5.2 fMRI Analysis

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 experimental conditions (negative and positive faces and shapes), instructions and 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 an autoregressive [AR(1)] correction for serial correlations was applied.

Contrast images for the comparisons of negative faces vs shapes and positive faces vs shapes were generated. Since we expected largest effects in the negative faces vs shapes condition, we concentrated on the respective contrast. Exploratory analyses of the positive faces vs shapes and negative vs positive faces are reported in the supplementary material. The task effect was assessed by means of a one-sample T-test and group differences by a two-sample T-test controlling for age, sex, IQ, medication, and site. For group comparisons, several brain regions, including amygdala, insula, OFC and ACC were defined as region of interest (ROI) thresholded at a corrected FWE $<.05$ level and corrected for each ROI analysis ($0.05/4=0.0125$). Further, the influence of subtypes of aggression was analyzed applying a regression analysis including continuous measurements of RA and PA, separately. Additionally, the influence of the CU traits was analyzed by a regression analysis coding groups as 1 CU+, 2 TDs, and 3 CU-. Participants for the CU+ group were selected based on the ICU means previously published (Lozier, Cardinale, VanMeter, & Marsh, 2014; Sebastian et al., 2014; Viding, Fontaine, et al., 2012). To obtain a reliable subgroup with CU+ traits in our sample, participants had to score ≥38, which represents 27.7% (n=30) of the cases sample.

Brain regions were defined with the Talairach Daemon atlas implemented in the Wake Forest University (WFU) PickAtlas (Lancaster et al., 2000) using the atlas for automated anatomical labeling (Tzourio-Mazoyer et al., 2002). Whole brain analyses are reported at an uncorrected $p<.001$ level for clusters including at least 10 voxels.

Finally, to account for possible influences of ADHD, we repeated the main analysis adding parent-rated ADHD (continuous variable measured with the SNAP-IV questionnaire. Sensitivity analyses were performed to rule out more confounding variables, such as site, medication, and sex. Additionally, we matched both groups for IQ and age and repeated the main analyses. Participants were randomly selected using MedCalc Software 18.9 (MedCalc Software, Mariakerke, Belgium)

2.3.3.5.3 Analysis of skin conductance response (SCR)

In analogy to the behavioral data, SCR data were analyzed by repeated measures ANOVA with within-subject factors experimental condition (negative faces, and shapes), and a between-subjects factor of group. Additionally, the relation between SCR, RPQ and ICU total score were investigated with Pearson's correlations. SCRs were defined as responses between 0.9 and 4 seconds after stimulus presentation that needed to exceed 0.01μS (Boucsein et al., 2012). The SCR amplitude was log-transformed by means of 1+ logSCR to obtain normally distributed data.

2.3.4 Results

2.3.4.1 Sample characteristics

Table 21 shows the sample characteristics. From the 208 participants available for fMRI analysis; 31 participants were excluded due to excessive motion. Finally, 177 participants were included for analysis, 69 TDs and 108 cases (43 [39.8%] with ODD, 10 [9.2%] with CD alone, 19 [17.6%] with both diagnoses and 36 [33.3%] with a CBCL T-value >70 in aggression or rule-breaking behavior. Compared to TDs, the cases group consisted of more males (p<.001) lower IQ (p<.001), and did differ marginally with regard to age (p=.078).

Table 21. Characteristics of the participants included in the functional magnetic resonance imaging analysis

	Cases (n=108)		Control (n=69)		ANOVA
	Mean	Std. Deviation	Mean	Std. Deviation	p-values
Age	13.19	2.69	13.91	2.59	0.078
Sex(m)	82.4%(m)		58.0%(m)		Chi ^{2}<0.001
IQ	99.28	10.62	107.44	10.69	<0.001
CBCL T-score Aggression	74.45	9.99	52.14	3.58	<0.001
CBCL T-score Rule breaking	67.05	9.05	52.03	3.66	<0.001
ICU total	32.99	10.02	20.45	7.73	<0.001
RPQ reactive[b]	12.40	4.73	5.85	3.54	<0.001
RPQ proactive[b]	4.71	4.69	0.88	1.45	<0.001
RPQ total[b]	17.11	8.33	6.73	4.42	<0.001
SNAP IV[c]	31.14	12.15	5.93	6.62	<0.001
Medication (%)	60.20%	-	-	-	-
Stimulants	60.00%	-	-	-	-
Antipsychotics	30.76%	-	-	-	-
Antidepressants	4.61%	-	-	-	-
Other	4.61%	-	-	-	-

Note: *CBCL, Child Behavior Checklist; CD, conduct disorder; ICU, Inventory of Callous-Unemotional Traits; RPQ, Reactive proactive Questionnaire; SANP –IV, ADHD total score; m, male; SD, standard deviation;* [a] *IQ estimated from a subset of the Wechsler Intelligence Scale for Children III;* [b] *For cases n= 98;* [c] *For cases n= 81; TD= Typically developing peers.*

2.3.4.2 Behavioral data

Repeated-measures ANOVA for accuracy of correct emotional matching showed only a trend for significance between groups [F(1,171)=2.826, p=.095]. Cases showed overall less accuracy compared to TDs. As expected, older participants showed a higher accuracy regardless of condition (p=.015). All other covariates were not significant. In a further exploratory RM-ANOVA with a within condition factor for further separating emotions into angry, fearful, happy, and neutral faces and shapes, the interaction term condition x group was significant [F(4,684)=2.805, p=.026]. Post-hoc tests revealed that the cases made more mistakes than TD in matching fear (0.018) or neutral faces (<0.001). Regarding reaction times, no significant group differences were found [F(1,171)=1.118, p=.292] but a trend for a condition x group interaction effect [F(1,171)=2.775, p=.098] was found (for details see Supplemental Table 24).

2.3.4.3 fMRI task effects

As reported in prior research using the emotional face-matching task, whole-brain analysis of main effects showed robust activation of the amygdala, fusiform area, inferior occipital area, and precuneus, when comparing negative faces with shapes (Figure 13; for brain activity during the other contrasts see Supplemental Table 25).

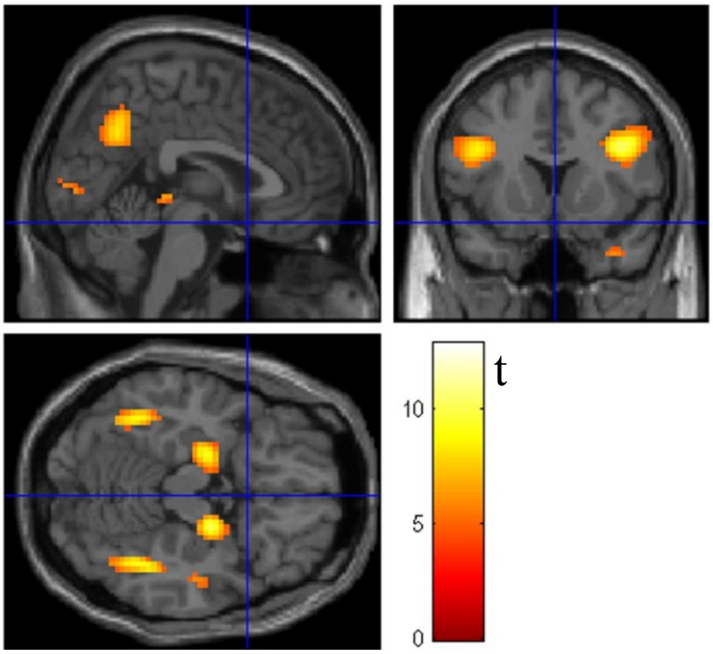

Figure 13. Whole brain analysis of main effects showed robust activation of the amygdala, fusiform area, inferior occipital area, and precuneus when comparing negative faces vs shapes. Whole-brain pfwe-corrected corrected at p<.05.

2.3.4.4 Group comparisons (Cases versus TDs) for negative faces vs shapes

Figure 14 shows the group comparisons for the amygdala ROI using a t-test, which revealed that cases had higher left amygdala activity compared to TDs [t(165)=3.61, $p_{fwe\text{-}corrected}$=.008, k=7; x= -27,y= -4, z= -13]. No other effects were found in the ROIs. Group effects on a whole-brain level are depicted in Supplemental Table 26. For positive faces vs shapes see Supplemental Table 27

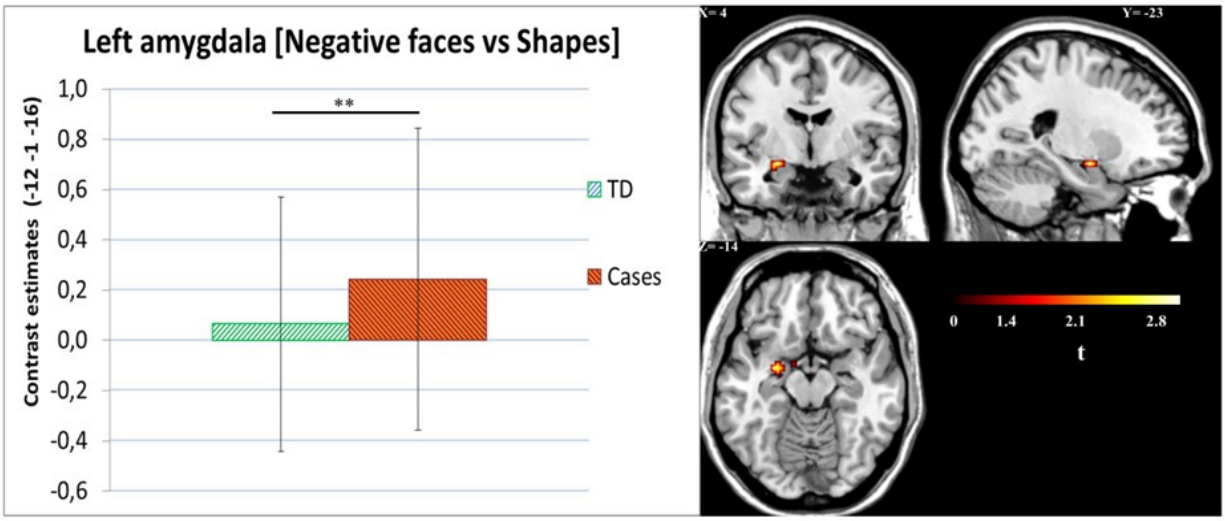

Figure 14. Left amygdala activity for ODD/CD vs TD group. ODD/CD group showed higher amygdala activity [t(165)=3.61, pfwe-corrected p=.008, k=7; MNI -27;-4;-13].Cases = ODD/CD: Oppositional defiant disorder, CD = Conduct disorder, TD= Typically developing peers.

2.3.4.5 Effects of reactive and proactive aggression subtypes

RPQ measured as a continuous variable did not show any significant association with any analyzed ROIs. Only at a trend level a negative relationship with the proactive subscale for the left amygdala [t(85)=2.37, $p_{\text{fwe-corrected}}$=.091, K=1, x= -12,y=-1, z=-16] were found in cases only. At whole brain level for both groups (at an uncorrected level) a positive relationship with the right fusiform area [t(150)=4.10, $_{\text{puncor}}$<.001, K=15, x= -42,y=-34, z=-16].

2.3.4.6 Effects of CU traits

In total, 167 participants were available with complete CU traits data, resulting in 30 cases CU+ group, 64 TDs, and 73 cases CU- group. Interestingly, CU+ participants were significantly older than the CU- subgroup, and showed significantly higher scores for proactive aggression (p<.001), but not for reactive aggression. For more details see Table 22.

Table 22. Characteristics of the participants included in the regression analysis

	CU -			TD			CU +			ANOVA	Post-hoc
	n	Mean	SD	n	Mean	SD	n	Mean	SD	p-values	
Age	72	12.75	2.64	64	13.93	2.54	30	13.91	2.77	0.019	CU - < TD = CU +
Sex(m)	72	84.9%		64	56.30%		30	83.30%		Chi ^{2}<0.001	TD < CU - = CU +
Medication (%)	72	53.4%		64	0.00%		30	63.30%		Chi ^{2}<0.001	TD < CU - = CU +
IQ	72	99.71	9.99	64	107.81	10.87	30	99.61	12.10	<0.001	CU - = CU + < TD
CBCL T-score Rule breaking	72	64.92	8.79	64	52.09	3.74	30	72.84	7.52	<0.001	TD < CU - <CU +
CBCL T-score Aggression	72	73.72	10.65	64	52.22	3.65	30	76.83	7.97	<0.001	TD < CU - = CU +
ICU total	72	27.89	5.96	64	20.45	7.73	30	45.23	6.55	<0.001	TD < CU - < CU +
RPQ reactive	69	12.24	4.50	63	5.83	3.55	29	13.10	5.05	<0.001	TD < CU - = CU +
RPQ proactive	69	3.59	3.90	63	0.90	1.48	29	7.45	5.56	<0.001	TD < CU - < CU +
RPQ total	69	15.82	7.24	63	6.73	4.47	29	20.55	9.68	<0.001	TD < CU - < CU +
SNAP -IV	58	28.80	10.87	61	5.92	6.75	23	38.74	12.41	<0.001	TD < CU - < CU +
Medication (%)		52.0%						63.3%		ns	CU - = CU +
Stimulants		73.6%						47.3%		Chi ^{2} = 0.040	CU - > CU +
Antipsychotics		31.5%						36.8%		ns	CU - = CU +
Antidepressants		5.2%						5.2%		ns	CU - = CU +
Other		2.6%						10.5%		ns	CU - = CU +

Note: *CBCL, Child Behavior Checklist; ICU, Inventory of Callous-Unemotional Traits; RPQ, Reactive proactive Questionnaire; SANP –IV, ADHD total score; SD, standard deviation;* [a] *IQ estimated from a subset of the Wechsler Intelligence Scale for Children III;, CU - = Low ICU, CU += High ICU, TD= Typically developing peers.*

Regression analysis showed a significant association with left amygdala activity [t(153)=3.27, $p_{fwe\text{-}corrected}$=.012, K=3,x=-12,y=-1, z=-16]. The CU+ group showed lower amygdala activity for negative faces versus shapes, whereas the CU- group showed higher activity compared to the CU+ and TD (Figure 15). The whole-brain analysis is depicted in Supplemental Table 28. For the positive faces versus shapes contrast, no significant group difference or an association with CU traits was found.

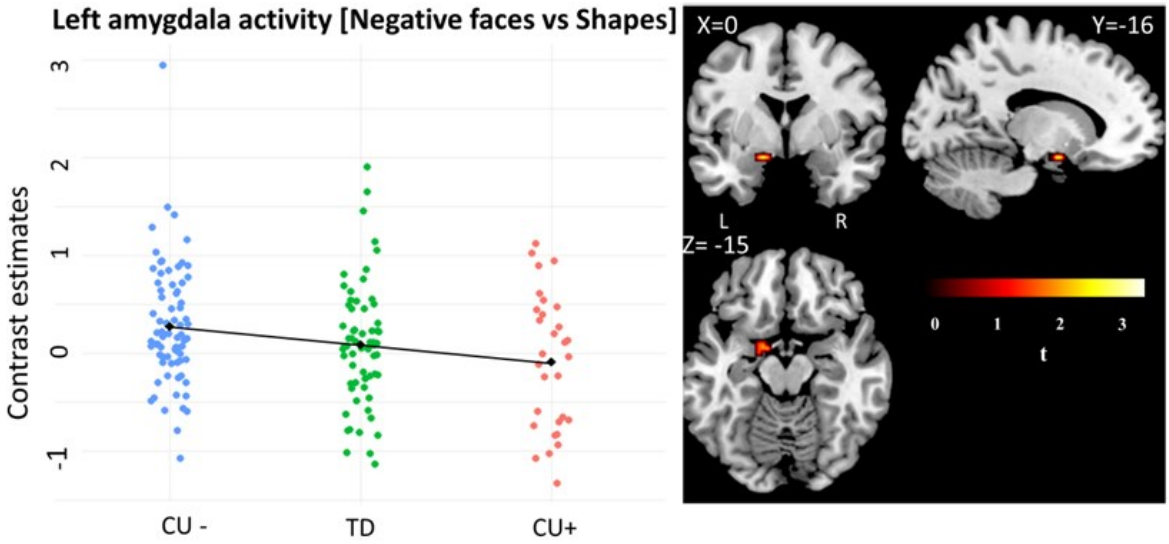

Figure 15. Group-specific amygdala activity for negative vs shapes contrast depending on the CU subtypes [t(153)=3.27, $p_{fwe\text{-}corrected}$ =.012, K=3,x=-12,y=-1, z=-16]. CU + = High callous-unemotional traits, TD= Typically developing peers, CU - = Low callous-unemotional traits.

2.3.4.7 Sensitivity analyses

2.3.4.7.1 ADHD as a covariate

To control for potential influences of ADHD symptoms, we added the SNAP IV as a covariate. In total, 158 participants were available with complete ADHD symptom data. The inclusion of this covariate further strengthened the results with higher amygdala activation in cases [left amygdala t(143)=3.63, $p_{fwe\text{-}corrected}$=.008, k=16; x= -24, y= -4, z= -13; right amygdala t(143)=3.35, $p_{fwe\text{-}corrected}$=.018, k=16;x= 27,y= -4, z= -13]. The whole-brain analysis is shown in Supplemental Table 29.

2.3.4.7.2 Analysis in non-medicated participants

Use of medication was related to amygdala activity [F(1,164)=7.814, p=.006], with higher amygdala activity during the negative versus shapes contrast in non-medicated participants [t(164)=3.32, $p_{\text{fwe-corrected}}$ p=.010, k=8, x=-15, y=2, z=-16]. Likewise, the main result of higher amygdala activity in patients remained unchanged, when only non-medicated participants were included in the analysis [t(100)=3.40, $p_{\text{fwe-corrected}}$=.008, k=16, x= -24,y=-4, z=-13; for whole-brain analyses see Supplemental Table 30].

2.3.4.7.3 Site, age, and sex effects

There was a significant effect of site on amygdala activity [F(8,164)=2.259, p=.026]. Nevertheless, when excluding four sites with fewer than 5 participants per group, and no effect of site remained [F(8,131)=1.159, p=.181], the results did not change [t(131)=3.53, $p_{\text{fwe-corrected}}$=.011, k=19, x=-24, y=-4, z=-13]. In addition, there was no significant effect of age and sex. For details, see Supplemental Table 31 and Table 32.

2.3.4.8 Skin conductance

Simultaneous fMRI and skin conductance data were available for 38 cases and 26 TDs. A significant interaction between experimental condition and group was found [F(1,62)=5.352, p=.024]. In the cases group, a lower skin conductance response to negative facial stimuli (p=.002), but not to shapes (p=.252) was seen compared to TDs. The total score on the ICU scale was negatively associated with SCR for negative faces (r=-.393, p=.001) and shapes (r=-.295, p=.019) (Figure 16). Additionally, significant correlations between RA (r=-.293, p=.020), PA aggression (r=-.277, p=.028) and RPQ total scale (r=-.320, p=.010) were found for SCR of negative faces only.

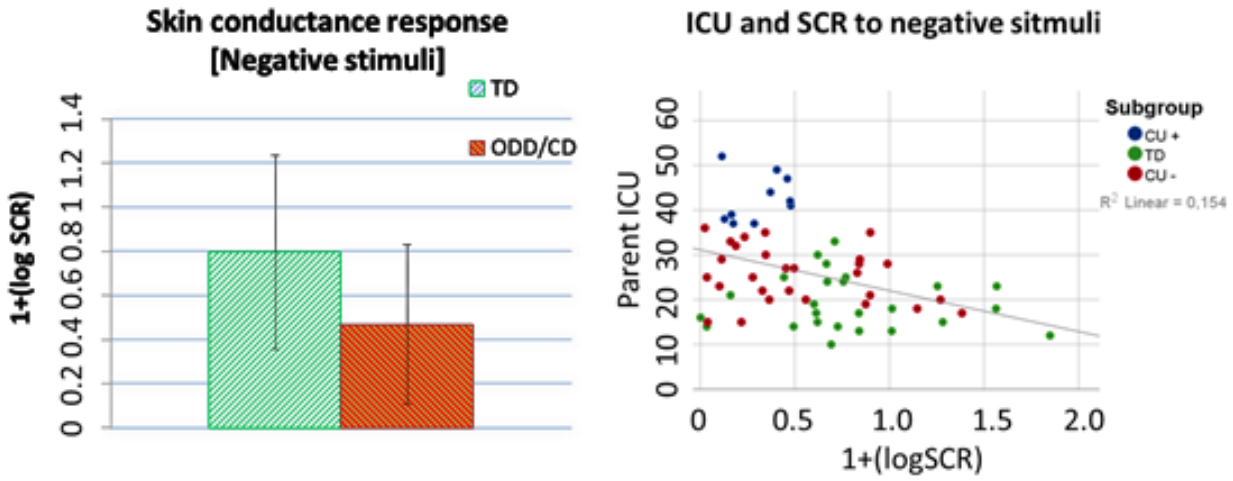

Figure 16. Skin conductance response activity to negative faces. ICU was negatively associated with SCR and the CU – subgroup showed less SCR response ODD/CD: Oppositional defiant disorder, CD = Conduct disorder, TD= Typically developing peers, CU + = High callous-unemotional traits, CU - = Low callous-unemotional traits. ICU=Inventory of callous-unemotional traits. *p<.05.

2.3.5 Discussion

Our study addressed the neural characterization of aggression-related subtypes and CU traits in children and adolescents with ODD/CD from a large multicenter cohort during a well-established and robust fMRI task. Cases showed higher amygdala activity during the presentation of negative faces versus shapes than TDs. This finding is in line with literature suggesting that individuals with ODD/CD show divergent neural activity and deficient face and emotion processing (Blair et al., 2014). Regarding subtypes of aggression, we did not find any significant association that survived family-wise correction, but there was a trend for a negative relationship between PA and amygdala activity to negative faces. With regard to CU traits, we demonstrated trait-specific alterations in the amygdala for negative faces. This finding is in line with previous studies showing higher amygdala activity in youth with low CU traits, but lower activity in those with high CU traits (Viding et al., 2014).

The general higher activity in the amygdala adds evidence to the heightened threat sensitivity theory in aggression-related disorders (Blair et al., 2014; Dotterer et al., 2017; Viding, Fontaine, et al., 2012). Importantly, this effect remained stable after controlling for age, sex, medication, site, IQ, ADHD, and internalizing symptoms. Additionally, this higher

amygdala activity showed a phenotype-specific pattern for participants with significantly lower PA.

Concerning the differential effect of CU traits, our results showed that these traits are able to disentangle specific neural alterations, which is in line with previous findings (Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding et al., 2014; White et al., 2012). It is worth noting, that in our study, only the most severe callous-unemotional patients (ICU>38) showed specific amygdala under-activation. Earlier studies using the same instrument, found CU-specific amygdala activity, in an even higher CU traits population (ICU mean 52) (Lozier et al., 2014; Sebastian et al., 2014; Viding, Fontaine, et al., 2012). In our opinion, this finding might be an important additional result that provides a cut-off (ICU ≥ 38) which could be used in the classification of aggression-related disorders (specifier) and probably subtypes. Interestingly, the phenotype of the CU+ subgroup showed higher scores for PA compared to the CU- subgroup. However, no differences between high and low CU subgroups were found for RA. Some studies showed that both aggression-related subtypes are associated with high CU traits (Kimonis et al., 2008; Pechorro, Ray, Gonçalves, & Jesus, 2017; Waller et al., 2015), while one study reported that only PA is correlated with CU traits (Urben et al., 2018). These mixed findings might suggest that CU traits measured via the parent reported ICU questionnaire is more sensitive than the self-reported RPQ questionnaire.

Finally, the skin conductance data showed general physiological hypo-activation in response to negative in cases compared to TDs. This finding is in line with numerous studies (Blair, 1999; Fanti, 2016; Herpertz et al., 2005, 2008) showing reduced skin conductance in aggression-related disorders. However, the SCR and fMRI data showed divergent patterns with higher amygdala activity in the CU- subgroup when compared with TDs, and a negative association between SCR, CU traits, PA and RA. This, together with the overall reduced SCR might suggest an interrupted physiological circuit with neural processes involved in response to affective stimuli in cases within the CU- subgroup. However, this should be interpreted with caution, since our fMRI-SCR data was only based on a small number of cases.

2.3.5.1 Strengths and Limitations

The strengths of this study include a large sample of cases with ODD/CD and TD children and adolescents, the assessments of reactive and proactive aggression and CU traits, enabling to disentangle subtype and trait-specific differences, and a well-established fMRI task to elicit amygdala activity. There are also limitations worth noting. First, the multicenter nature of this study, in which nine different institutes participated and contributed to a sample

size which would have been difficult to reach at an individual site, might have also introduced heterogeneity. However, sensitivity analysis with fewer sites did not change the main results, indicating that this did not negatively influence the results. Second, our relatively small proportion of subjects high in CU traits (29.1%) suggests that our cases sample is predominantly reactively aggressive, since there were no significant differences between low and high CU subgroup. Moreover, within this emotional face-matching task, the negative faces comprised two emotions (fear and angry) which could have diluted our effects as studies which showed CU effects on amygdala activity found mainly effects for fearful faces (Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding, Fontaine, et al., 2012). Interestingly, this is confirmed by our performance data with fewer correct responses specifically during the matching of fearful faces.

2.3.5.2 Conclusion

In summary, this large study compared children and adolescents with aggression-related problems to TD peers during an fMRI emotional face-matching task, taking subtypes of aggression and CU traits into account. Overall, children and adolescents with high aggression showed amygdala hyper-activity in emotion and face processing areas, particularly in the subgroup with low CU traits. In contrast, in those with high CU traits, amygdala hypo-activity was observed. Our findings underline the importance to specify subtypes and CU traits in aggression-related disorders, based on top-down evidence and therefore providing a possible biomarker, which could be used for personalized diagnostics and treatments.

2.3.6 Supplementary material

Scanner	Site	TR/TE (ms)	Number of slices	Slice scan order	Voxel size (mm)
Siemens	Nijmegen	2100/35	36	descending	3x3x3
	Mannheim	2100/35	36	descending	3x3x3
	Ulm	2100/35	36	descending	3x3x3
	Barcelona	2100/35	36	descending	3x3x3
	Madrid	2100/35	36	descending	3x3x3
	Rome	2100/35	36	descending	3x3x3
Philips	Groningen	2100/35	39	descending	3x3x3
	Zurich	2100/35	36	descending	3x3x3
GE*	London	2100/35	36	descending, inter-leaved	3x3x3

**All sites used a 32-channel head coil except for the General Electric 3-Tesla scanner (8-channel head coil).*

Table 23. Site and scanner details

Functional magnetic resonance imaging (fMRI) across nine sites in Europe (Radboud University Medical Center and the Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; Department of Neuroscience, University Medical Center Groningen, The Netherlands; Central Institute of Mental Health (CIMH), Mannheim, Germany; Department of Psychiatry III and Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Ulm, Germany; Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; Department of Child Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; Department of Child and Adolescent Psychiatry and Psychology, Neurosciences Institute, Hospital Clinic de Barcelona, Barcelona, Spain; Hospital Gregorio Marañón, Madrid, Spain; MR Center, Psychiatric University Hospital, Zurich, Switzerland; IRCCS Santa Lucia Foundation, Rome, Italy.

Table 24. Behavioral data – Accuracy and Reaction times

		Accuracy			Reaction time		
Emotion	**Group**	**Mean (%)**	**SD**	**p-value**	**Mean (s)**	**SD**	**p-value**
Anger	TD	83.82	17.61	.147	2.22	0.49	.173
	Cases	76.25	24.10		2.38	0.58	
Fear	TD	93.72	11.47	**.018**	1.94	0.45	**.030**
	Cases	87.41	18.68		2.16	0.48	
Happy	TD	86.72	17.29	.228	1.97	0.48	.314
	Cases	80.52	21.09		2.09	0.50	
Neutral	TD	94.93	11.89	**<.001**	1.95	0.44	.582
	Cases	83.32	23.13		2.01	0.50	
Shapes	TD	90.94	13.39	.404	1.43	0.49	.975
	Cases	84.13	20.37		1.50	0.53	

Note: TD: Typically developing peers, Cases = ODD/CD: Oppositional deviant disorder/Conduct disorder. Bonferroni corrected.

Table 25. Whole brain analysis for task effect (Negative vs Positive contrast)

Region	Voxel size	Peak level			MNI coordinates (mm)		
		T	Z-score	p-FWE	x	y	z
Temporal_Mid_R	61	6.00	5.59	0.000	57	-61	2
	16	5.13	4.93	0.007	54	-43	8
Temporall_Sup_R	5	5.04	4.85	0.010	48	-31	-1
Temporal_Mid_L	4	4.86	4.69	0.019	-48	-52	8

Brain regions were defined using the Automated anatomical labeling (AAL).

Table 26. Whole brain analysis for negative vs shapes between Cases and TDs

Region	Voxel size	Peak level			MNI coordinates (mm)		
		T	Z-score	p(unc)	x	y	z
Left superior occipital area	31	3.73	3.65	0.000	-24	-91	23
Frontal_Inf_Oper_L	59	3.69	3.61	0.000	-51	11	23
		3.67	3.59	0.000	-45	20	32
Left amygdala	10	3.61	3.54	0.000	-27	-4	-13
Left inferior parietal gyrus	13	3.48	3.41	0.000	-36	-61	53

Brain regions were defined using the Automated anatomical labeling (AAL).

Table 27. Whole brain analysis for positive vs shapes between Cases and TD

Region	Voxel size	Peak level			MNI coordinates(mm)		
		T	Z-score	p(unc)	x	y	z
Not labeled	20	4.11	4.00	0.000	9	2	-10
Occipital_Sup_L	28	4.09	3.98	0.000	-18	-94	29
Olfactory_L	22	3.97	3.88	0.000	-3	11	-10
		3.63	3.55	0.000	-6	-1	-13
Frontal_Mid_R	45	3.87	3.78	0.000	33	26	50
Frontal_Sup_R		3.45	3.39	0.000	24	38	44
		3.29	3.23	0.001	24	23	62
Frontal_Inf_Orb_R	21	3.74	3.66	0.000	24	14	-25
		3.69	3.62	0.000	18	17	-19
Frontal_Med_Orb_L	12	3.62	3.54	0.000	-9	44	-13
Frontal_Med_Orb_R	26	3.62	3.54	0.000	6	50	-7
		3.34	3.28	0.001	15	41	-10
		3.23	3.17	0.001	6	38	-13
Postcentral_R	32	3.60	3.52	0.000	51	-13	-25
		3.59	3.52	0.000	54	2	-28

Brain regions were defined using the Automated anatomical labeling (AAL).

Table 28. Regression analysis parent ICU total scale. Whole brain analysis

Region	Voxel size	Peak level			MNI coordinates (mm)		
		T	Z-score	p(unc)	x	y	z
Cingulum_Post_L	81	4.44	4.30	0.000	-6	-43	11
Temporal_Sup_R	14	4.15	4.03	0.000	45	-7	-13
	70	4.06	3.95	0.000	-18	47	-1
Not labeled		3.66	3.58	0.000	-15	35	-1
		3.58	3.50	0.000	-27	47	-4
Precuneus_L	47	3.80	3.70	0.000	0	-73	47
Cuneus_R		3.43	3.37	0.000	3	-79	38
Parietal_Inf_L	13	3.65	3.57	0.000	-36	-73	47
Cingulum_Mid_L	17	3.61	3.53	0.000	-9	-43	38
Insula_L	13	3.50	3.43	0.000	-36	-1	-1

Brain regions were defined using the Automated anatomical labeling (AAL).

Note: The influence of the CU traits were analyzed coding group as 1 ODD/CD CU+, 2 Typically developing children and 3 ODD/CD CU-.

Table 29. Correcting for ADHD

Region	Voxel size	Peak level			MNI coordinates (mm)		
		T	Z-score	p(unc)	x	y	z
Frontal_Mid_L	157	4.47	4.32	0.000	-36	-52	23
Occipital_Mid_L		4.00	3.89	0.000	-33	-70	32
		3.31	3.25	0.001	-45	-43	29
Frontal_Inf_Tri_L	35	4.18	4.05	0.000	-51	14	23
Frontal_Inf_Tri_R	42	3.98	3.87	0.000	51	41	5
Precuneus_R	49	3.81	3.71	0.000	6	-76	35
		3.45	3.37	0.000	9	-58	26
Occipital_Sup_L	35	3.81	3.71	0.000	-21	-91	20
Rectus_L	15	3.68	3.59	0.000	0	41	-16
		3.55	3.47	0.000	-6	50	-16
		3.19	3.13	0.001	3	53	-16
Frontal_Mid_Orb_R	14	3.66	3.57	0.000	27	35	-13
Amygdala_L	28	3.63	3.54	0.000	-24	-4	-13
Hippocampus_L		3.41	3.34	0.000	-15	-7	-16
Occipital_Mid_R	31	3.62	3.53	0.000	33	-79	23
Putamen_R	17	3.50	3.42	0.000	33	2	-4
Amygdala_R		3.35	3.28	0.001	27	-4	-13

Brain regions were defined using the Automated anatomical labeling (AAL). ADHD = Attention deficit and hyperactivity disorder. ADHD was measured with the SNAP IV questionnaire.

Table 30. Non-medicated participants only. Negative vs Shapes

Region	Voxel size	Peak level			MNI coordinates (mm)		
		T	Z-score	p(unc)	x	y	z
Frontal_Mid_L	136	4.26	4.07	0.000	-48	23	32
Frontal_Inf_Oper_L		3.95	3.80	0.000	-51	11	23
Precentral_L		3.56	3.45	0.000	-51	11	35
Parietal_Inf_L	38	3.80	3.66	0.000	-36	-67	47
Not labeled	10	3.66	3.53	0.000	-36	-49	35
Frontal_Mid_L	15	3.60	3.48	0.000	-27	5	53
Not labeled	22	3.58	3.47	0.000	-21	-43	47

Brain regions were defined using the Automated anatomical labeling (AAL).

Note: This analysis was based on 44 ODD/CD children and 69 typically developing peers.

Table 31 ANCOVA with ROI left Amygdala activity

Tests of Between-Subjects Effects

Dependent Variable: Left Amygdala_ROI [Negative faces vs Shapes]

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	9.918[a]	13	.753	2.614	.002
Intercept	.000	1	.000	.000	.989
Group	3.471	1	3.471	11,89	.001
Sites	5.274	8	.659	2.259	.026
Age	0.006	1	.006	0.19	.890
Medication	2.280	1	2.280	7.814	.006
Gender	.057	1	.057	.196	.658
IQ	.133	1	.133	.455	.501
Error	47.860	164	.292		
Total	63.166	178			
Corrected Total	57.778	177			

a. R Squared = .172 (Adjusted R Squared = .106)

ROI = Region of interest. ANCOVA= Analysis of covariance. Fixed factors: Sites and Group. Covariates: Age, Sex, IQ and Medication. Significant impact of group and medication for the left amygdala activity was found. Amygdala activity showed to differ between Sites, sex and age.

Table 32. ANCOVA with ROI left Amygdala activity excluding sites with less than 5 participants for each group

Tests of Between-Subjects Effects

Dependent Variable: Left Amygdala_ROI [Negative faces vs Shapes]

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	6.993[a]	9	.777	2.569	.009
Intercept	.015	1	.015	.049	.824
Group	3.559	1	3.559	11.770	.001
Sites	1.924	4	.481	1.591	.181
Age	.024	1	.024	.078	.780
Medication	2.227	1	2.227	7.366	.008
Gender	.325	1	.325	1.074	.302
IQ	.212	1	.212	.701	.404
Error	39.613	131	.302		
Total	50.373	141			
Corrected Total	46.606	140			

a. R Squared = .150 (Adjusted R Squared = .092)

ROI = Region of interest. ANCOVA= Analysis of covariance. Fixed factors: Sites and Group. Covariates: Age, Sex, IQ and Medication. Significant impact of group and medication for the left amygdala activity was found. Amygdala activity showed not to differ between Sites, sex and age

2.4 General Discussion

In this thesis, three main hypotheses were evaluated in a large multicenter randomized controlled trial comparing NF for children with ADHD to a semi-active control condition. First, we assessed the specificity of SCP-NF in children with ADHD by controlling for unspecific effects, and assessing self-regulation of slow-cortical potentials. Second, we looked at sustained and long-term effects six-month after treatment, and third, we assessed the modulation by and the effects on comorbid aggression. Importantly, this is the largest RCT assessing NF treatments in an ADHD outpatient sample to date (at least to the best of our knowledge). Additionally, we evaluated aggression-relevant subtypes in a large multicenter cohort of children and adolescents with disruptive behaviors and high comorbidity with ADHD, during a well-established and robust fMRI task, which might be useful for identifying new NF targets, and therefore for personalized treatment options.

The main findings of the studies reported here can be summarized as follows: (1) The SCP-NF group showed significantly greater symptom reduction than the comparison group on the primary parent-rated outcome, which in turn, might be interpreted as a confirmation of specific effects, given the strong control for unspecific effects by the semi-active EMG-BF control group. (2) An additional important hint for specificity is that we could demonstrate successful self-regulation of SCP, although the lack of prominent self-regulation learning and correlations with clinical outcomes limit these conclusions. (3) SCP-NF showed stable and large effects six-month after treatment end, suggesting long-lasting effects. (4) After SCP-NF, comorbid aggression symptoms were reduced, but mostly independent of group allocation; nevertheless, reduction of comorbid aggression correlated with SCP-NF self-regulation only, and (5) we provide a possible biomarker for subtype-specific aggression, which could be used for personalized NF treatments.

These main findings are highly relevant and provide additional important evidence that specific NF protocols, such as SCP-NF can be useful in treating ADHD. However, there are still important aspects which should be taken into account. In our first study, we showed that SCP-NF was significantly superior to the semi-active control group, with a medium to large effect size on the primary outcome. This effect was only seen for the more proximal parent ratings and not for the probably blinded teacher ratings. A comparable pattern of results was obtained in the meta-analysis of the European ADHD Guidelines Group, leading them to conclude that the current evidence failed to support NF as an effective treatment for ADHD, since no significant effect were found for probably blind teacher ratings (Cortese et

al., 2016). A significant advantage for standard protocols such as SCP-NF in probably blinded ratings in an exploratory analysis (Cortese et al 2016) could not be replicated here, except for the significant but uncontrolled within-group comparison. Conversely, to date, there is also an important recent debate about how the source of evaluation (i.e. parent, teacher ratings, or observers) also affects the sensitivity to assess ADHD symptom improvement. So far, current meta-analyses are considering teacher ratings or classroom observers mainly as probably blinded and therefore unbiased. This is because teacher ratings arise from a different context than the one where the training takes place (Sonuga-Barke et al., 2013). Strikingly, a recent study from Minder et al (2018), assessed the source of evaluation controlling for the context where these trainings were applied. Overall, the results of this RCT showed that teachers are at least as sensitive to waiting time effects as parents, but less sensitive than parents to behavioral change during the actual treatment phase, and thus did not support the assumption that teachers were more objective. Therefore they challenged the conclusion of the current meta-analyses. Besides this, one recent review of previous meta-analyses including the most recent RCTs showed that NF significantly improves inattention symptoms also for probably blinded raters with small effect sizes (Riesco-Matías et al., 2019). Additionally, in our RCT (study 1 and 2), the teacher ratings were not different between groups, but within-group analysis showed that symptom improvement was higher for the SCP-NF group with small to medium effect sizes. Interestingly, an additional new meta-analysis from Bussalb et al. (2019) which looked explicitly at the effects for probably blinded rates for standard NF protocols (in line with Cortese et al., 2016) found significant teacher ratings including the most recent two RCT (Streh & Aggensteiner, et al., 2017) and Baumeister et al., 2018), except for hyperactivity subscale.

With regard to the specificity of SCP-NF, our studies addressed two major aspects: First, the semi-active control group, as discussed in Strehl & Aggensteiner et al (2017), controls for unspecific effects, such as training setting, interaction, learning, time, motivation, trained parameters, and effort. Controlling for these factors is highly important since the clinical effects of this kind of time-consuming training might otherwise be attributed to psychosocial effects (Wood & Kober, 2018) which are not related to the self-regulation of neurophysiological states targeted by the NF training itself. A recent review highlighted that NF effects might be dominated by placebo effects (Thibault & Raz, 2017). Furthermore, NF training might be highly influenced by the participant's motivation, beliefs, and high-tech settings. To control for these aspects, a sham-feedback condition is often proposed and considered as a gold standard in intervention research (Schönenberg et al., 2017). However, sham-control has

also received some criticism. For instance, these kinds of sham-protocols use automatic thresholding which might prevent learning. Additionally, the use of sham conditions for NF treatments might be critically affecting motivation, since the lack of success in the first active NF session may lead to the impression of being allocated to an ineffective control condition (Strehl & Aggensteiner et al., 2017). Further, patients and trainer might detect the sham condition and may refuse further participation (Birbaumer, 1991). Therefore, it is an important aspect to select an adequate control group or condition. Other active control conditions, as for instance, pharmacotherapy do not control for unspecific effects as the variables of interest, motivation, time, effort cannot be controlled for. Considering all these points, there is probably not a single perfect control group or condition which is able to resolve all the above-mentioned complex questions.

In addition to the selection of the comparison group (EMG-BF) which controlled for most unspecific effects, we addressed the key question regarding evidence to the specificity of NF approaches, by examining the self-regulation of the trained parameters and its correlates. These are of paramount importance since the assumption that NF allows subjects with ADHD regulate deviant cortical excitation, which reflects cognitive and motor preparation, are only less systematically tested and reported. In study 1, we demonstrated successful self-regulation of the SCP-NF participants. First, we showed that participants were able to modulate cortical excitation, which means that they performed according to their task (to produce negative or positive cortical shifts). However, we could only show significant self-regulation through real-time feedback condition. During the transfer condition, we could not find any significant difference. The transfer condition is considered as the most important one since it should help to transfer the learned skills into daily life (i.e. school settings) (Strehl et al., 2006). This raises the possibility that more transfer and training session might be necessary to acquire transferred self-regulation skills. Additionally, it has been discussed that self-regulation, particularly for the transfer condition might show delayed learning. It has been shown that the performance in transfer trials improved substantially 6-month after training (Kotchoubey et al., 1999; Strehl et al., 2006). Interestingly, in our study 2, we could also demonstrate significant enhancement of self-regulation in the transfer skills six-month after training.

With regard to the association between clinical outcome and regulation of the trained parameters, our study 2 could only add limited evidence for such an association. As discussed in Aggensteiner et al., (2019), we obtained unexpected and mixed outcomes. Nevertheless, only very few studies reported so far this kind of associations (Drechsler et al., 2007; Gevensleben et al., 2009; Janssen et al., 2016; Strehl et al., 2006). Our studies, therefore, provide

important insights and matches the new consensus on reporting RCT regarding NF (Ros et al., 2019). Concerning the associations between self-regulation and clinical outcomes, we could show significant correlation for secondary outcomes only. Significant correlation with impulsivity and a trend for hyperactivity rated by parents and teachers one month after treatment end, nevertheless, the semi-active control group showed as well significant associations at follow-up. It is therefore complicated to disentangle specific from unspecific effects looking only at correlational data. Since both groups showed clinical improvement, and both groups had some enhancement of self-regulation skills, the correlations might be more spurious and unspecific than specific. Besides self-regulation, electrophysiological pre-post changes should be also taken into account (Doehnert et al 2008; Zuberer, Brandeis, & Drechsler, 2015) to be able to disentangle specific from unspecific effects.

Concerning sustained and long-term clinical effects, our study 2 provided clinical outcome six-month after treatment. The SCP-NF showed stable clinical improvement directly after treatment end. However, there were no significant differences in improvement between the two groups, which in turn might suggest strong unspecific effects common to both NF and EMG-BF training. Nevertheless, as discussed above, the selection of a good control group is crucial. In our study 1 and 2, we decided to use a different biofeedback modality which was electromyographic biofeedback, which is considered as a semi-active control condition (Arns et al. 2013). An alternative semi-active condition could be cognitive training. It should be noted that this kind of trainings (i.e. EMG-BF and Cognitive training) already showed some clinical improvements in ADHD population with small to medium effect sizes for unblinded raters (*EMG-BF*: Aggensteiner et al., 2019; Barth, Mayer, Strehl, Fallgatter, & Ehlis, 2017; Maurizio et al., 2013; *Cognitive training:* Minder et al., 2018; Cortese et al., 2015). Therefore, the comparison with control conditions which already showed specific clinical improvement themselves might dilute clinical and specific effects. This might resemble the findings of a recent meta-analysis that analyzed sustained and long-term effects after NF in comparison with active and non-active control groups. This meta-analysis showed that at follow-up, NF was clinically superior to the non-active groups, and that the effects were similar to the active groups (van Doren et al., 2018).

With regard to comorbid aggression and the effects of NF, we showed significant symptom reduction irrespective of group. Since only a few studies reported significant impact on comorbid aggression after NF, our findings, with no group-specific effects, highlights that there is a gap of knowledge for which NF training modality could be used to target aggression-related symptoms. Furthermore, since aggression-related problems show two distinct

phenotypes (reactive and proactive aggression) our study 3 might provide more insights with regards to this.

As already mentioned, study 3 aimed to disentangle the heterogeneity of aggression-related problems at a neural and peripheral level which reflects the activity of the autonomous nervous system. We showed that children and adolescents high on aggression showed amygdala hyper-activity during an emotion and face processing task, particularly in the subgroup with low CU traits. In contrast, in those with high CU traits and scoring high on proactive aggression, amygdala hypo-activity was observed. This finding is in line with previous studies (Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Sebastian et al., 2014; White et al., 2012). Additionally, we showed that this subtype-specific pattern could be demonstrated also at a peripheral level, with lower SC response for those children and adolescents with high proactive aggression and CU traits, which is also in line with previous findings (Fanti, 2016; Herpertz et al., 2008). Although, we found a general under-activity in children and adolescents with aggression-related problems compared to TDs. Which indicates a divergent pattern between central and peripheral indices of arousal for children and adolescents with aggression-related problems. This novel insight might suggest an interrupted physiological circuit with neural processes involved in response to affective stimuli. Putting together these findings, we might provide two distinct targets for new NF treatment modalities. Children and adolescents with higher proactive aggression and high on CU traits might potentially benefit from up-regulation of the amygdala activity and more reactive and impulsive aggression might benefit form down-regulation of the amygdala activity. Additionally, the findings of SCR might potentially suggest, that this peripheral measurement, might act as a proxy for both aggression-related subtypes, since a general under-activity was found for SCR, thus, NF training aiming to up-regulate SCR might be beneficial for both subtypes.

2.5 Limitations

In this section, the major shortcomings of the three studies forming this thesis are listed. First, with regards to the SCP-NF RCT (Study 1 and 2), a main limitation is the overall low self-regulation performance. As already discussed in Aggensteiner et al., 2019, the mean performance or reinforcement rate was 44% for SCP-NF. In contrast, the EMG-BF reinforcement rate was 82%. These SCP-NF reinforcement rates still are in line with the few studies that reported these outcomes (Baumeister et al., 2016; T. Takahashi, 2013). This might suggest that self-regulation of brain-related activity is far more difficult than body-related self-regulation, and therefore future studies should ensure sufficient learning after SCP-NF. A

second main limitation of the SCP-NF RCT might be that in both treatments pharmacotherapy was allowed. Despite that in study 1, a two to four weeks washout was implemented, at follow-up, this was not the case and probably added a confounding factor, although sensitivity analysis with non-medicated participants was performed and no changes of the main results were obtained. A third shortcoming, regarding aggression-related comorbidities, was that we only assessed these symptoms via the SDQ, which might limit our generalizability for these comorbidities. A fourth constraint might be the kind of feedback modality which was provided by the neurofeedback software. This old-fashioned (2-D images) method (see Figure 3) might not be appropriate for children and adolescents born in a more "digital world", and therefore newer methods that use 3D rendered images (Alegria et al.,2018) or virtual reality settings might lead to higher self-regulation and motivation. Finally, with regards to the study 3, the main limitation was the relatively small proportion of subjects high on CU traits and the chosen emotional face-matching task. These two points could have diluted the shown effect of CU traits on amygdala activity.

2.6 Outlook

Although the presented RCT showed long-lasting clinical impact on ADHD core symptoms and comorbid conduct problems, further well-controlled RCT are warranted to disentangle specific form unspecific effects of NF treatment. New studies, as already discussed above, should ensure enough self-regulation and learning, in particular in the transfer trials (i.e. providing more training sessions and giving some instructions/feedback after an intermediate evaluation of the learning/performance). Additionally, extending the follow-up assessment period (i.e. two years) might be of particular interest, since long-lasting effects (beyond six months) are less systematically studied. Moreover, different semi-active control groups (fNIRS, MEG or real-time fMRI feedback) might provide additional insights which probably could fully disentangle specific form unspecific effects.

With regard to NF targets for aggression-related problems, specific RCT such as those investigated in the EU-projects Aggressotype (skin conductance biofeedback) and MATRICS (amygdala/insula real-time fMRI) are needed to assess the effects of arousal-related parameters on aggressive behavior.

3. SUMMARY

The present thesis focused on specificity and long-term effects of slow-cortical potential neurofeedback (SCP-NF) treatment for children with ADHD in a large multicenter randomized controlled trial, on its relation to aggressive behaviors as a common comorbidity of ADHD, and on neuroimaging and psychophysiological subtypes of aggression. We assessed clinical efficacy on ADHD and comorbid aggression in comparison to a semi-active control group which controlled for unspecific effects. The role of self-regulation and learning of SCPs was systematically evaluated. Additionally, we investigated amygdala-specific activity in aggression subtypes in a large multicenter cohort, which might provide a possible putative NF target.

The first two studies assessed 150 children aged 7–9 years diagnosed with ADHD which were randomized to 25 sessions of feedback of SCPs (NF) or feedback of coordination of the supraspinatus muscles (EMG). The primary outcome was the change in ADHD symptoms rated by parents four weeks and six-month after treatment end. Slow-cortical potential neurofeedback showed significant superiority over the semi-active control condition with medium effect sizes four weeks after treatment. This superiority of SCP-NF over the semi-active control group became non-significant 6 months after treatment end. However, taking together all assessments, SCP-NF showed a stable improvement with large effect sizes following treatment and EMG-BF showed worsening of symptoms one month after treatment, with subsequent remission at follow-up, leading to non-significant group differences six months after treatment end. Assessment of self-regulation showed significant ability to self-regulate slow-cortical potential when direct feedback is given and improvement of self-regulation skills indicate specificity of SCP-NF for selected subscales after training, but not at follow-up. In sum, these findings suggest shared specific and unspecific effects contributing to this clinical outcome.

The third study aimed to disentangle aggression-related subtypes at a neural level. In total 177 participants (n=108 cases with aggression-related disorders and n= 69 typically developing peers), aged 8-18 years were assessed across nine sites in Europa during a well-established emotional face-matching fMRI task. Additionally, simultaneous skin conductance recordings were acquired in a subsample (n=64). Children and adolescents with aggression-related problems showed higher amygdala activity in response to negative faces compared to typically developing peers. Further, we showed distinct amygdala activity for subtypes of aggression.

Callous-unemotional traits showed to moderate both central (amygdala) and peripheral (SC) responses. These findings increase insights which could be used for personalized diagnostics and treatments.

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