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# **NEUROFEEDBACK AND WORKING MEMORY TRAINING IN CHILDREN AND ADOLESCENTS WITH ADHD**

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# Neurofeedback and Working Memory Training in Children and Adolescents with ADHD

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Leo, floor 8, Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND), Gävlegatan 22, entrance B | 113 30 Stockholm, on the 25th of March, at 10:00 CET.

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*In memory of Johnny Sigvard Hasslinger and Ursula Elfriede Therese Jeroschewitz.*



## POPULAR SCIENCE SUMMARY OF THE THESIS

ADHD has received increased attention over the past decades. It is one of the most common neurodevelopmental disorders in children, and often persists into adulthood. Genetic factors seem to play an important role in ADHD, yet its etiology is not fully understood. The core symptoms of ADHD, inattention and impulsivity, are primarily treated with stimulant medications, mostly with good results. However, side effects are common and there are questions concerning potential negative long-term effects. Also, many dislike the idea of treating children with stimulants, especially considering their increased non-medical and recreational use. Therefore, complimentary, alternative treatments for ADHD are sought for by many. Different cognitive training methods have emerged as potential alternatives.

Neurofeedback (NF) has received increasing attention in recent years. Here, participants' brain activity is measured via EEG. Similar to a mirror, the participant receives information on their brain activity by providing real-time feedback, via game-like programs. It is supposed that this allows the brain to adjust its activity towards a more attentive state, decreasing the symptoms of ADHD. Based on the specific brain activity being targeted, there are many different types of NF. In this thesis we will explore and evaluate two very different forms of NF, Slow Cortical Potential-NF (SCP-NF) and Live Z-Score Training (LZT). The former addresses a very specific brain function, and has been studied for more than four decades, with multiple prior studies indicating positive results for ADHD. The latter is newer and less researched, but is well established among many private practitioners, especially in the USA.

All studies in this thesis are part of the KITE-project, a single center randomized controlled pragmatic trial. In total 202 children and adolescents with ADHD, and some with common comorbidities, were included. Participants were then randomized into either one of the two NF groups, a group that underwent working memory training (WMT) or a passive control group that did not receive any extra intervention. Each group included 50 participants. The three intervention groups received daily training at our center, Monday to Friday, for a total of 25 sessions. All participants were assessed on multiple variables before their training started, after their training was completed, and at a 6-month follow-up. The passive control-group only partook at these three assessment points.

In **Study I**, we explored how participants were regulating their brain activity during SCP-NF. Via multiple short interviews conducted after training sessions, we mapped different types of strategies for their regulation. Based on a sub-sample of 14 participants, that had completed at least five interviews, we established 3 types of training profiles. Only one group (6 of 14) could elaborate on their strategy use, which focused on altering their "state-of-mind". Interestingly, this was the only group with intrinsic motivation, and the only one that described self-perceived improvements after training. Similarly, they were the only ones with positive trends in their actual regulatory performance. The other two groups focused either on physical strategies

(thereby likely manipulating the EEG-signal, rather than accomplishing an actual regulation of their brain activity), or were not aware of what they were doing at all.

In **Study II** we compared the two NF groups with WMT and the passive control-group. On a group level, no differences between the NF interventions and WMT were found. When compared to the passive control-group, at follow-up, we only found positive results for LZT on teacher ratings. Similar results were found when comparing WMT with the passive control-group. This contradicts some earlier findings, where positive results on parent ratings are more common. However, the results should be interpreted with caution. Overall, we did not find support for offering NF broadly to children and adolescents with ADHD. Instead, further research is needed, so that NF can be offered to those whom mostly likely can benefit from it.

In **Study III**, we looked at numerous cognitive functions commonly associated with ADHD, and evaluated how the different interventions (SCP-NF, LZT and WMT) impacted them, in comparison to the passive control-group. No significant results were found for any of the NF interventions. For WMT we found improvements only for a spatial working memory task. Overall, we did not find support that NF impacts cognitive functions. However, this must also be interpreted with caution, partly because of limitations in what the tasks are measuring.

Finally, in **Study IV**, we reviewed the literature on SCP-NF, indifferent of how and for what it was implemented. In total we screened 800 articles, including 63 in the review. Through the review we found that there are numerous variations in how SCP-NF is conducted, especially concerning technical details. However, we also found that articles generally are sparse in their reporting on what they did to ensure that the self-regulation skill is acquired. We also found that there is no standard method of evaluating self-regulatory success, as most studies implement their own method. Overall, we conclude that future studies should focus more on ensuring successful self-regulation, and standardize evaluation methods for self-regulation in order to increase comparability between studies.

In conclusion, the results in this thesis did not generate support for SCP-NF and LZT as effective treatment for ADHD. However, this does not mean that NF should be disregarded as treatment for ADHD, especially when considering the positive results from previous studies. Unique for our studies, was the high intensity of training, with daily training sessions. Comparable studies usually have 2-3 training sessions per week, and a break where self-regulation is practiced at home. Also, study I showed that far from all participants learned to self-regulate successfully. Future studies should focus on acquisition of self-regulation, as well as identifying whom benefits the most from the different forms of NF. Also, since NF is not necessarily a “plug-n-play” intervention, it ought to be contextualized within a broader intervention.



## ABSTRACT

**Background:** ADHD is one of the most prevalent neurodevelopmental disorders among children and adolescents. Although pharmacological interventions are highly effective in attenuating symptoms of inattention and impulsivity, adverse side effects are common, warranting the need for alternative treatments. Focused on “training” the brain, Neurofeedback (NF) has received much attention in recent decades, with promising results for ADHD. However, meta-analyses indicate somewhat mixed results, including variations between different neurofeedback protocols.

**Aims:** The aim of this thesis was to examine the efficacy of two NF protocols as treatment for children and adolescents with ADHD. In addition, this thesis also tried to add further understanding on the self-regulation process during SCP-NF, by qualitatively examining the use of regulatory strategies. Furthermore, this thesis examined how standardized SCP-NF is, by systematically reviewing the literature. The main focus concerned the technical implementation, and in particular how successful self-regulation is evaluated. For this a was conducted.

**Methods:** In total, 202 children and adolescents were randomized into one of the four groups (n=50-51), Slow Cortical Potential NF (SCP-NF), Live Z-score Training (LZT), Working Memory Training (WMT), or Treatment-as-usual-only (TAU-only). The groups were then compared with each other, and analyzed in a linear-mixed-model. Both primary symptoms from self-, parent- and teacher rating, as well as a battery of cognitive performance tasks, were evaluated at baseline, post-intervention and at a 6-month follow-up. Additionally, a thematic analysis of 133 short semi-structured interviews was conducted for the qualitative study. The systematic review was preregistered at PROSPERO (CRD42021260087) and followed the PRISMA guidelines.

**Results:** Contrary our expectations, between-group differences were scarce and did not show a distinct pattern, concerning our primary outcome measures in **study II**. Improved teacher-rating were found for LZT over TAU-only at 6-month follow-up. For SCP-NF we only found significant differences on meta-cognition compared to TAU-only. Concerning the cognitive tests examined in **study III**, sustained improvements were only found for spatial working memory in WMT. The thematic-analysis of **study I**, revealed that numerous different strategies were used in SCP-NF. Furthermore, three prototypical training styles were identified, where only one style described intrinsic motivation and self-perceived improvements. The same profile was the only one that had a positive trend in their self-regulation. For **Study IV**, of the 800 initial search hits, 63 were included and synthesized. The review revealed broad variations in protocol details, and in how successful self-regulation is evaluated, which limit comparability. Also, data concerning adequate skill application in everyday-situations, is sparsely reported.

**Conclusions:** We could not find support for NF as broadly implemented treatment for ADHD, when delivered at a high frequency. However, this must be interpreted with caution due to limitations. Future studies should focus on proper self-regulation and its significances on the symptomatology.

## LIST OF SCIENTIFIC PAPERS

- I. **Hasslinger, J.**, D'Agostini Souto, M., Folkesson Hellstadius, L., & Bölte, S. (2020). Neurofeedback in ADHD: A qualitative study of strategy use in slow cortical potential training. *Plos one*, *15*(6), e0233343.
- II. **Hasslinger, J.**, Bölte, S., & Jonsson, U. (2021). Slow Cortical Potential Versus Live Z-score Neurofeedback in Children and Adolescents with ADHD: A Multi-arm Pragmatic Randomized Controlled Trial with Active and Passive Comparators. *Research on child and adolescent psychopathology*, 1-16.
- III. **Hasslinger, J.**, Jonsson, U. & Bölte, S. (2022). Immediate and Sustained Effects of Neurofeedback and Working Memory Training on Cognitive Functions in Children and Adolescents with ADHD: A Multi-Arm Pragmatic Randomized Controlled Trial. *Journal of Attention Disorders*, 1-15, online first. doi.org/10.1177/10870547211063645
- IV. **Hasslinger, J.**, Meregalli, M. & Bölte, S. (2022). How Standardized are “Standard Protocols”? Variations in protocol and performance evaluation for Slow Cortical Potential Neurofeedback: A Systematic Review. (Submitted).

## SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

- I. **Hasslinger, J.**, Sirviö, S., Berggren, S., Myers, L., Flygare, O., Tammimies, K., & Bölte, S. (2016). A comparative randomized controlled pragmatic trial of neurofeedback and working memory training for children with attention-deficit/hyperactivity disorder: protocol. *Translational Developmental Psychiatry*, 4(1), 30556.

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## LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASD	Autism Spectrum Disorder
BCI	Brain-Computer-Interface
BRIEF	Behavior Rating Inventory of Executive Function
CI	Confidence Interval
CoV	Coefficient of Variability
CNV	Contingent Negative Variation
CPT-II	Conner's Continuous Performance Test, 2 <sup>nd</sup> edition
Cz	Vertex, Central position
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> edition
EEG	Electroencephalography
EF	Executive Functions
ES	Effect Size
EOG	Electrooculography
ERP	Event Related Potential
ICD-10	International Classification of Diseases, 10 <sup>th</sup> edition
IQ	Intelligence Quotient
LZT	Live Z-Score Training
$\mu$ V	Micro Volt
msec	Milliseconds
NCT	Neuro-Cognitive Training
NF	Neurofeedback
qEEG	Quantified Electroencephalography
SCP	Slow Cortical Potentials
SCP-NF	Slow Cortical Potential Neurofeedback
SD	Standard Deviation
SE	Standard Error
SMD	Standard Mean Difference
SMR	Sensorimotor Rhythm

TAU	Treatment-as-usual
WAIS-III NI	Wechsler Adult Intelligence Scales, 3 <sup>rd</sup> edition, as a Neuropsychological Instrument
WAIS-IV	Wechsler Adult Intelligence Scales, 4 <sup>th</sup> edition
WISC-IV	Wechsler Intelligence Scales for Children, 4 <sup>th</sup> edition
WMT	Working Memory Training





# 1 INTRODUCTION

This thesis examines neurofeedback as a potential intervention for children and adolescents with ADHD. Two different neurofeedback methods were compared with working-memory-training and treatment-as-usual, in a randomized controlled pragmatic trial. One of the neurofeedback methods, Slow Cortical Potential Neurofeedback, receives particular attention in this thesis, as both a qualitative study and a systematic review are devoted to this method.

First, this thesis will present a short summary of ADHD, its definition, causes and how it is treated. Thereafter, a short historical overview of neurofeedback is presented, before summarizing previous findings of neurofeedback as intervention for ADHD. Before describing the two neurofeedback methods, the mechanisms of actions are outlined. A short introduction of working-memory-training ends the introduction.

The following sections will then depict the four studies included in this thesis in detail, and discuss their findings, before culminating in the presentation of this thesis conclusions and suggestions for future directions.

## 2 LITERATURE REVIEWS

### 2.1 ATTENTION-DEFICIT / HYPERACTIVITY DISORDER

#### 2.1.1 Definition and Prevalence

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders in school-age children, with a global prevalence that is estimated at 5–7 % in children (Polanczyk et al., 2014; Thomas et al., 2015). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) divides the condition into three subtypes, based on the core symptoms of age inappropriate inattention, impulsivity and hyperactivity; 1) the predominantly inattentive presentation; 2) the predominantly hyperactive-impulsive presentation; and 3) the combined inattentive and hyperactive-impulsive presentation (American Psychiatric Association, 2013). Beyond these core-symptoms, ADHD is also characterized by executive malfunction, low emotional self-control, and motivational challenges (Rubia, 2018). To reach diagnostic threshold, these symptoms require to significantly negatively impact on several areas of adaptive functioning as reported by different informants. A skewed sex ration favours male over female with 2:1 and even up to 9:1 (Nussbaum, 2012). Comorbidities with other other psychiatric disorders (Reale et al., 2017),

learning disorder (DuPaul et al., 2013), migraine (Salem et al., 2018), and sleeping disorders (Mick et al., 2000) are common.

For the majority ADHD related impairments persist into adulthood (Asherson et al., 2016). Psychiatric comorbidity with mood-, anxiety-, substance-use- and impulse-control disorders, are most prevalent (Barkley & Brown, 2008). Moreover, people with ADHD experience more impairments surrounding employment (Adamou et al., 2013), work-performance, general health (Brook et al., 2013), poorer financial decision making and have lower income (Bangma et al., 2019). Hence, ADHD also incurs significant costs to society through healthcare consumption, loss of productivity, special education efforts and other societal services in diagnosed individuals as well as their relatives (Le et al., 2014).

### **2.1.2 Causes**

Genetic factors play an important role in the ethology of ADHD. Twin studies consistently indicate high heritability. Nevertheless, no single genetic risk factor has yet been identified (Thapar, 2018; Thapar et al., 2013). It has been suggested that the underlying genetic architecture of ADHD comprises both rare and common gene variants, but to a different extent among individuals (Martin et al., 2015). Genes in the dopamine and serotonin pathways have shown moderate association with ADHD, however, despite being one of the most studied mental disorders, the exact biological pathways leading to ADHD remain unknown (Thapar et al., 2013). There are also numerous associations with environmental risk factors, such as pre- and perinatal risk factors (maternal stress, tobacco and alcohol use during pregnancy, prematurity and low birth weight); environmental toxins (e.g., lead, organophosphates and polychlorinated biphenyls); unfavourable psychosocial conditions; as well as dietary factors (Faraone et al., 2015; Thapar et al., 2013; Thapar & Cooper, 2016).

An affluent body of research has emphasized the role of executive dysfunction in linking primary causes to the symptomatology of ADHD (Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant et al., 2003; Sonuga-Barke et al., 2010). Executive functions (EF) are defined as higher-order cognitive processes, that are needed for goal-oriented behaviours, e.g., working memory, inhibition and attention vigilance (Willcutt et al., 2005). All of these functions are important for the individual to be able to respond and interact in an adaptive manner, and have been found to be altered in ADHD (Pievsky & McGrath, 2018). Deficits in executive functions affect both verbal and spatial working memory, planning, attention and vigilance (Sergeant, 2005; Willcutt et al., 2005). Other prominent cognitive impairments include temporal

processing, inhibition (Sonuga-Barke et al., 2010), emotional dysregulation (Shaw et al., 2014), the preference of small immediate rewards (Marx et al., 2021) and impaired overall decision making (Sonuga-Barke et al., 2016). In addition, self-regulation, the ability to control one's emotions and actions toward a higher-order goal, has been highlighted (Christiansen et al., 2019).

Structural and functional neuroimaging studies have also corroborated the relation between EF deficits and ADHD. Brain areas and circuits most located in the frontal striatal system that correlate with EF functions like inhibition, working memory, and attention, have been found to be hypoactive in ADHD compared to typically developing control groups (Castellanos & Proal, 2012; Cortese et al., 2012). Some studies have also reported smaller volumes in brain areas associated with EF, as well as reduced total brain volumes in children with ADHD (Friedman & Rapoport, 2015; Valera et al., 2007). When ADHD is examined with Electroencephalography (EEG), studies most commonly yielded elevations in the brains lower frequencies (i.e., delta (1-4 Hz) and theta (4-8 Hz) waves), while the higher frequencies are demoted (i.e., alpha (8-12 Hz) and beta (12-25 Hz) waves) (Barry et al., 2003). This indicates that individuals diagnosed with ADHD may be cortically under-aroused (Clarke et al., 2002).

### **2.1.3 Treatment**

International and local guidelines recommend the use of multimodal treatment approaches, such as psychosocial and educational efforts with or without pharmaceutical interventions (Socialstyrelsen, 2014; Taylor et al., 2004). Nevertheless, pharmacological interventions are the most common treatments for ADHD, and are regarded as the only evidence-based treatments (SBU Council et al., 2013). Most prevalent is the use of central stimulants, with methylphenidate being the first-choice drug for children and adolescents (Cortese et al., 2018). If central stimulants are not tolerated, non-stimulant alternatives like atomoxetine or guanfacine are recommended (National Collaborating Centre for Mental Health, 2018). Although pharmacological interventions have high efficacy, still 20 to 30 % of children and adolescents with ADHD do not experience sufficient benefits from central stimulants (Pliszka, 2007). Furthermore, adverse side effects are common and include insomnia, increased blood pressure and heart rate, headaches and lack of appetite (Banaschewski et al., 2017). Therefore, blood pressure, heart rate, body weight and height ought to be regularly monitored during stimulant medication (Cortese et al., 2013). Also, while short-term effects on the core symptoms of ADHD are well documented, the outcome of long-term effects remain unclear (Smith et al.,

2010). Meanwhile, concerns endure regarding height suppression (Swanson et al., 2017), sleep disturbances (Faraone, Po, et al., 2019) and cardiovascular issues (Hamilton et al., 2012). Furthermore, adherence is often poor (Frank et al., 2015) and discontinuation is common (Edvinsson & Ekselius, 2018). In addition, the nonmedical use of prescription stimulants may be a significant public health problem (Faraone, Rostain, et al., 2019), which all add to the need for non-pharmacological alternatives.

Among dietary interventions, elimination diets and fish oil supplements, have shown most promising results (Heilskov Rytter et al., 2015; Sonuga-Barke et al., 2013). However, there were numerous limitations to these results, as many studies were uncontrolled and lacked blinded raters. Different types of behavioral management interventions, including parent training, are well supported in the literature for children and classified as possibly efficacious treatment for adolescents (Evans et al., 2018). Other promising interventions have been so-called neurocognitive training (NCT) methods. These entail methods such as Neurofeedback and Working Memory Training.

## **2.2 NEUROFEEDBACK**

Neurofeedback (NF) is a form of biofeedback, which aims to facilitate learning by providing real-time feedback from physiological measures. The method of delivery and/or measurement may vary. NF based on near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI) has received some attention in recent years (Barth et al., 2016; Birbaumer et al., 2013; Marx et al., 2015; Ruiz et al., 2014). However, the primary medium for NF is based on EEG, mainly due to its high temporal resolution, non-invasiveness and cost effectiveness.

### **2.2.1 History of Neurofeedback**

The first EEG was measured by British physician Richard Caton in the 1870's, while the first human EEG was recorded in the 1920's by German neurologist and psychiatrist Hans Berger (Berger, 1929). In the 1960's the first NF experiments emerged, when Joe Kamiya and his colleagues conducted experiments where subjects recognize and alter their own alpha waves (Kamiya, 1969; Nowlis & Kamiya, 1970). The first evidence for long-term effects of NF on the brain activity came from Barry Stermans experiments with cats. Sterman had trained cats to produce the sensorimotor rhythm (SMR) (Sterman & Wyrwicka, 1967). In a later experiment for NASA, Sterman exposed cats to rocket fuel. Over time the cats showed increasing symptoms, and within the hour most started to seizure. However, a subsample remained seizure

free for two hours (Sterman et al., 1969). These were the very same cats that Sterman had used in his previous SMR experiment. This sparked further interest into EEG-conditioning as a potential treatment and led to the training of SMR in epileptics (Sterman et al., 1974).

Joel Lubar replicated and extended on the research by Sterman, publishing a series of case studies showing the effects of SMR on seizure reduction (Lubar & Bahler, 1976). Within this research, Lubar discovered that increasing SMR (12-14 Hz) while suppressing theta activity (4-7 Hz), had a positive effect on attention and hyperactivity (Lubar & Shouse, 1976). These discoveries, together with findings that increased theta activities combined with decreased  $\beta$  activities are common in children with ADHD, would lead to the theta/beta protocol (Lubar, 1991).

Together with Slow Cortical Potential NF (SCP-NF), which will be discussed later, the SMR and the theta/beta protocols constitute the so-called standard protocols, as coined by Arns et al. (2014). These protocols are all well-researched, over many decades. However, although these protocols have been used in many studies, they are not standardized, and differences between studies may and do occur.

### **2.2.2 Neurofeedback in ADHD**

Although, the first investigation of using NF for ADHD, it was not until the recent past decade that NF had seen a considerable growth of the body of literature, concerning the effects on ADHD symptoms (Bussalb et al., 2019; Cortese et al., 2016; Hodgson et al., 2014; Holtmann et al., 2014; Sonuga-Barke et al., 2013).

A meta-analysis by Cortese et al. (2016) found robust immediate NF effects when considering parent ratings for ADHD symptoms (Standard Mean Differences [SMD] = 0.35, 95% CI = 0.11 to 0.59). However, when only looking at teacher ratings (i.e., probably blinded raters), the estimated effect size dropped considerably (SMD = 0.15, 95% CI = -0.08 to 0.38) and was no longer statistically significant. These findings were confirmed in an extended meta-analysis (Bussalb et al., 2019). However, by including the additional studies, Bussalb et al. (2019) found a significant result for teacher ratings, when only looking at the aforementioned “standard protocols” (Arns et al., 2014).

Another meta-analysis looked at the sustained effects of NF, that ranged from two to twelve months (Van Doren et al., 2019). They found that the effects of NF on inattention directly after the intervention were of small effect size (SMD = 0.38, 95% CI = 0.14 to 0.61), but grew to a

medium effect size by follow-up (SMD = 0.57, 95% CI = 0.34 to 0.81), when excluding trials comparing NF with pharmacological therapies. Similarly, though smaller, the effect size for hyperactivity/impulsivity also increased from post-treatment (SMD = 0.25, 95% CI = 0.05 to 0.45) to follow-up (SMD = 0.39, 95% CI = 0.19 to 0.59).

However, when compared to more non-passive comparators, NF has frequently failed to show superiority. When specifically examining trials with active and semi-active control conditions (i.e., physical activity, behavioral interventions, cognitive- and attention training, different forms of EMG-feedback), Cortese et al. (2016) found that only parent-rated hyperactivity/impulsivity symptoms remained significant (SMD = 0.25, 95% CI = 0.03 to 0.47).

Particular noteworthy are studies using so-called sham-NF (e.g., using random or pre-recorded EEG as feedback source), as these repeatedly lack clear differences between the sham-NF and the real-NF (Arnold et al., 2013, 2021; Lansbergen et al., 2011; Schöenberg et al., 2017; Vollebregt et al., 2014). Since improvements are found in both conditions, some authors have concluded that the main effects of NF are due to placebo and psychosocial factors such as expectations on the treatment and interaction with the practitioner (Thibault et al., 2018; Thibault & Raz, 2016, 2017). Others have argued that sham-NF studies are neglecting important principles of operant conditioning, e.g., by implementing high reward rates combined with frequent auto-thresholding (Pigott et al., 2021). This means that when a subject successfully strengthens the targeted EEG variable, the auto-thresholding withdraws reinforcement in order to reset the reward rate. Correspondingly, deviating from the target is rewarded by lowering the threshold. Hence, success is being punished by making it harder, and failure is rewarded by making it easier (Pigott et al., 2017). Similarly, sham-NF studies have been criticized for failing to show that the intended self-regulation was learned (Micoulaud-Franchi & Fovet, 2016). Nevertheless, the most recent sham-NF controlled, and double-blinded (Arnold et al., 2021), also failed to show superiority for real-NF, despite considering the aforementioned criticisms. However, only the theta/beta protocol (decreasing theta while increasing beta) was included, upon which little can be said about other NF protocols.

To date there are several options of NF when addressing ADHD. Different types of frequency training, like SMR and the theta/beta protocols, have been well-researched. Less-researched protocols may focus on other parameters such as the coherence or asymmetry between different sites (i.e., electrode positions), and use multiple channels. Popular among many private NF practitioners, are so-called Live Z-score protocols. Here, a multitude of parameters are targeted simultaneously and compared to values of a normative database.

### **2.2.3 Principals/ Mechanisms of action**

The aim of NF is to improve cortical functioning by training the brain's electrical activity, primarily through operant conditioning, and thereby enhance the brain's ability for self-regulation, i.e., the flexibility to adapt brain activity to more effectively meet the changing demands from the environment (Arns et al., 2014). Over time, the training may lead to neurophysiological changes in the brain (Lévesque et al., 2006), which in turn may lead to a decrease in different types of symptoms.

In NF training, the individual's brain activity is registered with EEG sensors placed in predetermined locations on the subject's head and face (Simkin, Thatcher, & Lubar, 2014). Meanwhile, the subjects are instructed to concentrate on a task being played on a screen in front of them. If the subject succeeds in carrying out the task by staying focused, he or she will receive some form of reinforcing feedback. By receiving such feedback every time, one manages to remain focused on the task, the individual gradually learns to associate a state of attention with the reward. Following the principals of operant conditioning, this positive association will reinforce the attention-maintenance behavior and encourage the individual to develop this ability through continuous practice. Furthermore, the expectation of the upcoming reward causes dopamine release which eventually may lead to functional and structural changes in the brain (Simkin et al., 2014).

However, the mechanisms of actions are not fully understood and there are a multitude of explanatory models. Gevensleben et al. (2014) presented two models representing opposite poles, based on a number of concurring assumptions. The "Conditioning-and-Repairing" model, encompasses a more traditional view of NF. It is based on a mono-causal framework, targeting specific causal deficits. It is assumed that the (neural) deficit can be corrected with NF, mainly via implicit operant conditioning, needing no conscious effort from the subject. Thereby, reducing the underlying neural deficit should also reduce the symptoms. Contrasting these assumptions, the "Skill-acquisition" model builds on a biopsychosocial model, that considers a multitude of factors that influence the symptoms. Here, neuro-regulation has to be learned explicitly and with effort, resulting in a regulatory skill. Symptoms are (at least initially) reduced as a result of the intentional application of the acquired self-regulation skill. These assumptions may also have an effect on the application of NF (Gevensleben et al., 2014). In table 1, a summary of the differences between the abovementioned models, based on their different assumptions and their implications for application, is provided.

**Table 1.** Summary of differences between the Conditioning and repairing model and the Skill acquisition model

<b>Assumption</b>	<b>Conditioning and repairing model</b>	<b>Skill acquisition model</b>
<i>Indication</i>	Specific neurophysiological deficit.	No specific deficit.
<i>Mechanisms of learning (EEG regulation acquisition)</i>	Automatic, unconscious (implicit) learning (operant conditioning of EEG pattern).	Controlled, effortful acquisition of regulation skills (explicit learning).
<i>Significance of psychological and social variables</i>	Susceptibility to basic learning mechanisms (operant conditioning), no higher-order cognitive processes involved.	Effects moderated/mediated by cognitive-attributional variables; generalization of effects moderated by social support, positive reinforcement of target behaviour.
<i>Effects of the treatment</i>	Automatic change in EEG-trait (tonic change).	Change in EEG-state (phasic changes), acquisition of self-regulation skills, enhancement of neurophysiological functioning.
<b>Ways of application</b>		
<i>Instructions, acquisition of self-regulation</i>	No active trainer, no specific instructions nor effort needed, <b>passive</b> participant	Active coaching, support in the search for regulation strategies, <b>active</b> participant, effort to enhance self-regulation skills.
<i>Generalization</i>	Automatic transfer to daily life → no effort necessary to support generalization.	Transfer-trials; tasks for generalization of effects (e.g., homework, transfer exercises).
<i>Setting</i>	Unimodal treatment (Repairing the EEG deficit “normalizes” behavior.)	Module in a multimodal treatment, involvement of parents/teachers.

**Note.** Source: Adapted from Gevensleben, H., Moll, G. H., Rothenberger, A., & Heinrich, H. (2014). Neurofeedback in attention-deficit/hyperactivity disorder—different models, different ways of application. *Frontiers in human neuroscience*, 8, 846.

## 2.2.4 Slow Cortical Potential Neurofeedback

Slow cortical potentials (SCP) are event-related-potentials (ERP) that last from several hundred milliseconds to several seconds, and are either electrically negative, or positively charged (Birbaumer, 1999; Gevensleben et al., 2014). SCPs regulate cortical activity and prepare for physical and cognitive actions, in addition to regulating attention and memory (Birbaumer, 1999; Birbaumer et al., 1990; Elbert, 1993). A shift in increased negativity decreases the threshold for neural excitability, thereby increasing the overall cortical activity. Contrary, a positive shift is associated with decreased excitability and inhibition (Gevensleben et al., 2012).

It is well established that healthy and neurotypical individuals can learn to intentionally self-regulate positivation and negativation shifts (Elbert et al., 1980; Lutzenberger et al., 1980). However, studies have indicated that individuals with schizophrenia (Schneider, Rockstroh, et al., 1992), and individuals with an alcohol substance abuse have impaired self-regulatory control (Schneider et al., 1993). However, when they stayed sober for a longer period, alcohol-dependent individuals did successfully regulate their SCP (Schneider et al., 1993). Similarly,



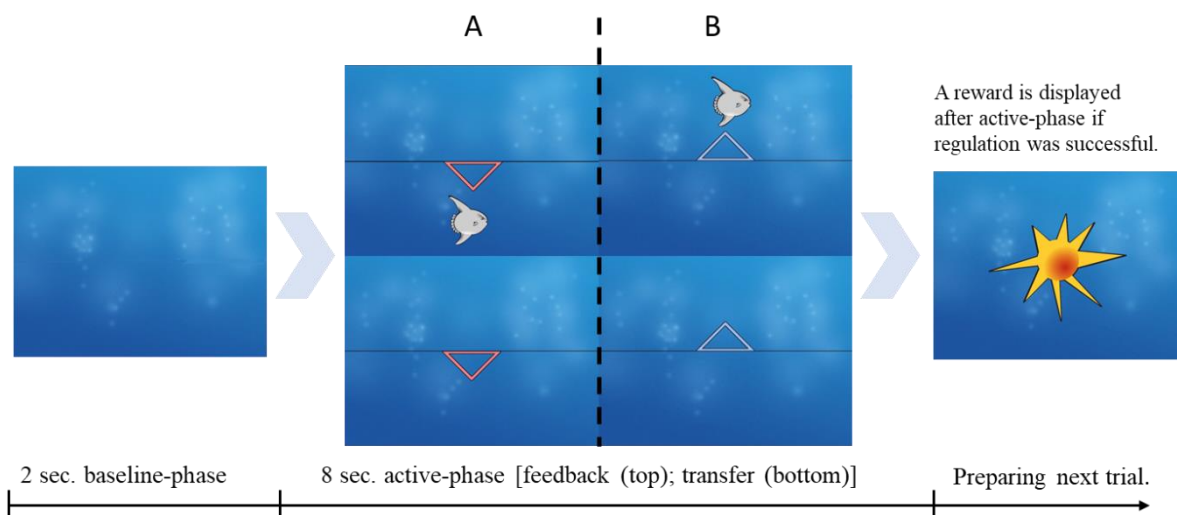
individuals with depression have shown successful regulation (Schneider, Heimann, et al., 1992).

Since then, SCP-NF has been utilized as a treatment for several conditions such as epilepsy (Kotchoubey et al., 2001), migraine (Siniatchkin et al., 2000), tinnitus (Milner et al., 2016), and ADHD (Aggensteiner et al., 2019). It has been postulated that the self-regulation of SCPs may impact the sleep-spindle circuitry and thereby improve sleep (Arns et al., 2014; Arns & Kenemans, 2014), which may be beneficial for a multitude of disorders. Although the aetiology of these disorders vary, the implementation of SCP-NF is rather similar, with only the ratio of negative to positive shifts departing dependent on the condition, and has even been considered a one-size-fits-all method (Mayer et al., 2013).

The increased focus on negative shifts in ADHD, is linked to the contingent negative variation (CNV), another ERP closely associated to both SCP and ADHD (Mayer et al., 2012; Sartory et al., 2002). The CNV appears in anticipation of a stimulus and has been found to be correlated with both IQ and executive functions (Sartory et al., 2002). The activity arising from this negative variation has been traditionally linked to attention and initiation of goal-directed behavior, two areas in which individuals with ADHD present difficulties. The deficiency in CNV (i.e., lower amplitude) suggests that individuals with ADHD have difficulties regulating their cortical activity. It has been indicated that the CNV can predict outcome of SCP-NF (Wangler et al., 2011), and changes thereof may differ in good and poor performers (Doehnert et al., 2008).

The aim in Slow Cortical Potential-Neurofeedback (SCP-NF), is to learn to produce positive and negative shifts intentionally. The training consists of several trials that last for around 6 to 10 seconds. Each trial is preceded by a passive segment of around 2 seconds, which serves as baseline for the active phase during which the desired shift is generated, by either increasing or decreasing the cortical activity relative to the baseline value. The active phase is usually initiated by an acoustic signal together with the appearance of a prompting cue, that indicates in what direction the shift is to be steered. Often, an increased activation (i.e., increased negativation) is indicated by steering “upwards”, while “downwards” steering indicates decreased activation (i.e., increased positivation). The participants performance is displayed in real-time on screen, e.g., via the altitude of an object that moves horizontal across the screen, based on an up/down modality. If the object is steered in the correct direction (as indicated by the cue), a rewards animation is displayed, and the trial is deemed successful. As the EEG signal is prone to artefacts, online artefact corrections are implemented. Artefacts generated by muscle tension and by eye-movements, measured via electrooculogram (EOG), are corrected

via different algorithms (Strehl, 2009). In order to enable the transfer of self-regulation from the training setting into daily life, trials with delayed feedback are implemented. During such trials, the participant is only prompted with the start signal and the cue, but is not receiving any contingent on-screen feedback. However, the reward is displayed if the trial was successful (see Figure 1). To further facilitate the transfer into daily-life, cards with pictures from the training screen are utilized to assist “dry runs” outside of the lab or clinic.



**Figure 1.** Example of SCP-NF trials. Each trial consists of a 2 sec. baseline-phase, an 8 sec active-phase, and, if the regulation was successful, a reinforcement phase. Thereafter the next trial is prepared. **A** illustrates the deactivation/ positivation condition, with or without contingent feedback; while **B** illustrates activation/ negativation condition, with or without contingent feedback. Source: SCP-Neurofeedback with THERA PRAX<sup>®</sup>, neurocare group AG, 2022.

### 2.2.5 Live Z-score Neurofeedback

Live Z-score training (LZT) is a NF protocol that utilizes quantitative EEG (qEEG), and has found increasing acceptance since the 1990’s (Thatcher, 1998; Thatcher & Lubar, 2009). Rather than carefully examining the raw EEG for aberrations, in qEEG the data is quantified and compiled into standardized databases (Wigton & Krigbaum, 2015). This allows for reliable comparisons of EEG data between individuals for diagnostic purposes, as well as assessing changes within the individual over time. Being reliable, cheap and non-invasive, qEEG assessments have become a useful assessment tools (Hammond, 2010).

In a normative qEEG based model of neurofeedback, a guiding principal is that any clinical symptom, or diagnosis (such as ADHD), can be related to different types of deviant EEG-patterns for different individuals. This means that training protocols must be tailored to fit the

individual EEG-patterns of each client (Surmeli et al., 2012). Treating symptoms or diagnoses based on individual qEEG patterns, rather than from a general concept of a symptom or neuropsychiatric diagnosis, allows for a more personalized approach. It has also been indicated that clinical effectiveness can be improved when participants are assigned to NF protocols based on qEEG assessments (Arns, Drinkenburg, et al., 2012; Krepel et al., 2020).

During LZT, the trainee receives continuously updated real time feedback, while the trainer can monitor multiple values, computed and updated in real time from EEG readings. Information for the trainer include whether Z-scores are currently within a pre-chosen boundary (e.g.,  $\pm 2.0$  SD). The main feature is that it uses real-time estimates of multiple measuring points, which provide feedback with the purpose of rewarding EEG activity closer to the norm, in an attempt to normalize brain activity (Collura, 2016; Collura et al., 2010). The training model is based on performing a task during LZT training, computed and compared to a norm value derived from a brain at rest. This means the “target value” during training, for any specific location, reflects the activity of a resting brain. The rationale for this practice is based on the idea that the resting brain represents a state of maximum flexibility, in essence, a brain ready to respond (Collura, 2017). Training the deviant Z-scores towards the mean has been observed to generate clinical benefit (Arns, Conners, et al., 2012; Breteler et al., 2010; Collura, 2010; Surmeli & Ertem, 2010), and has become popular and widely used among private practitioners (Thibault & Raz, 2017).

However, there is considerable variation in LZT regarding which parameters are used (e.g., amplitude, power ratios, coherence or asymmetry), how the frequency ranges for different brain waves are defined, and how the conversion of z-scores into feedback signals is done (Collura, 2016). Also, while LZT is popular, and applied by many private treatment providers due to its easy implementation, the support from peer-reviewed research is limited (Coben et al., 2019).

## **2.3 WORKING MEMORY TRAINING**

Working memory training (WMT) is a computerized intervention that targets different working memory functions. Usually, these interventions have elements of gamification, utilizes adaptive difficulty levels and are performed on a daily basis to enhance working memory capacities (Klingberg et al., 2002, 2005). There are encouraging results that training enhances the capacity of working memory, and it has also been indicated that there may be beneficial effects on behavioral measures in children with ADHD (Beck et al., 2010; Green et al., 2012; Klingberg et al., 2005).

However, there have been questions concerning the nature and durability of the effects, and meta-studies indicate limited effects on ADHD symptoms, even though improved working memory performance (Cortese et al., 2015; Melby-Lervåg & Hulme, 2013; Rapport et al., 2013).

Furthermore, it has been suggested that far-transfer effects are limited (Melby-Lervåg et al., 2016). Still, positive effects on academic performance has been suggested (Nutley & Söderqvist, 2017; Söderqvist & Nutley, 2015), although a recent meta-analysis on typically developed children has suggested the opposite (Sala & Gobet, 2020).

### **3 RESEARCH AIMS**

The overarching aim of this thesis was to investigate NF as a potential treatment for children and adolescents with ADHD, in a pragmatic and naturalistic setting.

#### **3.1 STUDY I**

The aim of this qualitative study was to investigate the participants subjective experience of SCP-NF. The main focus concerned the participants use of strategies while striving for self-regulation, and how these strategies may change over time as SCP-NF went on. In addition, participants' compliance to the training was considered. Finally, based on the strategies utilized, this study aimed to describe typical prototypes of how participants related to, and experienced the SCP-NF training.

#### **3.2 STUDY II**

The aim of study II was to test the effect of SCP-NF and LZT, compared to WMT and Treatment-as-usual (TAU), on ADHD core symptoms. Both immediate and sustained effects (at 6-month follow-up) were investigated. As secondary measures, behavior ratings of executive functions, health-related quality of life and adverse event were investigated.

#### **3.3 STUDY III**

The aim of study III was to investigate the immediate and sustained effect (at 6-month follow-up) of SCP-NF, LZT, WMT and TAU, on a wide range of cognitive function measures (i.e., working memory, time perception, inhibition, and inattention). Furthermore, the moderating effects of ADHD presentation, medication status, age, and sex were tested.

#### **3.4 STUDY IV**

With the results from study II and study III in mind, the objective of this study was to review the literature concerning SCP-NF protocols, and in particular how SCP self-regulation has been evaluated previously. The main aim was to map out differences in the protocols, i.e., concerning details such as trial length, training volume (total number of trials and sessions), electrode placement, etc., but also sample data (age, diagnoses and sample size). Components that were to promote acquisition of self-regulation were lifted specifically, primarily reward schemes and transfer-exercises. Furthermore, the definitions and evaluation of successful self-regulation, received particular attention. The final aim of this study was to synthesize suggestions for future SCP-NF protocols, to promote successful SCP self-regulation.

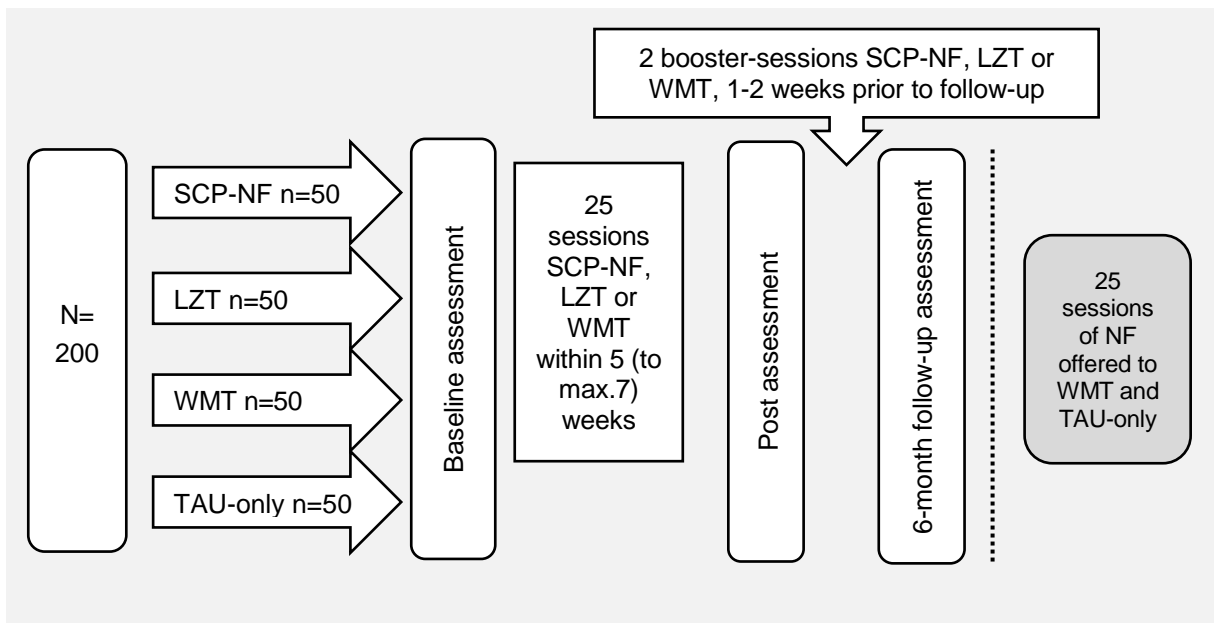
## 4 MATERIALS AND METHODS

All studies included in the thesis are part of the KITE-project (“*Kognitiva Inlärnings- och Träningmetoder Evidensbaserad*”), a four-armed comparative pragmatic single-center randomized controlled trial. The trial was registered at clinical-trial.gov (NCT01841151).

The rationale for the KITE-project was to further the knowledge on Neuro-cognitive training (NCT) interventions, by implementing the following methodological strength and novelties: (i) a comparative design (SCP-NF vs. LZT vs. WMT vs. TAU-only); (ii) a relatively large sized sample of patients with ADHD (N = 200, 4x n = 50); (iii) including (probably) blinded ratings via the teacher ratings; (iv) having well-defined inclusion and exclusions criteria that tolerate common comorbidities like ASD; (v) psychometrically sound outcome measures; (vi) multiple informants (participants, parents, and teachers); (vii) a naturalistic clinical setting to calculate the added value of NCTs in addition to TAU (pragmatic study); and (viii) a high-intensity delivery, with five training sessions per week for five weeks (Hasslinger et al., 2016).

The **inclusion** criteria for the participants were: (1) having a primary clinical diagnosis of ADHD according to DSM-IV-TR or ICD-10; (2) if medicated, dosage had to be stable for at least 1-month prior study engagement; and (3) having an IQ above 80, according to the General Ability Index of the Wechsler scales. The **exclusion** criteria for participants were: (a) having clinically unstable psychiatric comorbidities (e.g., acute depression, bipolar disorder, eating disorders, etc.), or severe somatic diseases (e.g., intractable epilepsy); (b) having very limited skills in the Swedish language.

Participants were assessed at baseline, at post-intervention (shortly after completing the 25 sessions, and at 6-month follow-up. All participants had to be free from psychoactive medication (i.e., stimulants like Concerta and Ritalin) for 48 h prior to the neurocognitive assessments. However, there was no washout period for participants on non-stimulant ADHD medication like Strattera (atomoxetine). While all participants received standard care by different obligatory pediatric, child- and adolescent psychiatric or habilitation services, the training and all assessments were exclusively conducted at BUP-KIND, a specialized child and adolescent psychiatric outpatient unit of the division of Child and Adolescent Psychiatry (BUP), Stockholm County Council. The NCT training was carried-out with a high frequency and consisted of five sessions per week for 5 weeks for a total of 25 sessions. One to two weeks prior the follow-up assessment, two booster sessions were conducted. After study completion, participants from the non-NF groups, were offered 25 sessions of NF (see Figure 2).



**Figure. 2.** KITE Study flow-chart. Source: Adapted from Hasslinger et al. (2016).

## 4.1 DESIGN

### 4.1.1 Study I

This qualitative study, explored the participants' subjective experience and strategy use during SCP-NF. Participants were asked every fifth session, about their training experience, what they were doing during training and how they were achieving it. Utilizing a semi-structured interview guide, the interviews were recorded directly after the session. Most of the interviews were short (median: 2:46 min.). However, this could vary notably between both participant and instant/ session (range: 0:21-8:57 min.). All interviews were transcribed verbatim and analyzed in NVivo 12 (QSR and Ltd, 2012).

In addition to the interviews, participants' behavior during each session was rated by the trainers. Assisted by these session ratings, an overall compliance score was appraised via consensus discussions between trainers.

As investigating the participants' subjective experience was not part of the initial protocol (Hasslinger et al., 2016), this was an add-on study, that was initiated during the second half of data-collection of the main study. Although interviews were conducted with participants from all active intervention groups, for study I, only interviews from SCP-NF were analyzed.

### 4.1.2 Study II

This study was a four-arm randomized controlled trial, that focused on the interventions' effects on ADHD core symptoms, both directly after the intervention and at the 6-month follow-up. Between-group effects were the main focus, in particular the comparison of the two NF protocols (SCP-NF and LZT) with WMT and TAU-only. However, within-group effects were also investigated.

The **primary** outcomes for changes in ADHD core symptoms were based on the attention-, and the hyperactivity/impulsivity-scales, as well as the ADHD-index, all from the Swedish version of the Conners-3 questionnaires (Thorell, L, Hammar, M., Berggren, S., Zander, E. & Bölte, 2015). Scores from all informants (self-, parent- and teacher-ratings) were considered. As **secondary** measures both the parents and teacher ratings of the metacognition-index and the behavioral-regulation-index from the Behavior Rating Inventory of Executive Functions (BRIEF) (Gioia et al., 2000) were included. Self-rated quality of life was measured with the KIDSCREEN-27 (Ravens-Sieberer et al., 2006). In addition, adverse events were tracked, using the Pediatric Side Effects Checklist (Pavuluri & Janicak, 2004), and the blindness of the teachers was assessed via a questionnaire.

### 4.1.3 Study III

Based on the same sample as study II, this study examined the effects of two NF protocols and WMT on a battery of cognitive function tests, both directly after the intervention and at the 6-month follow-up. Although some effects were anticipated, no specific hypotheses were postulated, as this study was mainly exploratory.

Three areas of cognitive functioning that are related to ADHD were investigated: **Working memory**, was measured with four tests, and included both spatial and verbal working memory measures; **Time perception**, was assessed by two tasks; and **inhibition and attention** was assessed using multiple measures from the Conner's Continuous Performance Test-II (CPT-II) (Conners et al., 2000).



#### **4.1.4 Study IV**

This systematic review was registered at Prospero (CRD42021260087) and followed PRISMA criteria (Moher et al., 2016). We implemented a broad search strategy based on the term “slow cortical potential\*”, in order to limit the risk of missing any relevant publications. Initially, we neither set any limitations concerning language, year or type of publication. Searches were conducted in: Medline (Ovid), Web of Science (Clarivate), PsycInfo (Ovid), and ERIC (ProQuest), by experienced librarians at the University Library of Karolinska Institutet.

## **4.2 INTERVENTIONS**

### **4.2.1 Slow Cortical Potential-NF**

SCP-NF was conducted using a TheraPrax™ (NeuroConn GmbH, Ilmenau, Germany). Using Ag/AgCl ring-electrodes, one active electrode was placed at the vertex, Cz. The mastoids served as reference and ground, and an additional four electrodes were placed around the eyes, measuring the vertical and horizontal electrooculogram. The sites were prepared using Nuprep® skin prep gel, and applied to the sites with Ten20® conductive paste (Weaver and company, Aurora, CO, USA). Impedance was kept under 5 kΩ. At the beginning of each session the participants’ horizontal and vertical eye movements, as well as blinking, were recorded in order to calibrate the online eye-movement correction, which eliminated or suppressed signals from the eyes. Also, signal shifts that exceed 200μV, were automatically rejected and the trial was retaken. No additional (offline) artifact correction was conducted.

Every SCP-NF session consisted of 4 blocks of 36 trials (144 trials per session). Each trial consisted of a 2 seconds baseline-phase and an 8 seconds active-phase. During each trial, a triangle that pointed upwards or downwards, was presented on a computer screen. Another object (a fish or a bird) was presented, that moved left to right across the screen. The task was to move this object in the same direction as the triangle, by regulating one’s SCPs. When the cortical excitability was increased, the object moved upwards, and downward if it was inhibited. A rewarding star was displayed when the SCP amplitude exceeded  $\pm 40\mu\text{V}$  for 2 consecutive seconds during the last 4 seconds of the trial. The ratio of activation- to deactivation-trials was set at 1:1.

So-called transfer trials constituted 20% of all trials during week 1, 40% during week 2, and 50% for the remaining training period. During these trials no contingent feedback was given, only the prompting triangle and, if successful, the reward star. Their purpose was to facilitate self-regulation without the need of real-time feedback.

#### **4.2.2 Live Z-score Training**

LZT was conducted with an Atlantis II™ amplifier (BrainMaster Ltd, Bedford, Ohio, USA), with AgCl snap connectors/ electrodes, for the active sites. The training protocol consisted of two 2-channel PZOK training blocks, using the ANI database (Applied Neuroscience Ltd, Florida, USA). PZOK stands for “Percent of Z-scores OK”, that is the percent of Z-scores that are within the targeted limits. In our case, the targeted Z-score corridor was kept between at +/- 1.5 SD, and the percentage of Z-scores within this corridor was adjusted manually to enable a success rate of 60-70%, although at times rates could temporarily lie between 50-80%.

For the first block, electrodes were placed at C3 and C4, and for the second block at Fz and Cz. A linked ear served as reference, using an ear-clip electrode. All sites were prepared using Nuprep® skin prep gel, and applied with Ten20® conductive paste (Weaver and company, Aurora, CO, USA). Impedance was kept under 5k Ohm

At the beginning of each session feedback was given using BrainCells™ (BrainMaster Ltd.). This is a visual animation game where blue dots (“brain cells”) appear faster and smoother on the screen, filling a jar., and was also reinforced via auditory effects. This is regulated by the participants performance (matching the set Z-score percentage). During session one, this game was used for 15-20 min, as introduction to the training. During subsequent sessions, the length was shortened to 5-10 min. For the rest of the training, participants could choose visual stimuli from DVDs, Netflix™ or Youtube™. During this phase, the feedback was provided via a transparent dimmer-window (Tor Ghai, Stockholm, Sweden) that was placed on top of the stimuli. Depending on the participants performance, the dimmer-window shifted between being transparent or opaque. Apart from sitting still during training, the participants received no other specific instructions. Overall, sessions lasted around 60 minutes.

### **4.2.3 Working Memory Training**

For WMT we used Minneslek Flex™ (www.flexprogram.org), which is a computerized program with visuospatial and auditory working memory tasks. It is commercially available and has been utilized within some schools. It is similar to and based on the same principles as the well-researched program CogMed™ (Roche & Johnson, 2014).

There were two versions, a Junior and a Senior, that the participants could choose between. Both versions shared the same structure, but differed in the thematic content of the exercises. Every session, for both versions, consisted of six different exercises with 12 trials each. There were two visuo-auditory exercises, two visuo-spatial exercises with fixed objects, and two visuo-spatial exercises that either contained movement and/or distraction. The level of difficulty was automatically adjusted based on the participants' performance, i.e., after a set number of correct consecutive responses, the number of objects increased, and after a set number of incorrect responses the number of objects decreased. Five exercises had a maximum number of objects that had to be recalled of eight. Recall was always forward, but once the maximum number of objects was reached, the reproduction order changed to backwards. The sixth exercise had a maximum of ten objects, and consisted of objects that had to be sorted. The recall direction did not change. Session length was influenced by the performance, as an incorrect response aborted the trial immediately, while it took more time to generate and repeat more objects than fewer objects. However, on average the sessions lasted around 45 minutes.

### **4.2.4 Shared elements for active intervention**

Starting from the beginning of the third training week, participants in the active interventions received so-called transfer cards. These were small cards with pictures from their training modality, e.g., a picture of the fish that is being steered in SCP-NF, a screen shot during Brain Cells in LZT, or a screen shot from the participants favorite WMT exercise. Participants were instructed to look at these cards every day and get into the same mindset as during training, preferably in situations that demanded attention (e.g., doing homework, or reading). Such tools are commonly used in SCP-NF, as an aid practicing regulation outside of the lab, facilitating the transfer of self-regulation into everyday situations. Parents were instructed to help remind the participants to use their cards regularly. Trainers followed-up the use of transfer cards, by asking the participants, after every session.

#### 4.2.5 Treatment-as-Usual

All participants were instructed to restrain from starting new treatments for ADHD during their participation in the study, while ongoing treatments should not be changed, including medication dosages which were to be kept stable. No additional restrictions were imposed. Only data concerning participants' medication status was collected at baseline, but not for other interventions, including dietary supplements. However, no psychological treatments for ADHD were reported by any participants during the assessment interviews at baseline. Yet, many participants' parents had undergone psychoeducational parent group-training prior to study inclusion, in accordance with the regional guidelines for treatment of ADHD (Axén et al., 2010).

### 4.3 MEASURES

#### 4.3.1 Questionnaires

ADHD core symptoms were evaluated with the Swedish full-length version of the **Conners-3** questionnaires. The ADHD-index, the inattention and the hyperactivity/impulsivity subscales, for all three raters (i.e., parent-, teacher- and self-ratings) served as primary outcome measures in study II. The Conners-3 full version consists of 99-115 items (dependent on informant), that are answered on a 4-point Likert scale. Ten items constitute the ADHD-index, with a maximum score of 20 for both the parent- and the teacher-rating, while the self-rating version has a maximum score of 18. The t-scores of ADHD-indices, also served as measure for overall symptom severity, when comparing the intervention groups, in both study II and study III. The inattention subscale consisted of 10 items for the parent- and teacher rating (max. score 30), or 11 items for the self-rated version (max. score 33), and covered different aspects of inattention and distractibility associated with ADHD. The subscale for hyperactivity and impulsivity consisted of 14 items for the parent- and self-ratings (max. score 42), or 18 items on the teacher rating (max. score 54), that measured hyperactivity and impulsivity elements of ADHD. The Swedish Conners-3 version has shown good internal consistency (Cronbach's alpha: ADHD-index:  $r = .81 - .95$ ; inattention:  $r = .90 - .95$ ; hyperactivity/impulsivity:  $r = .85 - .97$ ), and the test-retest reliability, measured by the teacher ratings, is also high ( $r = .96-.99$ ) (Thorell et al., 2018).

Both the parent- and teacher-ratings of the Swedish version of the **BRIEF** questionnaire, consists of 86-items, on a 3-point Likert scale. The metacognition index (MI) and the

behavioral regulation index (BRI), served as the secondary outcome measure in study II. While the MI score reflects the child's ability to cognitively self-manage tasks and is directly related to the ability to problem solve, the BRI measures the ability to shift and modulate emotions and behavior via appropriate inhibitory control. Both indices have shown good internal consistency (Cronbach's alpha  $r = .96 - .97$ ), and high test-retest reliability ( $r = .80-.92$ ) (Gioia et al., 2000).

The **KIDSCREEN-27** (Ravens-Sieberer et al., 2006) is a self-report questionnaire consisting of 27 items, on a 5-point Likerts scale, applicable to children between 8-18 years about their perceived health related quality of life. The general Health Related Quality of Life-index, consists of ten items that provide a global score ranging from 10 to 50, and was used as secondary outcome measure in study II. The KIDSCREEN-27 questionnaire has shown robust psychometric properties (Robitail et al., 2007).

#### **4.3.2 Cognitive tests**

Study III analyzed multiple measures of multiple cognitive tests, which all were administered by a certified psychologist or supervised clinical psychology student. Verbal working memory was measured via the forward and backward versions of Digit Span and Letter-Number Sequencing, administered face-to-face, from the WISC-IV/ WAIS-IV (Wechsler, 2009, 2011). In the **Digit Span** task, numbers are being read out loud, which the participant is required to repeat in the same order (forward) or in the opposite order (backward). In the **Letter-Number Sequencing** task, numbers and letters are being read out loud. The participant is required to first repeat the numbers (in numerical order) followed by the letters (in alphabetical order). The scaled scores ( $10 \pm 3$ ) of these subtests were used as outcome measures. The **Block-Tapping** task from WISC-IV-integrated/ WAIS-III NI (Wechsler, 2004; Wechsler et al., 2004) was also administered face-to-face, and measured spatial working memory. Here, the test leader pointed at cubes on a board, and the participant was required to point at them in the same order (forward), or in the reversed order (backward). The raw scores (max. 19) were used in the analysis, as the available scaled scores were not comparable between the WISC-IV-integrated and the WAIS-III NI versions. The computerized "**Find the phone**" task, which is a generic version from the spatial working memory task included in the Cambridge Neuropsychological Test Automated Battery (CANTAB), and has been used in previous studies (Owen et al., 1990; Sjöwall et al., 2013), was also administered. Here, phones are displayed on a computer screen. A phone ringing noise is presented, and the participant has to find which phone is ringing. Once

the correct phone has been found, another one rings, repeating the task. Two trials each with 4, 6 and 8 phones appearing were administered, and two performance measures were collected: between-search errors (BSE), which occur when clicking on a phone that has already been answered in a previous trial in the same level; and within-search errors (WSE), which occur when clicking on a phone multiple times in the same trial.

Time Perception was assessed in two computerized tasks; Time Anticipation utilized visual cueing, while Tapping utilized auditory cueing (Toplak & Tannock, 2005). **Time Anticipation** is mainly an impulsivity task, and is framed by a short story where participant has to “beam oxygen” over to a spaceship, in order to save the crew. In order to be successful, the participant has to press the space bar immediately when the spaceship appears on the screen, which always takes the same time every trial. Eventually, the spaceship gets cloaked, but still appears after the same duration. The task is to press the space bar at the correct moment, even if the spaceship is invisible (uncued trials). Feedback is given for each trial, notifying the participant if they were: on time, too early, or too late. Two versions were conducted, one with a response rate of 400 msec. and one for 2000 msec. The hit rate for correct and too early responses during uncued trials, served as dependent variables. In the **Tapping** task a tone was presented every 1200 msec. and the participants had to synchronously tap the left mouse button. After 15 trials the tone stopped, but the participant had to continue tapping the mouse button with the same rhythm (1200 msec. interval). Two identical runs were administered, and the mean tapping rate and standard deviation (SD) was calculated for the last 40 uncued trials per run. The coefficient of variability was calculated via the subjects’ SD/mean tapping rate x 100 and served as outcome measure.

The **Conner’s Continuous Performance Test-II** (CPT-II) was administered and served as measure for inhibition and attention functions. The CPT-II is a widely applied computerized task with incremental clinical utility (Tallberg et al., 2019), and generates a multitude of outcome measures. Participants sit in front of a computer screen, and are instructed to press the left mouse button as soon as a letter appears on the screen. However, they are to refrain from pressing the button if the letter is an “x”. Wrongfully responding to the non-target (x) constitute commission errors, reflecting impulsivity. Contrarily, missing to correctly respond to targets constitute omission errors, reflecting sluggish attention. In addition, reaction time and standard error thereof, also indicate inattentiveness. The normative t-values ( $50 \pm 10$ ) for the above variables were used as the outcome measure. The ADHD-index, based on the overall response pattern during the CPT-II, was also included.

### 4.3.3 Other measures

For study II data was also collected concerning adverse events and the blindness of teachers. The former, were tracked with the comprehensive **Pediatric Side Effects Checklist**, which covers 47 discomforting problems on a 4-point Likert scales (Pavuluri & Janicak, 2004). These problems were rated from “no problem” to “highly-problematic/intolerable”. Caregivers, or when deemed appropriate the participant him/herself, were asked to fill out the checklist at each assessment point and weekly during the intervention period. We focused on adverse events that were either newly emerging, or that deteriorated from baseline. In addition, adverse events could also be reported spontaneously or observed during the training. However, these were not documented in a systematic manner. The latter was tracked via a **Teacher Blindness Rating**, a short questionnaire design within the KITE-project. Here, teachers were asked about their awareness of their student’s participation in the study. Those that responded “yes”, were also asked which intervention, according to the teacher’s belief, the student partook in (i.e., NF, WMT or control condition), together with their reason for their assumption (i.e., information from student or parents, due to behavioral changes, or guessing).

In order to assess how “well” the participants participated during training, we implemented a so-called **Compliance Rating**. Here, we operationalized compliance as both the adherence to successfully perform during training. This included both attendance and motivation, but also how well the task was performed. Moving around, talking and other activities that affected the task (e.g., artefacts in EEG or unforced errors in WMT), would lower the rating. Being effortful and determined to succeed, as well as conformity to instructions (i.e., adjusting behavior during training) would increase the rating. After each training session, the trainer rated the participants’ compliance on a 0-3 scale, where “0” represented a complete lack of compliance and “3” very high compliance. As the final rating, we did not utilize the average of the daily session ratings. Instead, the daily session ratings served as base for discussion, as trainers evaluated whether a participant showed “low” or “high” compliance, or “in between”, until consensus was reached.

## **4.4 SAMPLE**

### **4.4.1 Study I**

In total 30 participants (9 girls and 21 boys; mean age  $M = 12.41$ ,  $SD = 2.73$ ), were included in the analysis. In addition to participants who had been randomized into the SCP-NF group ( $n = 21$ ), participants from the WMT- or TAU-group who after their completion in the KITE-study were offered NF, and chose SCP-NF, were also included ( $n = 9$ ).

The number of interviews per participants varied much, and ranged from 1-7. Fourteen participants completed at least five interviews, and constituted the underpinning for the in-depth analysis for typical training profiles. In total of 130 interviews were included in the analysis

### **4.4.2 Study II & Study III**

Of the 224 applicants that were evaluated,  $N = 202$  children and adolescents started in the study. Seven applicants did not meet the studies inclusion criteria, and another fifteen that had been randomized, ultimately chose not to partake in the study. In total 22 participants dropped out, eight participants by the post-intervention assessment, and another 14 dropped out before the 6-month follow-up assessment. Overall, 180 participants completed at least part of the final assessments.

### **4.4.3 Study IV**

Of the initial 800 unique publications,  $k = 63$  articles were included. The samples of the original studies reviewed in this study, included both healthy subjects and clinical populations, including ADHD, amyotrophic lateral sclerosis, autism, epilepsy, migraine, Parkinson's disease, psychopathy, and tinnitus. Both children and adults were included, and age ranged from 7-75.



## **4.5 ANALYSIS**

### **4.5.1 Study I**

The transcribed interviews were analyzed primarily according to thematic analysis (Braun & Clarke, 2006), and some elements from qualitative content analysis (Graneheim & Lundman, 2004). First, the material was sorted and coded into meaningful groups based on its explicit content. The coded data was then sorted into possible themes, which then were reviewed, named and organized into a hierarchical structure. In the final stage the sorted material was merged and the themes reanalyzed, and the themes were named and structured by two to three researchers.

For the in-depth analysis of training profiles, an inductive-deductive approach was utilized. The transcripts of all interviews from the fourteen participants that had completed at least five interviews, were condensed, reread, and the entire series of interviews (per participant) were summarized. All material was then analyzed for emerging profile consensus discussions. Once a clear description had emerged for one participant, that description was contrasted to the other participants, and revised if needed, until all participants had been sorted into a prototype.

### **4.5.2 Study II & Study III**

For both study II and study III, we used a linear mixed-effects model (Gueorguieva & Krystal, 2004). The model was specified by using time (baseline, post-intervention, follow-up), group (SCP-NF, LZT, WMT, TAU), and the time by group interaction as fixed effects, as well as a random intercept for each participant. Each comparison was run as a separate model, i.e., SCP-NF was compared to TAU, then SCP-NF was compared to WMT, then LZT was compared to TAU, and so on, for all combinations.

### **4.5.3 Study IV**

The literature search rendered 800 unique articles. All titles and abstracts were screened independently by two reviewers, and full-texts were retrieved for articles that at least one of the reviewers deemed eligible. The full-text screening was conducted by the same two reviewers independently. Discordance regarding eligibility was discussed between the reviewers until consensus was reached. Information concerning the sample, electrode placement and the used equipment were extracted. The number of sessions, number of runs/blocks, number of trials, the trial length/duration (baseline and active phase), the use of thresholds, the ratio of deactivation to activation trials, the use of transfer trials, and the use of

transfer-promoting exercises (e.g., transfer card) were also extracted. Furthermore, information on how successful regulation was defined and evaluated, as well as the outcomes for successful regulators, was also extracted and synthesized.

## **4.6 ETHICAL CONSIDERATIONS**

Study II and III were approved by the regional ethics review board for Stockholm, Sweden (Dnr.: 2013/739-31). An amendment was filed and approved (Dnr.: 2017/301-32), covering the interviews conducted in study I. The systematic review in study IV, did not necessitate ethical considerations.

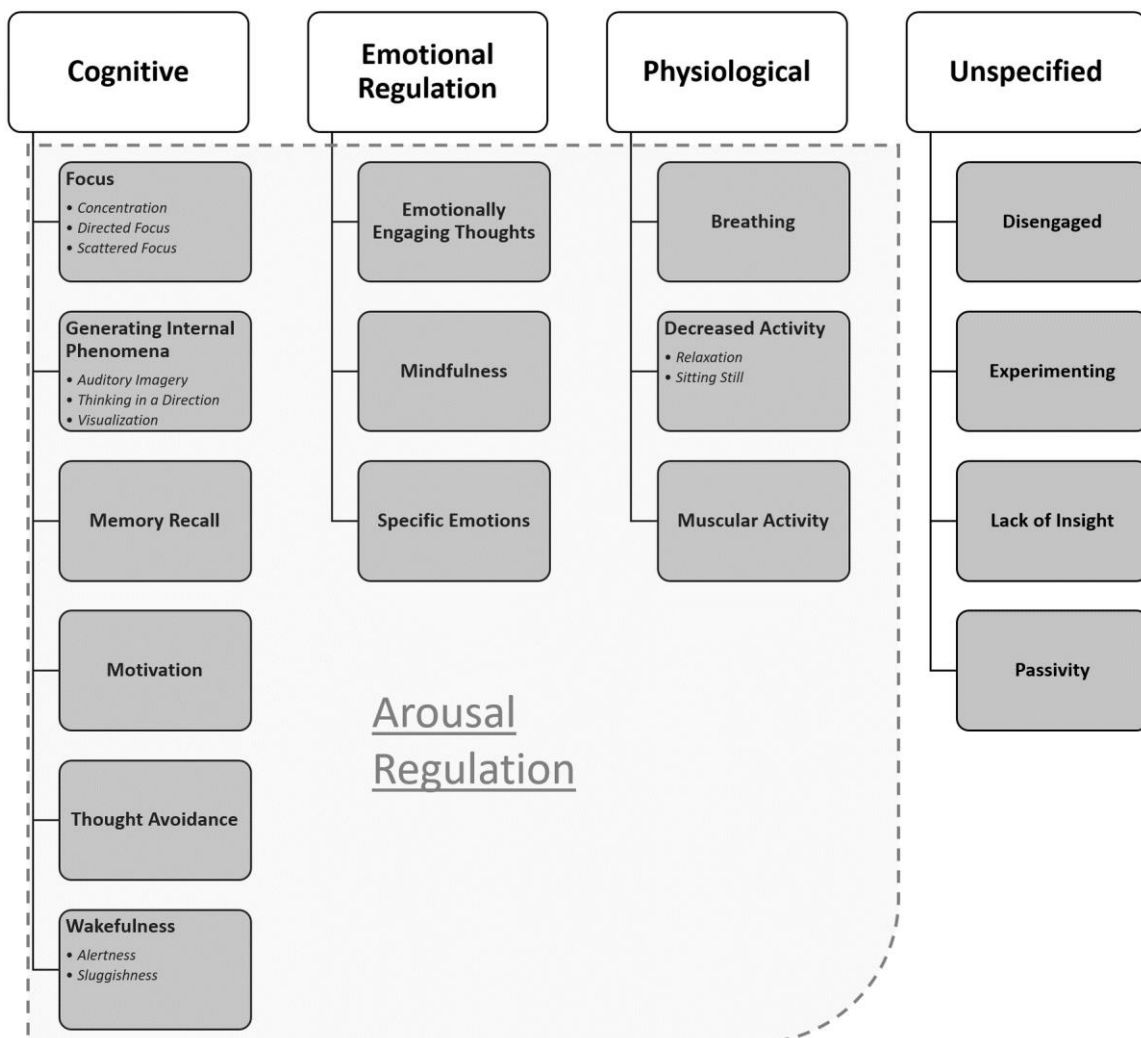
Since the participants were minors, informed consent was given via the parents. To ensure the participants' assent, an easy-to-read version of the study information was provided and written assent was also obtained. Furthermore, participants were offered to visit the lab beforehand, for a rundown of their trial participation. Nonetheless, most participants received their information on the study from their parents. Similarly, the parents' motivation may have superseded the participants' motivation for participation, especially for the younger participants. This could particularly be an issue when participants wanted to discontinue their participation, but were repeatedly persuaded to continue.

However, no harmful or painful procedures were included in the studies; hence the participants were not exposed to any particular risks. Still, the interventions were delivered with daily sessions over a five-week period, which for many could be stressful and wearisome. For some participants this meant missing school, after-school activities or time friends. However, based on previous research, we clearly found the potential benefits outweighing any harm.

# 5 RESULTS

## 5.1 STUDY I

Concerning the use of strategies, four domains emerged: Cognitive strategies, Emotional regulation strategies, Physiological strategies and Unspecified strategies. Each domain contained three to six themes, and four themes comprised additional sub-themes. In addition, twelve of the sixteen themes were connected by a latent theme, as they all intended to regulate the participants arousal level. A hierarchical overview is presented in figure 3.



**Figure 3.** Hierarchical overview of themes and sub-themes. Source: adapted from Hasslinger et al., (2020).

Overall, we did not find any clear patterns concerning changes over time. Regarding differences based on rated compliance level, the highly compliant participants reported emotional strategies more frequently, as well as the strategy *focus*. While participants with a neutrally rated compliance reported the use of the strategies *muscular-activity* and *passivity* more often.

From the in-depth analysis of the fourteen participants, for whom we had at least five completed interviews, three prototypical patterns emerged. Based on the strategies predominantly described and the overall attitude and approach toward the SCP-NF training, we found six subjects that focused on their “State of Mind”, four subjects who described their approach in terms of “Manifest and Concrete” strategies, leaving four subjects whose descriptions gave an overall impression of being somewhat “Unaware” of what they were doing.

Participants in the State-of-Mind-profile, predominantly implemented strategies from the cognitive domain, and their overall strategy pattern was stable over time. They seemed intrinsically motivated, and could see a benefit of completing the training even if they found the task to be boring. Also, only participants within this group described self-perceived improvements after training.

Contrarily, participants in the Manifest-and-Concrete-profile distinguished themselves by their non-abstract approach towards training. They described their strategies more vaguely, and often included statements such as “*I’m thinking up or down*”. Their motivation came mostly from external incentives (e.g., extra rewards from parents), and when they reported improvements after training, these were not self-perceived, but rephrases of comments from parents or teachers.

The Unaware-profile never found a stable approach towards training. They frequently tried different strategies, without settling and refining any particular strategy. There was no intrinsic motivation for symptom improvements, and a lack of insight on why the training is done was common. Avoiding artefacts (e.g., movements) and getting the training session over with was often present.

## **5.2 STUDY II**

Results from the linear mixed model were sparse and inconsistent. When comparing SCP-NF with the TAU group, mean group differences at the post-assessment showed small effects for inattention on both teachers’ ( $p = .018$ ; Cohen’s  $d' = .34$ ) and parents’ ratings ( $p = .41$ ;  $d' = .31$ ), as well as parents’ ratings of overall ADHD symptoms ( $p = .26$ ;  $d' = .34$ ). However, none of these effects were maintained until the follow-up assessment (see Table 2). The only measure that showed significant differences at follow-up, was the metacognition-index from the BRIEF, on both the parents’ ( $p = .005$ ;  $d' = .49$ ) and teachers’ ( $p = .011$ ;  $d' = .58$ ) ratings. When comparing SCP-NF with WMT, no significant mean group differences were found, except for teachers overall ADHD-symptom rating, which was superior in favor of WMT.

**Table 2.** Slow Cortical Potential neurofeedback versus treatment as usual and working memory training from baseline to posttreatment and 6-month follow-up

Measure (Rater)	Comparison	Posttreatment			6-month follow-up		
		Group difference in change score (95% CI)	Sig.	Cohen's <i>d</i>	Group difference in change score (95% CI)	Sig.	Cohen's <i>d</i>
IN-C3 (T)	vs. TAU	2.57 (0.45 to 4.69)	<b>0.018*</b>	<b>0.34</b>	2.64 (-0.05 to 5.32)	0.054	0.35
IN-C3 (P)	vs. TAU	1.78 (0.08 to 3.49)	<b>0.041*</b>	<b>0.31</b>	0.92 (-0.85 to 2.69)	0.308	0.16
IN-C3 (S)	vs. TAU	0.83 (-1.17 to 2.82)	0.415	0.12	1.21 (-1.18 to 3.59)	0.319	0.17
HY-C3 (T)	vs. TAU	1.12 (-1.86 to 4.10)	0.459	0.08	0.80 (-3.17 to 4.78)	0.691	0.05
HY-C3 (P)	vs. TAU	1.48 (-0.49 to 3.45)	0.140	0.14	0.84 (-1.76 to 3.43)	0.525	0.08
HY-C3 (S)	vs. TAU	-0.18 (-2.14 to 1.78)	0.858	-0.02	0.01 (-2.18 to 2.20)	0.994	0.00
ADHD-C3 (T)	vs. TAU	1.33 (-0.19 to 2.86)	0.086	0.25	1.13 (-0.89 to 3.15)	0.271	0.21
ADHD-C3 (P)	vs. TAU	1.68 (0.20 to 3.16)	<b>0.026*</b>	<b>0.34</b>	1.27 (-0.37 to 2.91)	0.127	0.26
ADHD-C3 (S)	vs. TAU	0.73 (-0.47 to 1.93)	0.229	0.19	0.59 (-0.70 to 1.88)	0.365	0.16
MI-BRIEF (T)	vs. TAU	5.99 (0.04 to 11.94)	<b>0.049*</b>	<b>0.32</b>	10.99 (2.56 to 19.42)	<b>0.011*</b>	<b>0.58</b>
MI-BRIEF (P)	vs. TAU	6.25 (2.43 to 10.06)	<b>0.001*</b>	<b>0.49</b>	6.31 (1.92 to 10.71)	<b>0.005**</b>	<b>0.49</b>
BRI-BRIEF (T)	vs. TAU	0.54 (-3.18 to 4.27)	0.773	0.04	3.30 (-1.43 to 8.02)	0.170	0.22
BRI-BRIEF (P)	vs. TAU	1.84 (-0.71 to 4.39)	0.156	0.16	-0.19 (-3.54 to 3.16)	0.911	-0.02
HRQoL (S)	vs. TAU	-0.31 (-2.26 to 1.64)	0.753	-0.05	1.19 (-0.97 to 3.35)	0.279	0.21
IN-C3 (T)	vs. WMT	0.38 (-1.79 to 2.55)	0.729	0.05	-1.02 (-3.73 to 1.70)	0.461	-0.13
IN-C3 (P)	vs. WMT	0.34 (-1.39 to 2.06)	0.702	0.05	-0.38 (-2.22 to 1.46)	0.683	-0.06
IN-C3 (S)	vs. WMT	0.75 (-1.25 to 2.75)	0.461	0.10	-0.62 (-3.06 to 1.83)	0.619	-0.08
HY-C3 (T)	vs. WMT	-1.95 (-5.00 to 1.11)	0.210	-0.13	-3.72 (-7.74 to 0.30)	0.070	-0.26
HY-C3 (P)	vs. WMT	0.41 (-1.59 to 2.41)	0.688	0.04	-1.37 (-4.06 to 1.31)	0.314	-0.12
HY-C3 (S)	vs. WMT	0.74 (-1.23 to 2.71)	0.460	0.08	0.52 (-1.73 to 2.77)	0.647	0.06
ADHD-C3 (T)	vs. WMT	-0.85 (-2.43 to 0.73)	0.289	-0.15	-2.26 (-4.35 to -0.18)	<b>0.034*</b>	<b>-0.39</b>
ADHD-C3 (P)	vs. WMT	0.55 (-0.99 to 2.09)	0.482	0.10	-0.55 (-2.21 to 1.11)	0.511	-0.10
ADHD-C3 (S)	vs. WMT	0.26 (-0.94 to 1.47)	0.665	0.06	-0.29 (-1.60 to 1.03)	0.670	-0.07
MI-BRIEF (T)	vs. WMT	-0.02 (-5.97 to 5.92)	0.993	0.00	3.06 (-5.55 to 11.68)	0.482	0.16
MI-BRIEF (P)	vs. WMT	2.73 (-1.26 to 6.72)	0.179	0.18	3.33 (-1.47 to 8.14)	0.172	0.22
BRI-BRIEF (T)	vs. WMT	0.26 (-3.43 to 3.94)	0.891	0.02	-0.74 (-5.51 to 4.03)	0.759	-0.05
BRI-BRIEF (P)	vs. WMT	0.04 (-2.63 to 2.70)	0.979	0.00	-3.11 (-6.77 to 0.55)	0.095	-0.24
HRQoL (S)	vs. WMT	-0.14 (-2.14 to 1.87)	0.893	-0.02	0.21 (-2.04 to 2.45)	0.857	0.03

**Note:** Negative numbers favor control condition.

IN-C3 = Inattention subscale Conners-3; HY-C3 = Hyperactivity subscale Conners-3; ADHD-C3= ADHD-index Conners-3; MI-BRIEF = Metacognition Index BRIEF; BRI-BRIEF = Behavioral Regulation Index BRIEF; HRQoL = Health-Related Quality of Life index from KIDSCREEN-27; T = Teacher; P = Parent; S = Self

\* p. <=0.05; \*\* p.<0.01.

Source: adapted from (Hasslinger et al., 2021)

When comparing LZT with the TAU, mean group differences of medium effect size were found at follow-up for teachers' ratings of inattention ( $p = .010$ ;  $d' = .47$ ), hyperactivity ( $p = .004$ ;  $d' = .40$ ), overall ADHD-symptoms ( $p = .002$ ;  $d' = .60$ ) and the metacognition index ( $p = .012$ ;  $d' = .50$ ). Notable, only the difference of overall ADHD-symptoms had already been significant at the post-assessment (see Table 3). Concerning rating by parents, no significant results were found at follow-up, although the metacognition-index and overall ADHD-symptoms were significant at the post-assessment. No significant mean group differences were found, when comparing LZT with WMT.

**Table 3.** Live Z-Score neurofeedback versus treatment as usual and working memory training from baseline to posttreatment and 6-month follow-up

Measure (Rater)	Comparison	Posttreatment			6-month follow-up		
		Group difference in change score (95% CI)	Sig.	Cohen's <i>d</i>	Group difference in change score (95% CI)	Sig.	Cohen's <i>d</i>
IN-C3 (T)	vs. TAU	1.27 (-0.65 to 3.18)	0.193	0.17	3.44 (0.84 to 6.05)	<b>0.010*</b>	<b>0.47</b>
IN-C3 (P)	vs. TAU	1.13 (-0.56 to 2.83)	0.189	0.20	1.01 (-0.83 to 2.84)	0.280	0.18
IN-C3 (S)	vs. TAU	1.77 (-0.31 to 3.85)	0.095	0.26	1.91 (-0.46 to 4.28)	0.114	0.28
HY-C3 (T)	vs. TAU	2.67 (-0.06 to 5.39)	0.055	0.17	6.14 (1.97 to 10.31)	<b>0.004**</b>	<b>0.40</b>
HY-C3 (P)	vs. TAU	1.84 (-0.23 to 3.91)	0.081	0.18	1.24 (-1.32 to 3.80)	0.341	0.12
HY-C3 (S)	vs. TAU	-0.14 (-2.25 to 1.97)	0.896	-0.02	0.79 (-1.53 to 3.11)	0.502	0.10
ADHD-C3 (T)	vs. TAU	2.02 (0.32 to 3.73)	<b>0.021*</b>	<b>0.37</b>	3.26 (1.21 to 5.30)	<b>0.002**</b>	<b>0.60</b>
ADHD-C3 (P)	vs. TAU	1.41 (0.02 to 2.81)	<b>0.047*</b>	<b>0.30</b>	1.77 (-0.01 to 3.54)	0.051	0.37
ADHD-C3 (S)	vs. TAU	0.63 (-0.56 to 1.82)	0.299	0.17	0.71 (-0.57 to 1.96)	0.277	0.20
MI-BRIEF (T)	vs. TAU	3.42 (-1.70 to 8.55)	0.188	0.18	9.33 (2.07 to 16.60)	<b>0.012*</b>	<b>0.50</b>
MI-BRIEF (P)	vs. TAU	3.80 (0.41 to 7.19)	<b>0.028*</b>	<b>0.30</b>	3.30 (-1.33 to 7.92)	0.161	0.26
BRI-BRIEF (T)	vs. TAU	-0.20 (-3.71 to 3.31)	0.909	-0.01	4.92 (-0.40 to 10.24)	0.070	0.31
BRI-BRIEF (P)	vs. TAU	1.16 (-1.37 to 3.70)	0.366	0.10	1.22 (-2.24 to 4.68)	0.487	0.11
HRQoL (S)	vs. TAU	0.92 (-0.80 to 2.64)	0.293	0.17	1.50 (-0.39 to 3.40)	0.120	0.28
IN-C3 (T)	vs. WMT	-0.91 (-2.87 to 1.05)	0.360	-0.12	-0.22 (-2.86 to 2.41)	0.867	-0.03
IN-C3 (P)	vs. WMT	-0.31 (-2.03 to 1.40)	0.718	-0.05	-0.30 (-2.21 to 1.61)	0.760	-0.05
IN-C3 (S)	vs. WMT	1.67 (-0.43 to 3.75)	0.118	0.24	0.04 (-2.39 to 2.47)	0.976	0.01
HY-C3 (T)	vs. WMT	-0.47 (-3.27 to 2.33)	0.740	-0.03	1.58 (-2.64 to 5.80)	0.461	0.10
HY-C3 (P)	vs. WMT	0.77 (-1.33 to 2.87)	0.469	0.07	-1.00 (-3.66 to 1.66)	0.458	-0.09
HY-C3 (S)	vs. WMT	0.71 (-1.41 to 2.83)	0.509	0.08	1.23 (-1.15 to 3.61)	0.308	0.14
ADHD-C3 (T)	vs. WMT	-0.14 (-1.91 to 1.63)	0.875	-0.02	-0.09 (-2.21 to 2.03)	0.932	-0.02
ADHD-C3 (P)	vs. WMT	0.28 (-1.18 to 1.75)	0.700	0.05	-0.03 (-1.85 to 1.79)	0.974	-0.01
ADHD-C3 (S)	vs. WMT	0.14 (-1.05 to 1.34)	0.814	0.04	-0.19 (-1.50 to 1.12)	0.772	-0.05
MI-BRIEF (T)	vs. WMT	-2.55 (-7.67 to 2.57)	0.327	-0.14	1.45 (-5.98 to 8.89)	0.699	0.08
MI-BRIEF (P)	vs. WMT	0.28 (-3.28 to 3.83)	0.877	0.02	0.29 (-4.76 to 5.34)	0.909	0.02
BRI-BRIEF (T)	vs. WMT	-0.69 (-4.16 to 2.77)	0.693	-0.04	0.79 (-4.59 to 6.18)	0.771	0.05
BRI-BRIEF (P)	vs. WMT	-0.65 (-3.30 to 1.99)	0.626	-0.05	-1.72 (-5.49 to 2.06)	0.370	-0.13
HRQoL (S)	vs. WMT	1.10 (-0.66 to 2.86)	0.218	0.19	0.53 (-1.43 to 2.49)	0.595	0.09

**Note:** Negative numbers favor control condition.

IN-C3 = Inattention subscale Conners-3; HY-C3 = Hyperactivity subscale Conners-3; ADHD-C3 = ADHD-index Conners-3; MI-BRIEF = Metacognition Index BRIEF; BRI-BRIEF = Behavioral Regulation Index BRIEF; HRQoL = Health-Related Quality of Life index from KIDSCREEN-27; T = Teacher; P = Parent; S = Self;

\* p. <=0.05; \*\* p.<0.01.

Source: adapted from (Hasslinger et al., 2021)

WMT showed significant mean group differences when compared to TAU, on the same teachers' ratings as LZT. However, differences were significant at both post assessment and at follow-up, with effect sizes ranging from .20 to .37 at post-assessment, and .30 to .57 at follow-up. When comparing SCP-NF and LZT with WMT, the only significant result was found for the overall ADHD-symptoms rated by teachers at follow-up, where WMT was superior to SCP-NF ( $p = .034$ ;  $d' = .39$ ). Similarly, LZT was showed superior results over SCP-NF at follow-up for teachers' hyperactivity ( $p = .028$ ;  $d' = .36$ ) and overall ADHD-symptoms ( $p = .030$ ;  $d' = .41$ ) ratings. No differences on the quality of life measures were found. Nor were any severe adverse events reported during the trial, although passing stress-related problems were quite frequent.

### 5.3 STUDY III

At both post-assessment and follow-up, we did not find any significant between group differences, when comparing SCP-NF nor LZT to TAU. However, WMT showed a significant difference over TAU on both block-tapping forward and backward, both at post-assessment and follow-up. Table 4 provides an overview of the between-group effects at post-assessment for all interventions compared to TAU-only. Table 5 provides the results for the follow-up assessment.

**Table 4.**  
Comparison active interventions to treatment-as-usual from baseline to posttreatment

Measurement	Slow Cortical Potentials vs. TAU-only			Live Z-Score vs. TAU-only			Working Memory Training vs. TAU-only		
	Treatment effect (95% CI)	Sig.	Cohens d'	Treatment effect (95% CI)	Sig.	Cohens d'	Treatment effect (95% CI)	Sig.	Cohens d'
Digit Span- forward <sup>1a</sup>	-0.29 (-1.19 to 0.62)	0.529	-0.12	-0.31 (-1.21 to 0.60)	0.505	-0.12	<b>1.17 (0.13 to 2.21)</b>	<b>0.028</b>	<b>0.39</b>
Digit Span- backward <sup>1a</sup>	-0.38 (-1.53 to 0.77)	0.513	-0.14	-0.59 (-1.58 to 0.41)	0.245	-0.21	0.49 (-0.72 to 1.70)	0.426	0.18
Number Letter Sequences <sup>1a</sup>	-0.73 (-1.68 to 0.22)	0.129	-0.26	-0.77 (-1.64 to 0.09)	0.079	-0.27	-0.32 (-1.23 to 0.59)	0.491	-0.11
Block Tapping - forward <sup>1b</sup>	-0.25 (-0.96 to 0.47)	0.498	-0.11	-0.26 (-0.96 to 0.43)	0.455	-0.12	<b>1.69 (0.95 to 2.43)</b>	<b>&lt;0.001</b>	<b>0.79</b>
Block Tapping - backward <sup>1b</sup>	0.09 (-0.77 to 0.94)	0.841	0.04	-0.14 (-1.07 to 0.80)	0.773	-0.06	<b>1.24 (0.34 to 2.15)</b>	<b>0.008</b>	<b>0.55</b>
Telephone task - BSE <sup>↓</sup>	-1.36 (-5.15 to 2.44)	0.480	-0.14	0.16 (-4.14 to 4.47)	0.940	0.02	-2.26 (-6.29 to 1.78)	0.270	-0.23
Telephone task - WSE <sup>↓</sup>	-0.70 (-1.89 to 0.48)	0.242	-0.40	-0.76 (-1.99 to 0.48)	0.229	-0.40	-1.18 (-2.44 to 0.07)	0.065	-0.56
CPT-II - Omissions <sup>↓</sup>	0.53 (-3.63 to 4.68)	0.802	0.05	1.61 (-2.61 to 5.84)	0.451	0.16	4.13 (-0.51 to 8.77)	0.081	0.35
CPT-II - Commissions <sup>↓</sup>	-0.75 (-3.78 to 2.27)	0.623	-0.08	1.53 (-1.43 to 4.48)	0.309	0.14	2.19 (-0.98 to 5.35)	0.174	0.22
CPT-II - Hit RT <sup>↓</sup>	1.13 (-2.11 to 4.37)	0.490	0.10	0.40 (-2.72 to 3.53)	0.799	0.04	1.50 (-1.67 to 4.67)	0.350	0.13
CPT-II - Hit RT SE <sup>↓</sup>	0.61 (-2.40 to 3.62)	0.690	0.06	0.17 (-3.23 to 3.57)	0.920	0.02	3.30 (-0.32 to 6.92)	0.074	0.35
CPT-II - ADHD- index <sup>1c</sup>	1.82 (-4.61 to 8.25)	0.576	0.10	3.20 (-2.98 to 9.38)	0.307	0.18	<b>7.41 (0.38 to 14.44)</b>	<b>0.039</b>	<b>0.38</b>
Tapping - CoV <sup>↓</sup>	2.21 (-0.76 to 5.17)	0.143	0.29	1.23 (-1.53 to 3.99)	0.380	0.16	-1.09 (-5.19 to 3.02)	0.601	-0.09
TA 400ms – Hit rate <sup>↑</sup>	0.01 (-0.06 to 0.07)	0.864	0.04	0.00 (-0.06 to 0.05)	0.892	-0.03	0.01 (-0.06 to 0.07)	0.808	0.05
TA 400ms – Too Early <sup>↓</sup>	-0.01 (-0.06 to 0.04)	0.634	-0.10	0.01 (-0.04 to 0.06)	0.767	0.06	0.00 (-0.05 to 0.05)	0.947	0.01
TA 2000ms – Hit rate <sup>↑</sup>	-0.04 (-0.13 to 0.05)	0.422	-0.14	-0.09 (-0.18 to 0.00)	0.058	-0.35	0.00 (-0.09 to 0.10)	0.922	0.02
TA 2000ms – Too Early <sup>↓</sup>	-0.01 (-0.10 to 0.08)	0.825	-0.04	0.08 (-0.01 to 0.16)	0.098	0.32	-0.01 (-0.11 to 0.08)	0.768	-0.05

**Note:**<sup>1</sup>=Negative values favor the first intervention; <sup>1</sup>=Positive values favor the first intervention; BSE = Between-search-errors (raw score); WSE = Within-search-errors (raw score); CPT-II = Conners' Continuous Performance task (t-scores; 50±10); CoV = Coefficient of Variability (SD/mean tapping rate x 100); TA = Time Anticipation (percentages; max score 1.00); RT = Reaction Time; SE = Standard Error; <sup>a</sup> = Scale scores (10±3); <sup>b</sup> = raw scores (max score 14); <sup>c</sup> = percentages (max score 100); Significant results are **bold**.

Source: adapted from Hasslinger et al., (2022).

WMT was superior to both NF methods on the block-tapping task, with medium to large effect sizes at both post-assessment ( $d' = .51$  to  $.99$ ) and follow-up ( $d' = .42$  to  $.97$ ). However, no consistent effects were observed for the time perception tasks, nor the attentions and inhibition task (CPT-II). No clear indications that effects were moderated by ADHD presentation, ongoing medication, age, or sex, were found.

**Table 5.**  
Comparison active interventions to treatment-as-usual-only from baseline to 6-month follow-up

Measurement	Slow Cortical Potentials vs. TAU-only			Live Z-Score vs. TAU-only			Working Memory Training vs. TAU-only		
	Treatment effect (95% CI)	Sig.	Cohens $d'$	Treatment effect (95% CI)	Sig.	Cohens $d'$	Treatment effect (95% CI)	Sig.	Cohens $d'$
Digit Span- forward <sup>1a</sup>	0.11 (-0.78 to 1.00)	0.803	0.05	<b>-0.98 (-1.90 to -0.07)</b>	<b>0.035</b>	<b>-0.40</b>	0.55 (-0.43 to 1.53)	0.267	0.18
Digit Span- backward <sup>1a</sup>	-0.98 (-2.18 to 0.22)	0.107	-0.35	-0.40 (-1.55 to 0.74)	0.485	-0.14	0.20 (-0.96 to 1.36)	0.737	0.07
Number Letter Sequences <sup>1a</sup>	-0.92 (-2.05 to 0.20)	0.108	-0.33	-0.57 (-1.59 to 0.46)	0.276	-0.20	-0.11 (-1.28 to 1.05)	0.848	-0.04
Block Tapping - forward <sup>1b</sup>	-0.34 (-1.09 to 0.41)	0.374	-0.16	-0.66 (-1.49 to 0.17)	0.118	-0.31	<b>1.26 (0.48 to 2.05)</b>	<b>0.002</b>	<b>0.59</b>
Block Tapping - backward <sup>1b</sup>	0.34 (-0.54 to 1.23)	0.444	0.16	0.36 (-0.57 to 1.29)	0.445	0.17	<b>1.31 (0.38 to 2.23)</b>	<b>0.006</b>	<b>0.57</b>
Telephone task - BSE <sup>↓</sup>	2.73 (-0.94 to 6.39)	0.143	0.27	2.40 (-1.67 to 6.46)	0.245	0.22	2.37 (-1.49 to 6.24)	0.227	0.25
Telephone task - WSE <sup>↓</sup>	-0.03 (-0.89 to 0.83)	0.951	-0.02	-0.46 (-1.38 to 0.46)	0.322	-0.25	-0.53 (-1.49 to 0.43)	0.279	-0.25
CPT-II - Omissions <sup>↓</sup>	-2.39 (-7.23 to 2.44)	0.329	-0.22	-3.41 (-7.86 to 1.05)	0.132	-0.35	-1.28 (-6.53 to 3.97)	0.630	-0.11
CPT-II - Commissions <sup>↓</sup>	0.37 (-3.09 to 3.83)	0.832	0.04	-1.84 (-5.36 to 1.67)	0.300	-0.17	-0.08 (-3.78 to 3.63)	0.968	-0.01
CPT-II - Hit RT <sup>↓</sup>	0.54 (-2.70 to 3.77)	0.744	0.05	0.73 (-2.43 to 3.89)	0.648	0.07	1.70 (-1.74 to 5.14)	0.329	0.15
CPT-II - Hit RT SE <sup>↓</sup>	-0.50 (-3.93 to 2.92)	0.772	-0.05	-2.08 (-5.73 to 1.57)	0.262	-0.21	-0.76 (-4.32 to 2.81)	0.675	-0.08
CPT-II - ADHD- index <sup>1c</sup>	0.29 (-6.59 to 7.18)	0.933	0.02	-1.10 (-7.59 to 5.38)	0.737	-0.06	1.32 (-6.27 to 8.91)	0.731	0.07
Tapping - CoV <sup>↓</sup>	1.01 (-2.55 to 4.58)	0.573	0.13	0.39 (-2.68 to 3.45)	0.802	0.05	-2.45 (-5.71 to 0.80)	0.138	-0.20
TA 400ms – Hit rate <sup>↑</sup>	-0.02 (-0.08 to 0.05)	0.647	-0.10	-0.03 (-0.09 to 0.03)	0.321	-0.21	0.01 (-0.05 to 0.08)	0.703	0.08
TA 400ms – Too Early <sup>↓</sup>	0.00 (-0.06 to 0.06)	0.982	0.01	0.01 (-0.04 to 0.07)	0.588	0.12	-0.03 (-0.08 to 0.03)	0.321	-0.24
TA 2000ms – Hit rate <sup>↑</sup>	-0.02 (-0.12 to 0.07)	0.652	-0.08	-0.08 (-0.16 to 0.00)	0.058	-0.33	0.02 (-0.07 to 0.12)	0.639	0.09
TA 2000ms – Too Early <sup>↓</sup>	-0.02 (-0.12 to 0.07)	0.668	-0.08	0.05 (-0.03 to 0.13)	0.217	0.22	-0.03 (-0.12 to 0.06)	0.518	-0.12

**Note:**<sup>↓</sup>=Negative values favor the first intervention; <sup>↑</sup>=Positive values favor the first intervention; BSE = Between-search-errors (raw score); WSE = Within-search-errors (raw score); CPT-II = Conners' Continuous Performance task (t-scores;  $50 \pm 10$ ); CoV = Coefficient of Variability (SD/mean tapping rate x 100); TA = Time Anticipation (percentages; max score 1.00); RT = Reaction Time; SE = Standard Error; <sup>a</sup> = Scale scores ( $10 \pm 3$ ); <sup>b</sup> = raw scores (max score 14); <sup>c</sup> = percentages (max score 100); Significant results are **bold**.

Source: adapted from Hasslinger et al., (2022).



## 5.4 STUDY IV

This systematic review revealed that there were wide variations on numerous protocol-detail. This comprised aspects such as the number of trials conducted (per session and in total), the ratio between activation and deactivation trials, the use of transfer trials, the length of each trial, how eye-movements were corrected, the use of thresholds that had to be surpassed for a trial to be successful, as well as the utilization of incentives (i.e., token-plans) and transfer promoting exercises. Only the placement of the active electrode was mostly unchanging.

Token-systems to maintain participants motivation were frequently used in studies concerning ADHD. Nonetheless, only half reported a performance-based component. Transfer exercises were also commonly implemented. Instructed to practice their regulatory strategies at home, participants were often aided by transfer cards. However, no study reported any data on these transfer exercises, whether the participants performed them or whether the transfer exercises had any impact on self-regulation.

Concerning the evaluation of self-regulation, many different methods were used. Sometime the percentage of correct trials served as measure, while other studies focused on changes in the amplitude or on differentiation between activation and deactivation trials. Some studies classified participants as learners or non-learners, while other studies examined the sample as a whole. Overall, comparable data from individual participants was rarely reported.

Studies utilizing SCP as Brain-Computer-Interface, mainly focused on the acquisition of successful self-regulation, while clinically oriented studies often neglected this. Congruently, in clinical studies the rate of successful regulation was mostly low (<50%). However, comparability was limited due to the heterogeneity of evaluation methods.



## 6 DISCUSSION

### 6.1 STUDY I

This qualitative study explored the participants subjective experience of how they were trying to self-regulate during SCP-NF. The first part of the study focused on the strategies that participants use to regulate. A total of 16 themes and an additional 11 sub-themes were identified, indicating that there was great diversity of strategies among our sample. With the exception of the “Unspecified” domain (where participants were lacking clear strategies), all strategies modulated the participants level of arousal (cognitive, emotional or physiological).

We also tried to look at how the use of strategies shifted over time, as well as how they were influenced by the participants’ level of compliance (i.e., adherence, motivation and conformity). Trends concerning changes over time were limited. When stratifying the sample based on compliance, there was a trend for more Emotional Regulation among high-compliant participants, and more strategies from the Physiological and Unspecified domain among participants with lower levels of compliance, especially at the follow-up booster sessions. However, this was a rather miscellaneous sample, as we utilized all interviews for the analysis, rather than only included interviews from participants with full sets of interviews (as in the prototype analysis). Since the individuals represented in each time points vary, as well as the sample size per time point, these trends should be interpreted with caution.

When comparing the results of the three self-regulation prototypes, the State-of-Mind group showed the most improvement overtime concerning differentiation ability, for both the feedback and the transfer conditions. For the other two groups there was a much weaker improvement trend for the feedback condition, and even a negative trend concerning the transfer condition. However, it was the Manifest-and-Concrete group that showed the greatest difference between activation and deactivation trials throughout training. This may have been due to their prominent use of more physiological strategies, leading to artifacts from muscle tension, that induced higher signal amplitudes.

Furthermore, the subjects in the State-of-Mind group were both older and had lower symptom severity, compared to the other two groups. Being more mature and less impaired by their symptoms may likely have been beneficial for the SCP-NF training. Also, participants from this group were the only ones that reported self-perceived improvements, and could elaborate on examples with specific situation where they had noticed improvements. Overall, results from this study illustrated that 1) there is a wide variety of strategies being used in SCP-NF; 2) despite the variety, most strategies have a common purpose, namely the regulation of one’s

arousal level; and 3) there is indication that only a subsample is able to fully conform to and benefit from SCP-NF.

## 6.2 STUDY II

The aim of this study was to evaluate the impact of SCP-NF and LZT on ADHD core symptoms, compared to WMT and TAU-only. Our linear mixed model analysis did not reveal many distinct between-group results. For SCP-NF, parent rated inattention and overall ADHD symptoms, and teacher rated inattention, showed superiority over TAU-only at the post-assessment, but these results were not sustained at follow-up assessment. Still, metacognition was improved and sustained at follow-up. However, when compared to WMT, no between-group differences were found at all. These findings are not in line with previous findings from similar studies (Aggensteiner et al., 2019). This may have been influenced by the high-frequency the training was delivered. The daily sessions for a five-week period may have been overwhelming to some participants, and instead of the anticipated opportunity for intensified learning, this high-frequency may have instead have been mostly strenuous and demotivating. Previous studies that utilized such high-frequencies, only did so during a one- or two-week introduction phase. The usual training frequency has mostly been 2-3 sessions per week. This set-up may have had a negative impact on the acquisition of self-regulation, which was low (26%). Although transfer-cards were implemented, their benefits are likely restricted to the strategies implemented by the participants. As study I showed, the use of strategies varied considerably among participants. Without proper self-regulation, and the transfer thereof into everyday-life, symptom improvements seem to be limited.

No superiority of LZT over WMT was found. However, compared to TAU-only, we did find significant improvement of medium ES ( $d' = 0.4 - 0.6$ ) on most teacher rating at follow-up. This may indicate that LZT may improve ADHD symptoms in a school-setting, but not necessarily in the home-setting. However, these finding should be interpreted with caution until replicated. WMT showed improvement both at post-assessment and at follow-up, on teacher ratings. In addition, WMT also showed improvements on overall ADHD symptoms on parent ratings. Similar to LZT, this may indicate that WMT primarily provides benefits within a school-setting.

Overall, results from this study did not provide support for broadly implemented NF treatment for children and adolescents with ADHD. Especially not when delivered at a high-intensive frequency, i.e., daily-training sessions. Ensuring proper self-regulation needs more attention, perhaps especially concerning SCP-NF where active skill-acquisition seems pivotal.

### **6.3 STUDY III**

In this study we compared SCP-NF, LZT and WMT, with TAU-only, for multiple cognitive functions commonly associated to ADHD. The test battery included test measuring verbal and spatial working memory, time perception, and a test that measured attention and impulsivity variables. No significant effects over TAU-only were found for SCP-NF nor LZT, on any of the outcome measures. For WMT we found significant results on multiple working memory measures when compared to TAU-only, as well when compared to the SCP-NF and LZT. No significant outcomes were found on the other measures. Nevertheless, the lack of results should be interpreted with caution. The cognitive profile is very heterogeneous in ADHD, were most show cognitive deficits on some measure but not all (Pievsky & McGrath, 2018). Therefore, perhaps improvements were limited to the subsample that had deficits on these measures in the first place, diluting any effects. Some support for this assumption may be found in our sensitivity analysis. Although we did not find any clear patterns, there were miscellaneous results. Subdividing the sample based on the specific neurocognitive deficit profile, may have yielded more results.

For WMT we found improvement on the working memory measure. However, only results for block-tapping remained significant at follow-up. The exercises that were trained in WMT, were very similar to those tasks that were used to measure working memory. These outcomes may therefore mostly be interpreted as a near-transfer effect. Nonetheless, the spatial working memory improvements were sustained until the follow-up assessment, indicating that the participants acquired an enhancement, regardless of the underlying mechanism.

Overall, results from this study did not provide support that SCP-NF or LZT provided specific neurocognitive benefits for children and adolescents with ADHD. However, some support for near-transfer benefits for WMT was found.

### **6.4 STUDY IV**

In this study, the literature on SCP-NF was reviewed. All types of studies that comprised the intentional regulation of SCP studies, were included. This also entailed studies that utilized SCP-regulation within the context of Brain-Computer-Interfaces (BCI). 800 unique hits were found and screen, emitting 63 articles since the year 2000. Data concerning protocol-details and the evaluation of self-regulation were extracted.

The systematic Review revealed, that there is considerable variation in SCP-NF protocol-details. Only the electrode placement did not vary much, and was set at Cz. However, as commercial SCP-NF systems have become more available, a tendency for to more uniform

protocols emerged. These findings suggest that although being a so-called “standard protocol”, SCP-NF is far from standardized. However, due to the increasing availability and use of commercial systems, there seems to be a trend toward more homogeneity.

Beside variations in the abovementioned protocol-details, there were substantial differences in how the success of self-regulation was evaluated, if it was evaluated at all. We identified two main approaches; one focusing on the *ability* to self-regulate (most often at the end of training), and the second focused on the *progression* of the former. Furthermore, outcome variables could either focus on the percentage of correct trials, on amplitudinal changes or on differentiating between activation and deactivation. The chosen approach and variable, together with what time segment (epoch) of each trial that is being measured, may all affect the outcome of who is being classified as a successful regulator, which limits the comparability between studies.

Furthermore, so-called token-systems are frequently implemented to keep participants motivated, especially in trials concerning children with ADHD. However, only a minority of studies reported having a performance-based component, failing to incentivize the acquisition of self-regulation. Similarly, transfer exercises like so-called transfer-cards were common. Unfortunately, descriptions thereof were scarce and no data was reported on adherence or similar measures. Some studies reported that participants were to practice their regulation strategies, e.g., during training breaks. However, no data was provided on whether the participants were successfully self-regulating, i.e., whether these strategies were effective. Based on the sparse reporting, helping participants to acquire sufficient self-regulation is far from optimal, which is also reflected in the generally low numbers of successful regulators.

Overall, this systematic review showed that there can be many variables that differ between SCP-NF studies. Most importantly, the acquisition of successful self-regulation has not been sufficiently addressed. Similar to the early studies on epilepsy (Kotchoubey et al., 1996), SCP-NF should be accompanied with a behavioral intervention, that is structured around the identification of both regulation strategies and relevant everyday-life situation, where these strategies are practiced and implemented. Additionally, methods and techniques that help to motivate and optimize the learning of self-regulation are also recommended.

## 6.5 LIMITATIONS

The finding of these studies should be viewed in the light of some limitations. Concerning **Study I**, we included all available interviews when mapping the strategies. Data from participants with only few interviews may have skewed the possibility to find patterns for the changes over time, and the influence of compliance. Perhaps focusing on the data provided from the complete set interviews (i.e., those used for the profile analysis) would have yielded more correct outcomes. Also, describing internal mental processes is hard, perhaps especially for children with ADHD. The descriptions of strategies did not necessarily match the actual activity, which may have affected the reliability to a certain extent. Another important limitation concerns the interaction with the trainer, through which some strategies may have been supplied. Similarly, by asking the participants about how they are steering the object in SCP-NF, it was insinuated that more explicit strategies were expected by the trainer.

Outcomes in **Study II**, may have been affected by the missing data. Especially concerning teacher ratings, there may have been a bias that teachers that perceived changes in their students were more prone to complete the questionnaires, which could have limited the differences between groups. Another limitation concerns the poor acquisition of self-regulation in SCP-NF, as just above on quarter of participants were classified as learners. The beneficial potential of self-regulation on ADHD symptom was therefore small in our sample. This may have been affected by not including performance-based rewards, that perhaps could have increased skill-acquisition. Also, implementing rather high thresholds during SCP-NF may have incentivized physiological strategies, which generated muscular artefacts that slipped through the online corrections. Offline artefact checks, and individually adjusted threshold may have yielded better self-regulation outcomes.

Perhaps important for **Study III**, was that the same personnel administered both the training and the assessments. Part of the personnel's undertaking was to create a comfortable atmosphere in order to maintain motivation and secure adherence during the intense training period. However, this may have led to an overly "relaxed" setting during the latter assessments. This aspect differed between the active intervention groups and the TAU-only condition, who only came to the clinic for the assessments. Another factor that may have influenced performance, may have been caused by the 48-h medication washout prior assessment. Although this was the same at each assessment point, the effects of the withdrawal may likely have increased the volatility in performance.

Outcomes in both **Study II** and **Study III**, may have been limited by the heterogeneity of the sample. On one side being very representative of how the clinical population looks like, including common comorbidities, a wide age-range (9 to 17 years), the different presentations of ADHD, as well as tolerating medication, may have deluded the sample to some extent, especially when looking for moderating effects. For example, other SCP-NF studies had previously found different moderating effects of methylphenidate depending on the age group (Zuberer et al., 2018). However, our sensitivity analyses did not account for potential interaction.

As for most systematic reviews, a limitation for **Study IV** concerns the risk of having missed relevant articles. Another limitation concerns our broad approach, with numerous extraction variables, increased the risk of overlooking relevant data. Further, the quality of the included articles was not assessed. Hence, unnecessary low-quality data may have been included, and may have diluted our findings.



## 7 CONCLUSIONS

Based on the results in this thesis, we did not find additional support for neurofeedback as an effective intervention for children and adolescents with ADHD. However, comparable studies have found significant improvements for SCP-NF. Therefore, one may assume that qualities unique to our study may have impaired some benefits, most saliently, the high-frequency of the training and the acceptance of common co-morbidities.

Concerning LZT, comparable research is limited. The results in this thesis are mixed, as only teacher ratings improved at follow-up (compared to TAU-only), while self- and parent-ratings did indicate improvements. However, improvements specific to the school-setting are possible, and deserve further investigating. Similarly, we found improvements for WMT over TAU-only on teacher-ratings, both at the post-assessment and at the 6-month follow-up. These results do support that WMT may be beneficial for children and adolescents with ADHD, especially in their school-setting.

No specific results were found for NF on cognitive functions, while WMT only sustained improvements for spatial working memory.

Based on the results of the qualitative study, we can conclude that there are many different strategies that are being used in SCP-NF. However, it seems that primarily strategies that regulate the participants' "State-of-Mind" are associated with more beneficial outcomes, at least when considering self-perceived improvements, and self-regulation. It can also be concluded that a substantial portion of participants fail to grasp how to self-regulate.

The systematic review concluded that there have been considerable technical differences between different SCP-NF protocols. Furthermore, there is no standard at all considering how self-regulation is evaluated. Each research team, more or less, implements their own methodology, focusing on different regulatory-qualities (e.g., the ability to shift accurately, or increasing the positivation/negativation amplitude). This limited the comparability significantly. Furthermore, seemingly small differences like the length of each trial, may influence the outcome of regulatory abilities. The review also concludes, that reward plans and transfer exercises are generally poorly reported, despite of being a vital ingredient for the acquisition of self-regulation in SCP-NF.



## 8 POINTS OF PERSPECTIVE

On the basis that SCP-NF resonates the best within a skill-acquisition model, the specific regulatory components in SCP-NF need to be explored further, as to how they impact the individual and their behavior. For example, in epilepsy it seems that improved positivation and the ability to create positive shift in order to ward off seizures, constitutes the main benefit. Within a BCI-context, i.e., utilizing SCP shift for communication, the ability to shift between positive and negative shifts seems pivotal. However, little certainty surrounds what regulatory qualities benefit children and adolescents with ADHD the most. Some have addressed the increased negativation, mostly based on its relation to the CNV, and its relation to attention. However, under other circumstances, the ability to generate positivations may be just as important, i.e., when inhibiting impulsivity. Another mechanism that has been lifted, concerns SCP-NF effects on improved sleep-spindles, that may have general positive effects despite of disorder. Future research should therefore illuminate these issues further.

Also, future studies need to report self-regulation based on standardized measures, perhaps in addition to disorder specific measures, to facilitate comparability. When applied as treatment, future SCP-NF studies also need to put greater emphasis on the acquisition of self-regulation. Before evaluating symptom outcomes, it is important that individuals have sufficient self-regulatory abilities. Since the regulation in SCP-NF is an effortful process, self-regulation may preferably be accomplished during specific evaluation sessions or blocks, comparatively to simply evaluating the average performance of all or at least multiple sessions. Another aspect concerns the importance of utilizing the regulatory abilities in relevant situations. Similar to the studies on epilepsy, the learned self-regulation strategies must be implemented for maximum benefits (i.e., seizure prevention or reduction). Hence, it is reasonable to assume that children and adolescents also would benefit more, if SCP-NF also entailed the identification of situations where regulation would be relevant. Combining SCP-NF with a behavior therapeutic component, that focuses on these issues, seems warranted.

Contrary to SCP-NF, LZT requires much less effort in its administration, and is not premised around effortful skill-acquisition that needs to be transferred into every-day situations. Furthermore, the equipment is both simpler and cheaper. Although the positive results that we found for LZT on teacher ratings at follow-up should be interpreted with caution (due to the lack of supporting results on other measures), it is possible the positive effects are specific to the school-setting. It may therefore be feasible to inquire the efficacy of LZT on ADHD

symptoms and academic performance, when administered at home, by the parents via borrowed equipment. Parents could receive basic training and supervision by experienced personnel, while assessments would be conducted at the clinic. Such a set-up would considerably lower the cost of NF, and may also have empowering benefits for the parents. Similarly, based on our findings, WMT may also deserve further investigation in a home-setting.

Furthermore, participants may benefit more from individualized protocols, e.g., adapting the exercises in WMT to the individuals' deficits, targeting specific areas of interest, rather than being composed of a one-size-fits-all design. The same concerns LZT, which in this thesis was very standardized, with identical electrode placement and a stable z-score corridor. Only the targeted percentage of "OK" z-score was adjusted to the individual. Future studies should adapt the training protocol according to the individuals' deviations, and adjust the protocol based on their progress. Many questions concerning neurofeedback and working memory training remain in need of further investigations.

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