Neurotherapeutics for Attention Deficit Hyperactivity Disorder (ADHD): a Review

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Abstract

This review focuses on the evidence for neurotherapeutics for Attention Deficit Hyperactivity Disorder (ADHD). EEG-Neurofeedback has been tested for about 45 years with latest meta-analyses of randomised controlled trials (RCT) showing small/medium effects compared to non-active controls only. Three small studies piloted fMRI-Neurofeedback or near-infrared spectroscopy (NIRS)-neurofeedback of frontal activations in ADHD and found no superior effects over control conditions. Brain stimulation has been applied to ADHD using mostly repetitive transcranial magnetic and direct current stimulation (rTMS/tDCS). rTMS has shown mostly negative findings on improving cognition or symptoms. Meta-analyses of tDCS studies targeting mostly dorsolateral prefrontal cortex show small effects on cognitive improvements with only two out of three studies showing clinical improvements. Trigeminal nerve stimulation has shown to improve ADHD symptoms with medium effect in one RCT. Modern neurotherapeutics are attractive because they are relatively safe and -unlike ADHD medications- have neuroplastic effects. However, systematic testing of their clinical and cognitive effects across settings and beyond core symptoms and of their use for individualised therapy is paramount.

Keywords: Attention Deficit/Hyperactivity Disorder; ADHD; functional magnetic resonance imaging; fMRI; Neurofeedback; EEG-Neurofeedback; fMRI-Neurofeedback; brain stimulation; transcranial magnetic stimulation (TMS); transcranial direct current stimulation (tDCS); trigeminal nerve stimulation (TNS).

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined by the DSM-5 as a disorder with persisting and impairing symptoms of age-inappropriate inattention and/or hyperactivity/impulsivity (DSM-5) (American Psychiatric Association, 2000). ADHD has a high prevalence of around 7% and is therefore one of the most common childhood disorders (Thomas et al., 2015). Most patients with ADHD have still attention problems when they are adults and many have comorbidities and academic and social problems (Thomas et al., 2015).

People with a diagnosis of ADHD have been shown to have problems with higher-order cognitive skills that are developing late into adulthood, called “executive functions” (EF). EF are supported networks that include frontal, parietal and striatal and cerebellar regions that develop late in adolescence (Rubia, 2013). People with ADHD are particularly impaired in “cool” EF, which include working memory, inhibitory control, selective and sustained attention, cognitive flexibility and intraindividual response variability (Pievsky & McGrath, 2018b; Rubia, 2011; Willcutt et al., 2008), as well as in temporal processing (Noreika et al., 2013; Rubia et al., 2009). Deficits in “hot” EF including reward-based decision making or control of their motivation are less consistently observed, with some evidence for problems with temporal discounting (Noreika et al., 2013; Plichta & Scheres, 2014; Willcutt et al., 2008). This is in line with the diagnostic criteria which focus more on attention and inhibitory problems. Cognitive problems are more commonly found in children than adults with ADHD (Groen et al., 2013; Pievsky & McGrath, 2018b). Studies have also shown large heterogeneity whereby up to 30% of people with ADHD have no problems in EF (Nigg et al., 2005; Roberts et al., 2017).

The most successful treatment is with psychostimulant medication which enhance catecholamines in the brain, reaching an effect size of ~ 0.8, with about 70% of patients with ADHD responding to it (Cortese et al., 2018). Functional magnetic resonance imaging (fMRI) studies have shown that stimulant medication increases the activation of inferior frontal and striatal regions and their interconnectivity and decreases activation in areas of the default mode network (Rubia et al., 2014). It is likely that the increase of activation in task-relevant areas together with the decrease of activation in the DMN is causing improvements in cognitive functioning (Coghill et al., 2014; Pievsky & McGrath, 2018a). Second-line treatment is with noradrenaline transporter/receptor blockers Atomoxetine and Guanfacine that also enhance brain catecholamines with effect sizes of 0.56 and 0.67, respectively (Cortese et al., 2018). Stimulant prescription has increased dramatically over the last decades worldwide which is controversial due to abuse and diversion potential. Furthermore, stimulants commonly have adverse effects, on sleep, appetite, irritability, nausea/vomiting, abdominal pain, headaches, labile mood and growth suppression, although they are typically non-serious and can be transient (Cortese et al., 2018). Also, only 50% of patients tolerate it sufficiently, caution is indicated for certain comorbid conditions (such as cardiovascular malfunctions, sleep problems) and adherence can be poor, in particular in adolescence. Importantly, longer-term efficacy has not been demonstrated in meta-analyses, observational or epidemiological studies (Cortese et al., 2018; Swanson, 2019), although there is controversy (Coghill, 2019).

While the efficacy of stimulant medication for treating ADHD was a chance finding, as it was originally used for other medical conditions such as bronchodilatation, headache, and blood pressure (Connolly et al., 2015) and the first neurofeedback treatment in ADHD also used EEG conditioning developed for seizure control (Lubar & Shouse, 1976), modern neurotherapeutics have the advantage that they can target directly the key brain function

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deficits that have been found in ADHD over the past decades. There has been substantial research on differences in brain activation in ADHD compared to age-matched controls with electroencephalography (EEG) since the 1970 (e.g. (Satterfield, 1973a; Satterfield et al., 1973b) and with fMRI over the past 2.5 decades that have provided us with neurofunctional biomarkers that could be targeted with neurotherapeutics such as neurofeedback or non-invasive brain stimulation techniques.

Functional neuroimaging markers of ADHD that could provide targets for neurotherapeutics

Electrophysiological biomarkers

Electrophysiology findings in ADHD showed that increased slower oscillations such as delta, theta or alpha during resting conditions, but also faster beta frequencies bands are most relevant to ADHD (Loo & Makeig, 2012). The oscillatory or spectral profile reflects maturation and arousal problems, since particularly slower frequencies decrease with age. An increasingly controversial finding in ADHD is a higher frontocentral theta/beta ratio (TBR) (Snyder et al., 2015) which has been related to reduced attention, hypoarousal or maturational lag suggesting a strong association between ADHD and markers of EEG during rest. During the last decades, scientific efforts to replicate this hypothesis did not show consistent TBR increase in ADHD despite maturational effects (Buyck & Wiersema, 2014a, 2014b, 2015; Liechti et al., 2013) and questioned a relation between TBR and arousal (Clarke et al., 2019). A meta-analysis about TBR in ADHD showed that the TBR effect size is negatively related to the year of publication,

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and might be related to methodological factors, and to a trend for increasing TBR over the years in healthy controls, which may be related to decreased sleep duration, diminishing differences to ADHD (Arns et al., 2012). Importantly, advances in the field showed that the heterogeneity within ADHD might explain the inconsistent findings. Indeed, it was shown that subgroups of patients with ADHD have increased TBR (Clarke et al., 2011), in 3 EEG waves, with 60% of ADHD children had higher activity in the theta range compared to healthy controls. A more recent study showed that high TBR is present in 35% of the ADHD population (Bussalb et al., 2019). However, the concept of TBR as a biomarker for ADHD could potentially be confounded by differences in concentration, cognitive effort, activation, and drowsiness (Drechsler et al., 2020), consistent with findings that theta activity increases in ADHD appear only after longer EEG recordings (Zhang et al., 2019). Further, a recent review on resting EEG power research in ADHD concluded that given the current evidence in the field it would be premature to make definitive statements about the utility of the TBR ratio as a diagnostic test for ADHD (Clarke et al., 2020). Importantly, recent EEG-NF studies which assume deviating TBR, have taken this into account, proposing a cut-off for TBR-NF (i.e. >4,1), and thus applying TBR-NF only to the subgroup with high TBR ratio (Arnold et al., 2020; Bioulac et al., 2019).

Compared to this controversial research regarding inconsistently altered electrophysiological oscillations, there are somewhat more consistent findings concerning event-related potentials (ERPs). ERPs are defined as a task-locked activity, reflecting cognitive, sensory or motor brain responses. Different ERP components showed deviations in ADHD for stimulus discrimination, resource allocation, inhibition, preparation, error detection, and conflict processing (Barry et al., 2003, Johnstone et al., 2013). However, these alterations seem to be non-specific to ADHD and provide only limited relevance as diagnostic biomarkers (Loo &

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Makeig, 2012). A current meta-analysis (Kaiser et al., 2020) found significant and moderate to large effects for specific ERPs associated with late cognitive processing related to attentional preparation and resource allocation, such as P300 and contingent negative variation (CNV); however, the results were characterized by substantial heterogeneity and modest effect sizes which limit the use for clinical applications. Importantly, there is a need to systematically investigate those components, since most of the studies used different tests and measures, which makes it difficult to provide a reliable interpretation with respect to the accuracy of the classification and the effect size (Gamma & Kara, 2020).

fMRI biomarkers

The past two decades of MRI research have consistently shown evidence for underlying brain structure and function deficits in ADHD. As a consequence, ADHD is now considered a neurodevelopmental disorder. Meta-analyses and mega-analyses of brain structure have demonstrated consistently reduced grey matter in the basal ganglia and insula in people with ADHD (Hoogman et al., 2017; Lukito et al., 2020; Nakao et al., 2011; Norman et al., 2016), but also limbic areas including the hippocampus and the amygdala (Hoogman et al., 2017). Meta-analyses have also found a reduction in the grey matter, the cortical thickness and the surface area in frontal, parietal and temporal brain areas (Hoogman et al., 2019; Lukito et al., 2020; Norman et al., 2016). Longitudinal studies have furthermore shown that the peak of cortical thickness and surface area are delayed in their development in frontal, temporal and parietal brain areas (Shaw et al., 2007; Shaw et al., 2012). People with ADHD also have abnormal white matter tracts in particular in tracts that connect fronto-striatal, interhemispheric

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and fronto-cerebellar connections and long-distance tracts such as fronto-occipital tracts (Aoki et al., 2018; Chen et al., 2016, Rubia 2018).

Studies that used fMRI have provided consistent neurofunctional biomarkers in ADHD, several of which have been targeted with neurotherapeutics. ADHD has been associated with relatively widespread dysfunctions, mostly underactivations compared to age-matched controls.Meta-analyses of fMRI studies have found abnormalities in several frontal regions such as dorsolateral, inferior, orbital and medial prefrontal cortices, the cingulate, the basal ganglia and the networks they form including fronto-limbic, fronto-parietal, and fronto-cerebellar networks (Rubia, 2018). A well replicated finding across our 3 meta-analyses of whole-brain fMRI studies of cognitive and motor inhibition, the latest and largest including 1001 ADHD patients, is that people with ADHD compared to healthy age-matched controls have lower recruitment of brain areas that mediate cognitive control, in right inferior prefrontal cortex (IFC), anterior insula, the supplementary motor area (SMA), anterior cingulate cortex (ACC), and striatal regions (Hart et al., 2013; Lukito et al., 2020; Norman et al., 2016). Similar findings were observed in smaller meta-analyses focusing on inhibition tasks, some including left IFC (Cortese et al., 2012; Lei et al., 2015; McCarthy et al., 2014), and others also finding DLPFC underactivation (Cortese et al., 2012; Lei et al., 2015; McCarthy et al., 2014). Our meta-analysis of fMRI studies of attention tasks observed lower brain activation in 171 patients with ADHD compared to 178 age-matched controls in the right dorsolateral prefrontal cortex , inferior parietal lobe and caudal basal ganglia and thalamus. On the other hand, people with ADHD patients had higher brain function compared to controls in the left cuneus and the right cerebellum which plausibly compensated for the reduced function of frontal parts of the dorsal attention network that is mediated by the DLPFC, parietal lobe and the cerebellum (Hart et al., 2013). Another meta-analysis reported significantly reduced activation in right anterior

cingulate during attention tasks from a sub-analysis of 11 fMRI datasets (Cortese et al., 2012). A meta-analysis of fMRI studies of timing functions, including 11 fMRI studies of time discrimination, time estimation, motor timing and temporal discounting (temporal foresight), showed consistently reduced activation in 150 ADHD patients relative to 145 healthy controls in left IFC, left inferior parietal lobe and right lateral cerebellum (Hart et al., 2012), all key regions mediating timing functions (Wiener et al., 2010). During fMRI tasks of working memory, a meta-analysis showed that people with ADHD (N 111) compared to healthy controls (N = 113) underactivated middle and superior PFC in both hemispheres and the left MFC/ACC (McCarthy et al., 2014), although some large fMri studies and other meta-analyses also found right and left IFC underactivation (Cortese et al., 2012; van Ewijk et al., 2015). The right IFC dysfunction during cognitive control tasks, in particular, has been shown to be disorder-specific to ADHD relative to OCD and to ASD in two large comparative meta-analyses (Lukito et al., 2020; Norman et al., 2016). These findings show that ADHD patients have different abnormalities depending on the domain in different inferior fronto-striato-thalamic networks for inhibition, in right dorsolateral fronto-striato-thalamo-parietal networks for attention, and in bilateral dorsolateral and inferior PFC, middle frontal regions including ACC for working memory, and in left inferior fronto-parieto-cerebellar regions for timing functions. The findings therefore show that people with ADHD have multisystemic problems which affect distinct fronto-striato-parieto-cerebellar networks that mediate a range of cognitive skills (Rubia, 2018).

In addition to deficits in several of these lateral fronto-striato-parietal and fronto-cerebellar regions that mediate so-called “cool” EF, ADHD children have also shown reduced activation in ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC) and striato-limbic regions during tasks of “hot” EF such as reward-related decision making or temporal

discounting tasks. However, deficit findings have been less consistent (Plichta & Scheres, 2014; Rubia, 2018).

There is furthermore evidence for reduced inter-regional functional connectivity between these task-relevant regions during cognitive tasks and during the resting state, in particular in the dorsal and ventral attention and cognitive control networks (Rubia, 2018; Sripada et al., 2014a; Sripada et al., 2014b).

However, people with ADHD do not only have abnormalities in task-positive brain areas, but also areas of the default mode network (DMN), which comprise ventromedial frontal cortex, posterior cingulate, precuneus and inferior parietal and temporal regions, and which is thought to reflect task-irrelevant thoughts and mind wandering (Raichle, 2015). Thus, meta-analyses and individual fMRI studies also show abnormally enhanced brain activation in areas of the DMN including the posterior cingulate and precuneus during motor inhibition, attention and other cognitive control functions (Fassbender et al., 2009; Hart et al., 2013, Christakou et al., 2013; Salavert et al., 2018), as well as timing tasks (Hart et al., 2012) and the rostromedial prefrontal cortex during interference inhibition (Hart et al., 2013). It thus appears that people with ADHD patients have less ability to switch off their wandering (Bozhilova et al., 2018) which is likely to cause inattention and impulsiveness. This pattern of underactivation of brain regions that are important for mediating EF and of overactivation of the DMN may be responsible for underperformance underlying in higher-level EF (Rubia, 2018).

The most consistently found dysfunctional regions, in particular right IFC, followed by right DLPFC, ACC, right inferior parietal lobe or the basal ganglia could potentially be used as targets for neurotherapeutics. Some of these regions such as IFC, DLPFC and ACC have already been used as targets of neuromodulation in fMRI/NIRS-Neurofeedback or for brain

stimulation therapies. Furthermore, with fMRI-NF, entire networks that are affected in ADHD could also potentially be targeted such as the dorsal and ventral attention, or the cognitive control systems (Sripada et al., 2014). Downregulating the DMN could potentially also be a suitable, yet unexplored neurotherapeutic target for fMRI-NF. Given evidence for the anti-correlation between the IFC/DLPFC and the DMN (Sripada et al., 2014), the upregulation of IFC/DLPFC with brain stimulation or neurofeedback may indirectly downregulate areas of the DMN, which we have indeed shown to be the case in ADHD patients after fMRI-NF of right IFC (Rubia et al., 2019)

Neurotherapeutics in ADHD

One of the most revolutionary findings of the last decade of neuroimaging has been the discovery of high brain plasticity. Neuroplasticity is even higher in childhood and adolescence, because the brain is developing still and more susceptible to change (Jancke, 2009; Rapoport & Gogtay, 2008). However, neuroplasticity has also been demonstrated in mid and older adulthood (Draganski et al., 2004; Draganski & May, 2008). Even a few weeks or months of training of a particular skill in mid and older adults, for example, juggling (Draganski et al., 2004; Draganski & May, 2008), learning for an exam (Draganski et al., 2006) or learning to meditate (Dodich et al., 2019) can change the structure of the brain. These insights into the brain's neuroplastic potential make novel neuromodulation treatments, such as non-invasive brain stimulation or neurofeedback, attractive clinical interventions (Ashkan et al., 2013; Rubia, 2018). Three is evidence that they are more effective in young people (Anderson et al., 2011). Brain stimulation studies have shown that children and adolescents compared to adults have enlarged neuroplasticity after non-invasive brain stimulation (Brunoni et al., 2012).

The establishment of neurofunctional biomarkers for ADHD with EEG and fMRI studies over the past decades has made it possible to target these biomarkers using neurotherapeutics. Given evidence for electrophysiological and neuroimaging functional deficits in ADHD, it seems plausible that treatments that try to reverse these underlying brain function deficits could potentially be promising, given that they are targeting the key neurobiological abnormalities associated with the disorder. There has been over 45 years of studies testing EEG-NF in ADHD. However, the findings have been inconsistent. fMRI or NIRS-Neurofeedback is still very much in its infancy with too few and underpowered applications to provide a clear insight on potential efficacy. There has been an exponentially increasing number of non-invasive brain stimulation studies over the past 10 years. Studies have, however, been relatively small numbered with very heterogenous study designs. Consequently, findings have been inconsistent with respect to improving cognition with very little evidence, so far, on improving clinical behaviour.

Neurofeedback

Neurofeedback (NF) is based on operant conditioning. The participant learns by trial and error, to upregulate the activation of specific areas of his/her brain in the form of auditive or visual feedback of these brain activity which is processed and fed-back in real time on a PC. For children this is often done in a playful way by using a videogame that is connected to the brain activity. Because children with ADHD have low self-control (Schachar et al., 1993), it has been thought that teaching these children to increase control over their brain activity may be a useful treatment. Therefore, electrophysiology (EEG)-NF has been applied more to ADHD than any other psychiatric disorder (EEG-NF).

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EEG-NF

EEG-NF trains self-regulation of oscillatory or task-related EEG-markers associated with ADHD, like increased theta and TBR linked to compromised activation, decreased sensorimotor rhythm (SMR) related to impaired state regulation and sleep, and attenuated task-related slow cortical potentials (SCP) like the CNV correlated with impaired preparation and activation (standard protocols) (Arns et al., 2014)

EEG-NF has been tested in people with ADHD for over 45 years. However, the majority of the studies had important methodological shortcomings like the lack of an appropriate control condition, randomization, unblinded outcome measures, non-standardized feedback-methods, limited or no reporting of self-regulation and appropriate learning. During the last two decades, large improvements have been made to address these major drawbacks resulting for example in a very recent consensus publication on the reporting and experimental design of neurofeedback studies (Ros et al., 2020).

During the last decade, a large number of meta-analyses were published which scrutinize the clinical efficacy of EEG-NF in ADHD. The first meta-analysis based on ten controlled studies reported large effect sizes in favour of EEG-NF when parents rated the clinical outcome of inattention or for impulsivity measured in tests, and non-inferiority compared to the gold standard of stimulant medication treatment, and recommending therefore EEG-NF as "*efficacious and specific"* (i.e., the therapy performs better than a sham treatment in at least two independent studies (Arns et al., 2009) *(for updated, more stringent criteria see (Arns et al., 2020).* More than ten years and more than ten meta-analyses later (Arns et al., 2009, 2014, Cortese et al., 2016, Van Doren et al., 2019, Micoulaud-Franchi et al., 2014, Riesco-Matías et

al., 2021, Sonuga-Barke et al.,, 2013, Yan, et al., 2019, Lambez et al., 2020, Bussalb et al., 2019, Hodgson, et al., 2014), the latest comprehensive meta-analysis to date, reported significant, albeit small to medium effect sizes and inferiority compared to stimulants (Riesco-Matías et al., 2021). This drop of more than half of the effect size (for a historical/chronological viewpoint see Figure 1) is interesting and probably related to the growing research using stricter control conditions and improved scientific standards for EEG-NF studies which will be discussed in the following. The first meta-analysis (Arns et al., 2009) included non-randomized studies which are considered a weak experimental design to determine clinical efficacy (Norris & Atkins, 2005), whereas randomized controlled trials (RCT) are considered gold-standard in clinical research. The following meta-analysis (Sonuga-Barke et al., 2013) addressed this issue by including only RCTs, together with the inclusion of blinding criteria of the clinical outcome, such as ADHD core symptoms. These authors introduced the term of "probably blinded" raters which refers to the assessment, most often by teachers, who do–*probably*- not know to which treatment the patient was allocated. These two new requisites blunted the clinical effect which still remained significant for unblinded raters (such as parents) with medium effect sizes but was reduced to a trend-level for the probably blinded raters. Following these new insights, the recommendation to consider EEG-NF in ADHD as *efficacious and specific* was ameliorated. One year later, Micoulaud-Franchi et al., (Micoulaud-Franchi et al., 2014) conducted another meta-analysis, including the subdomains of the core ADHD symptoms, i.e., inattention, hyperactivity, and impulsivity. When evaluating the core symptom domains separately, a significant effect emerged also for the probably blinded raters, but only for the inattention subdomain. Subsequently, two years later, an update of Sonuga-Barke's meta-analysis was published by the same group (Cortese et al., 2016) on behalf of the European ADHD guidelines group, incrementing the analysis from 8 to 13 RCTs with parent-ratings and from 4 to 8 RCTs with probably blinded ratings. This updated meta-analysis resulted in insignificant findings for

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all probably blinded ratings including inattention, but still showed a significant medium effect size for parents' ratings. The discrepancy regarding the blinded findings in the subdomain of inattention in Micoulaud-Franchi (Micoulaud-Franchi et al., 2014) appears due to selecting different blinded outcomes in the same studies. The meta-analysis of Cortese (Cortese et al., 2016) also reported an exploratory sensitivity analysis including only three EEG-NF studies that used standard protocols (Arns et al., 2014), where the effects on ADHD symptoms became also significant for probably blinded raters, but subsequent large standard NF trials (i.e. (Arnold et al., 2020; Strehl et al., 2017) could not substantiate this. Importantly, Bussalb et al., (Bussalb et al., 2019) in their meta-analysis systematically evaluated further factors which influenced the efficacy of NF. They concluded that the intensity of NF but not the treatment duration was associated with higher efficacy, teachers were less sensitive to patients' symptoms and suggested that NF needs to be evaluated with placebo-controlled interventions. As can be observed from this, progress has been made to enhance the quality and certainty of the consideration and evaluation of the efficacy of EEG-NF in ADHD. Neurofeedback should be considered an umbrella term since there exist a large number of different training modalities that are only limited by the available technology (such as Coherence training, asymmetry feedback, etc). This issue is of paramount importance and a standardization should be aimed for. To date, the already mentioned standard protocols fulfil these criteria and so far, very recently a few larger studies were published. The latest comprehensive meta-analysis (Riesco-Matías et al., 2021) addressed an additional important point, which is the selection of an adequate control group, and compared EEG-NF vs non-active control groups (waiting-list controls, treatment as usual) and active control groups. The main findings showed superiority of EEG-NF compared to non-active control groups for parent ratings and for the inattention subdomain rated by probably blinded raters, resembling the findings of Micoulaud-Franchi et al., (Micoulaud-Franchi et al., 2014). However, when EEG-NF was compared with an active

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control condition, such as pharmacotherapy, EEG-NF was no longer superior. These findings underline the importance of considering active elements in control conditions, and the need to grade these active elements consistently across Neurofeedback and other neurotherapies studies. The recent consensus statement on evidence-based ADHD treatments excluded studies and meta-analyses with non-active or heterogeneous controls such as waiting control or treatment as usual (Faraone et al., 2021). However, this approach may underestimate some genuine NF-effects in real life settings that are also detectable by blinded raters or are slower to develop. Still, it is also important to take into consideration the cost-benefit aspects and preferences for the individual patient. As discussed above, pharmacotherapy has limitations due to side effects and no consistent longer-term effects. One recent meta-analysis addressed the question of longer-lasting effects of EEG-NF six months after treatment and showed small to medium effects in favour of neurofeedback when compared to non-active conditions and comparable effects relative to active conditions, mainly pharmacotherapy, contrasting with the superiority of the active control conditions shortly after treatment (Van Doren et al., 2019). EEG-NF thus seems to have delayed beneficial effect, as for example in a study where the superiority of stimulants over NF observed at treatment end (Geladé et al., 2016) was no longer significant at the six-month follow-up, and ADHD core symptoms compared to a semi-active (physical exercise) control condition were similar at treatment end but became reduced with NF relative to the exercise control condition at follow-up (Geladé et al., 2016). However, contradictory findings from the largest study to date which assessed longer-term effects of EEG-NF, showed that although the improvement of ADHD core symptoms relative to the baseline remained large and stable after treatment at six month follow-up, it was no longer superior to a semi-active condition (Aggensteiner et al., 2019), suggesting considerable unspecific long-term effect. In general, the specificity of the efficacy of EEG-NF is controversial and still under debate. During the last decade, disentangling the true effect related

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to neuromodulation from non-specific effects, has been under investigation. In Strehl et al., (Strehl et al., 2017) this was addressed by comparing EEG-NF with a semi-active control EMG-BF group controlling for unspecific effects, such as the high-tech training setting, interaction, learning, time, motivation, expectation, and effort, which showed clinical superiority in favour of EEG-NF one month after treatment end. Controlling for these factors is highly important since the clinical effects of this kind of time-consuming training might otherwise be attributed to unspecific psychosocial (Wood & Kober, 2018) or placebo effects which seem particularly strong with treatments that involve high-tech settings (Schönenberg et al., 2021; Thibault et al., 2016, 2017; Thibault et al., 2018; Thibault & Raz, 2016). To control for these aspects, a sham-feedback condition is often considered a gold standard in intervention research. The recent large double-blind placebo-controlled study of the Collaborative Neurofeedback Group (2020) which compared TBR-NF with a double-blind sham-NF placebo group not only followed this approach, but also introduced individualization by selecting only participants with an elevated TBR. The results showed large uncontrolled clinical effects until 13 month follow-up in both groups relative to baseline, and a reduced need for medication in the Neurofeedback group at follow-up, but failed to demonstrate clinical superiority for EEG-NF despite more TBR learning in the NF than in the sham group (67% vs 59%) (Arnold et al., 2020). The mechanism which explains the large nonspecific clinical effects in both groups remains unclear. Given that the main aim of neuromodulation is to self-regulate the trained parameters, improvement of brain modulation should be related to clinical improvement and explain clinical outcome. This relation remains understudied (Zuberer et al., 2015) and is complicated due to delayed effects as discussed above, or indirect effects of effort and skill acquisition (Gevensleben, Albrecht, et al., 2014). However, the outcomes seem to be mixed, as fewer than 70% of those treated with NF improve self-regulation (Aggensteiner et al., 2019) and only about 50% show the expected “dose-response” relation between learned regulation

and clinical improvement (Drechsler et al., 2007). Specifically, three studies found some significant association between brain self-regulation and ADHD core symptoms after SCP-NF (Aggensteiner et al., 2019; Drechsler et al., 2007; Strehl et al., 2006). However, some recent frequency band NF studies could not find any association between self-regulation and symptom reduction (Arnold et al., 2020, Janssen et al., 2016), or were contrary to the expectations, with associations found in the semi-active control group (Aggensteiner et al., 2019). These brain-behaviour association analyses are necessary to be able to disentangle specific from unspecific effects. However, so far, no firm general conclusion can be drawn regarding the specific effects related to self-regulation. Predicting who responds to EEG-NF is particularly relevant. One SCP neurofeedback study found that increased theta activity predicts clinical responses to theta-modulating neurofeedback, and that stronger oscillatory parietal alpha activity along with stronger task-related preparatory SCPs together explained nearly 30% of the clinical outcome variance after SCP-NF (Gevensleben, Kleemeyer, et al., 2014; Gevensleben, Moll, et al., 2014; Wangler et al., 2011). However, these intriguing results await independent replication. It is paramount that studies systematically test for the specificity of self-regulation and the mechanisms which underlie the individual clinical effects, considering also reduced medication use, and long-term improvement in ecological settings. Also, whether individualization of NF (e.g., limiting TBR training to those with elevated TBR) improves outcomes remains to be tested with appropriate control conditions.

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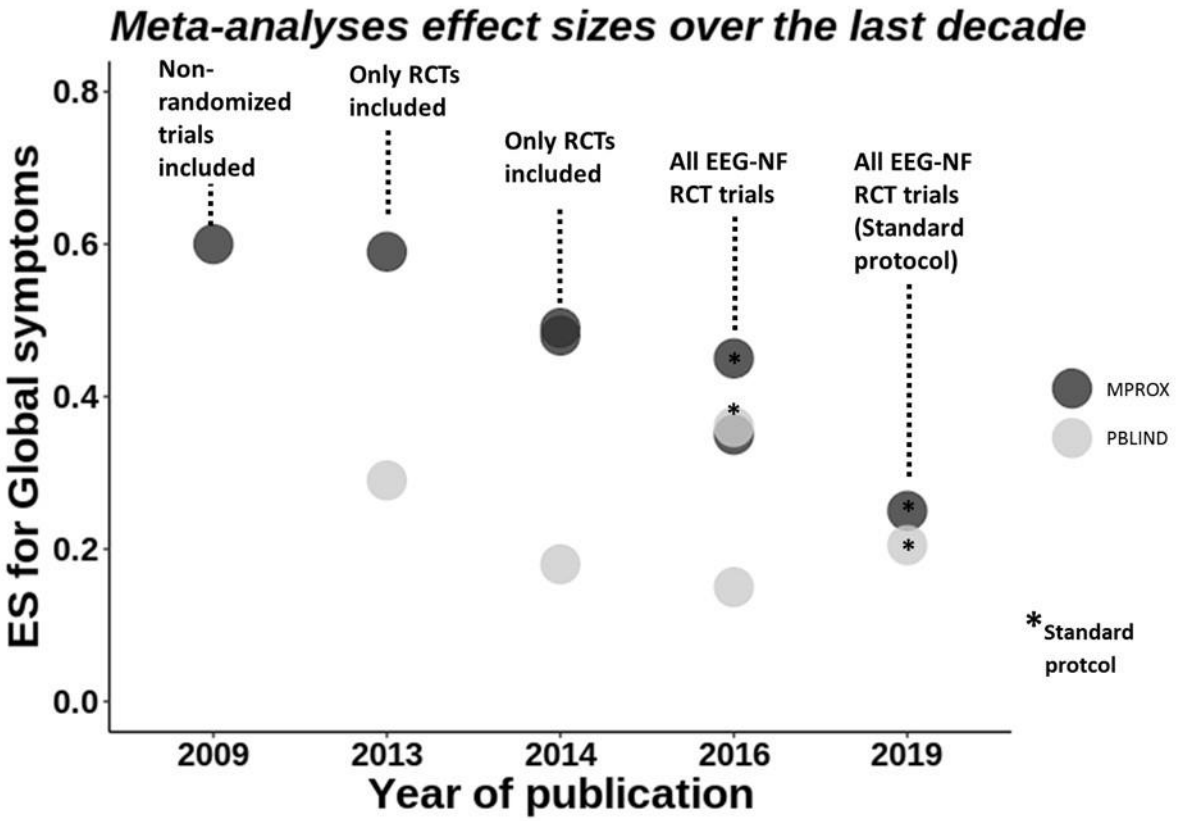
Figure 1.



Effect sizes (ES) in meta-analyses of EEG Neurofeedback studies for effects on global ADHD symptoms by year of publication. MPROX: Ratings by parents/ proximal raters; PBLIND: Ratings by probably blinded raters. *Studies that used a standard protocol.

fMRI-Neurofeedback

Real-time fMRI neurofeedback (fMRI-NF), despite its lower temporal resolution relative to EEG-NF (seconds compared to milliseconds), has superior spatial resolution (millimetre rather than centimetre) and has the advantage that it can target the key cortical and subcortical brain function deficits that have been established in ADHD over the past 25 years

of fMRI research (Rubia, 2018). fMRI-NF enables participants to self-regulate the blood-oxygen level-dependent (BOLD) response of a targeted brain region, or network, through real-time feedback of their brain activity and has shown some promise in improving clinical symptoms and cognition in psychiatric disorders (Thibault, MacPherson, et al., 2018). To date, however, there are only two published fMRI-NF studies in ADHD.

The first fMRI-NF study was a small underpowered randomised controlled trial in seven adults with ADHD who underwent four weekly 1-hour fMRI-NF of dorsal anterior cingulate cortex (dACC), combined with a mental calculation task while six ADHD patients completed the same task in the scanner but were presented with visual cues indicating level of task difficulty instead of fMRI-NF (Zilverstand et al., 2017). Both groups significantly increased dACC activation over the NF runs, including the transfer runs, and improved in an interference inhibition task. Both groups showed trend-level improvements in ADHD symptoms but did not differ from each other. However, only the neurofeedback group showed significantly stronger performance improvement in a sustained attention and working memory tasks after treatment but not the ADHD group that received no fMRI-NF, indicative of some positive effects of fMRI-NF of dACC on cognition in adults with ADHD (Zilverstand et al., 2017).

A randomised controlled trial from our lab tested fMRI-NF of the rIFC compared to fMRI-NF of the left parahippocampal gyrus (lPHG) in adolescents with ADHD (Alegria et al., 2014). Thirty-one boys with a clinical ADHD diagnosis underwent 11 runs of 8.5 min of fMRI-NF during 4 hour-longs scans over a 2-week period, with a rocket movie as feedback. Eighteen participants learned to self-upregulate the target region, the rIFC (rIFC-NF group); while 13 participants self-upregulated a control region, the lPHG (lPHG-NF group). In both groups, activation of their target regions increased linearly across the 11 fMRI-NF runs. However, only the rIFC-NF group showed a transfer effect (self-regulation without feedback, as a proxy of

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transfer to real life) that significantly correlated with reduced ADHD symptoms. Although ADHD symptoms significantly improved in both groups, only the rIFC-NF group showed a large reduction of symptoms at 11 months follow-up, with an effect size of almost 1, compared to a trend-level reduction in the lPHG-NF group. Only the rIFC-NF group also showed trend-level improvement in their sustained attention performance. In addition to the linear increase of activation of the rIFC in the rIFC-NF group, there was an increase in functional connectivity between the rIFC and the ACC and caudate, and a decrease in functional connectivity between the rIFC and regions of the posterior default mode network (DMN). This suggested that the NF of an isolated region led to positive network changes in cognitive control and DMN networks (Rubia et al., 2019). In order to measure the effects of fMRI-NF on brain function in ADHD, the participants of this study also performed a motor response inhibition fMRI task, the tracking stop signal task, before and after fMRI-NF. There was a significant group by time effect for the fMRI data, where post minus pre fMRI-NF, the rIFC-NF group had higher brain function relative to the lPHG-NF group during successful inhibition in the rIFC and parietal regions (Alegria et al., 2014). Furthermore, during failed inhibition they had higher activation in error monitoring brain areas, in left IFC, premotor cortex, insula and putamen, which correlated with ADHD symptom improvements and were concomitant with increased post-error reaction time adjustment at the behavioural level (Criaud et al., 2020). Interestingly, we observed similar upregulation effects in ADHD children in the same regions when comparing the effects of stimulant medication relative to placebo, using the same stop task (Cubillo et al., 2014; Rubia et al., 2014; Rubia et al., 2011), suggesting that fMRI-NF of the rIFC has similar brain activation effects on the disorder as stimulant medication, but without the side effects. In fact we found no group differences in side or adverse effects. However, not everyone is capable of learning fMRI-NF. Similar to the EEG-NF literature (Zuberer et al., 2015; Zuberer et al., 2018), we found that only 48% of patients learned successfully to upregulate their target region with

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fMRI-NF (Lam et al., 2020). Furthermore, fMRI-NF learning was better predicted by fMRI than clinical or cognitive data. Thus, increased activation in left inferior fronto-striatal cognitive control regions and reduced activation in posterior temporo-occipital and cerebellar regions during successful inhibitory control in the fMRI stop task predicted fMRI-NF self-regulation capacity. Clinical measures were not associated with general fMRI-NF learning and within a task battery of executive function tasks, only faster processing speed during inhibition and attention tasks predicted fMRI-NF learning (Lam et al., 2020).

NIRS Neurofeedback

Only one pilot study so far tested the related neural haemodynamic modulation method of NIRS Neurofeedback (NIRS-NF) of the left dorsolateral prefrontal cortex in 9 ADHD children, compared to EEG-NF (N = 9) and electromyography-NF (N = 9). Only NIRS-NF resulted in significant improvements in clinical ADHD symptoms and in cognitive inhibition and attention functions after 11 hourly sessions over 4 weeks, which was, however, not superior to EEG-NF or electromyography-NF (Marx et al., 2015).

Conclusions from Neurofeedback studies

In conclusion, there has been over 45 years of research in ADHD of EEG-NF. This has produced a large number of meta-analyses of randomized controlled trials showing consistent small to medium effect sizes. Controversy however exists with respect to “probably” blinded raters (Bussalb et al., 2019; Cortese et al., 2016). Furthermore, the specific effects of EEG-NF and the association between NF self-regulation and clinical improvement are still unclear and

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need more systematic research. Additionally, future studies should optimize the designs to promote EEG-NF self-regulation and improvement over time, considering increased artefacts and altered reward learning in ADHD (e.g., Aase & Sagvolden, 2005), and further systematically investigate why some participants show low regulation performance.

fMRI-NF and NIRS-NF research is still in its infancy with only small proof of concept studies conducted so far. These have elicited promising findings. It will be necessary, however, to test these novel neurotherapies for their therapeutic benefits for ADHD in much larger double-blind, placebo-controlled randomised controlled trials. We do not know the optimal protocol, such as optimal regional target of neurofeedback, or the number and duration of sessions of NF. Also, we do not know whether the brain reaches a point of optimal brain activation or a plateau after which effects may decline. It is also unknown whether there are interindividual differences that influence the learning effect of brain auto-regulation and what these are. Furthermore, we do not know whether NF effects transfer to daily life. It would also be helpful to investigate the best reinforcement strategies related to NF in children. In NF studies, potential side effects of brain upregulation on other regions that were not self-regulated such as potential downregulation effects in areas in the homologue hemisphere on the other side via hemispheric inhibition or on neighbouring regions needs to be explored. It is entirely possible that the self-regulation training of a particular brain region has a downregulation effect on neighbouring, interconnected or contralateral regions and the potential costs of such downregulations need to be assessed.

NF studies have shown very interesting delayed longer-term consolidation effects which seem to be pronounced some time after the therapy than immediately after treatment (Alegria et al., 2014; Arns et al., 2014; Arns & Strehl, 2013; Marx et al., 2015); however, one recent study showed no superiority over an semi-active control group at six month follow-up

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(Aggensteiner et al., 2019). If effects are delayed then this supports the hypothesis that NF improves neuroplasticity. This would be a clear advantage over pharmacological medication such as stimulants which do not modify brain plasticity with some evidence that effects may wane with time (Cortese et al., 2018; Molina et al., 2009; Swanson, 2019). We have shown in a meta-analysis of positron emission tomography study that this could be related to brain tolerance (Fusar-Poli et al., 2012). Studies have indeed found that NF leads to changes in cortical excitability and to changes in the brain structure including white matter tract, suggesting brain plasticity effects (Sitaram et al., 2017). We do not currently know, however, how long these effects last. The fact that side effects are minor and that NF has the potential to induce neuroplastic changes makes NF therapies very attractive for children with ADHD.

Brain stimulation

The past 10 years has seen an exponential increase in the number of non-invasive brain stimulation therapies applied to ADHD. Most studies have used rTMS and tDCS. It has been shown that rTMS and tDCS can change the plasticity of synapses. There is also evidence for potentially longer-term effects which could be mediated by GABA and glutamate (Demirtas-Tatlidede et al., 2013). In fact, several studies in healthy populations and patient groups have shown longer-term cognitive effects of up to 1 year after stimulation (Katz et al., 2017; Ruf et al., 2017). Positron emission tomography (PET) studies have shown that anodal frontal tDCS can release neurotransmitters such as dopamine (Borwick et al., 2020; Fonteneau et al., 2018; Meyer et al., 2019), which furthermore correlated with better attention (Fukai et al., 2019), with some indirect evidence for effects on noradrenaline (Adelhöfer et al., 2019; Mishima et al., 2019). This is relevant for ADHD where these neurotransmitters are typically abnormally

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low (Cortese et al., 2019). Similarly, rTMS over prefrontal regions in animals and humans has been shown to induce changes to neurotransmitter systems including alterations to serotonin, striatal dopamine release and metabolite levels, as well as to the release and concentrations of striatal glutamate (Moretti et al., 2020; Poh et al., 2019). It has furthermore been shown that the combination with cognitive training which can prime the areas to be stimulated with a cognitive task is more effective than stimulation alone, due to the synergistic effects of functional targeting (Cramer et al., 2011; Kuo & Nitsche, 2012; Ziemann & Siebner, 2008).

Repetitive transcranial magnetic stimulation (rTMS)

rTMS applies an electromagnetic current to a coil placed on the subject's head. It is non-invasive and has been shown to be relatively safe. The electrical current triggers action potentials in the underlying brain areas brain and can modulate the underlying activity of neurons. Different stimulation intensity and duration, the number of pulses and their frequency have different effects. In general, high-frequent rTMS of more than 5 Hz increases the excitability of neurons, while low frequency below 1 Hz reduces it (Lefaucheur et al., 2014). Longer-term clinical improvements with rTMS have been demonstrated in several psychiatric disorders (Janicak & Dokucu, 2015; Mehta et al., 2019), supporting its neuroplastic potential. Relative to tDCS, rTMS has greater specificity in targeting neural regions (Parkin et al., 2015) but is more expensive. The most common side effects are transient scalp discomfort underneath the coil due to stimulation of the pericranial muscles and peripheral nerves (Rossi et al., 2009). The majority (4 out of 6) of rTMS studies were conducted in adults with ADHD. Two double-blind, sham-controlled crossover studies targeted the right DLPFC. In 13 ADHD adults, one session of 20Hz-rTMS relative to sham significantly improved overall self-rated ADHD

symptoms and inattention but had no effect on hyperactivity, mood or anxiety scores (Bloch, 2012). In 9 ADHD adults, 10 daily sessions of 10Hz-rTMS relative to sham showed no effect on self-rated clinical symptoms, nor on EEG or EF measures (Weaver et al., 2012). In a single-blind sham-controlled randomised study in 22 ADHD adolescents, 20 daily sessions over 4 weeks of 18Hz deep rTMS over bilateral DLPFC (n = 13) compared to sham (n = 9) showed no effect on self-rated clinical or cognitive measures of sustained attention (Paz et al., 2018). A parallel, semi-blind, randomised, active and sham-controlled study in 43 young adults with ADHD tested 15 sessions of 18 Hz-rTMS over 3 weeks and a 1-month follow-up maintenance session over right prefrontal cortex, targeting both DLPFC and IFC. Stimulation was combined with a short cognitive training session targeting the right prefrontal cortex, which was conducted before and after stimulation. While patients were blind, researchers were only blind for the sham and real but not the active stimulation control condition, which was off-target focal stimulation 5-6 cm away from the DLPFC or IFC and which did not target DLPFC or IFC (Alyagon et al., 2020). The DLPFC/IFC stimulation compared to the other conditions showed significant improvements in the primary clinical outcome measure, which were self-rated ADHD symptoms, with an effect size of 0.96 versus sham and 0.68 versus the active control stimulation, and there was only a significant improvement in the hyperactivity/impulsiveness in the self-rated subscales. Superiority of real versus control conditions was no longer significant at follow-up a month later. There were no significant effects on depression ratings, behavioural executive functions (as measured on the BRIEF), or cognitive inhibition measures except for a trend of improving Stroop task performance relative to sham but not active control which was correlated with the clinical changes in the DLPFC/IFC stimulation group. EEG measures showed a negative correlation between alpha activity and a positive correlation between low gamma activity under the stimulation area with clinical symptom improvements in the DLPFC/IFC stimulation group.

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Two studies were conducted in children with ADHD. An open label tolerability and safety trial in 10 children with ADHD without a sham condition showed fewer teacher-rated inattention and parent-rated hyperactivity/impulsivity symptoms one week after five daily sessions of 1Hz-rTMS over left DLPFC compared to baseline (Gómez et al., 2014). A larger study randomised 60 children with ADHD into either 30 daily 25min sessions of 10Hz rTMS over right DLPFC, Atomoxetine (1.2mg/kg) or combined treatment over 6 weeks. The combined group compared to the individual treatment groups improved significantly post relative to pre-treatment in inattention and hyperactivity/impulsiveness but not in oppositional defiant behaviours nor in cognitive measures of sustained attention, working memory and gambling tasks. All groups improved in these clinical and cognitive measures (Cao et al., 2018). However, without a sham condition, placebo or practice effects cannot be ruled out in both studies (Table 1).

With respect to safety, one study reported a seizure in one patient after 3 sessions who was excluded from the study (Alyagon et al., 2020) while most other studies reported no or few side or adverse events other than transient headaches and scalp discomfort localized to the stimulation area.

In conclusion, rTMS is relatively safe. The majority of studies were conducted in relatively small samples, using few session numbers of rTMS, and 2 out of 6 studies did not include a sham condition, making it impossible to rule out placebo or practice effects. Based on the conducted studies so far, there is relatively little evidence that several sessions of rTMS improve ADHD symptoms or cognition with exception of one study in adults that used multisession rTMS and stimulated right DLPFC and IFC combined with cognitive training and which needs replication. More multisession sham-controlled RCTs in large patient numbers are needed in particular in pediatric ADHD to more thoroughly test TMS effects using different

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protocols.

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Table 1. Clinical and cognitive effects of sham-controlled rTMS studies

					Stimulation Protocol			Outcome measures (bold/underlined = improvement)	
Study	**Design**	**N**	**Age**	**Target**	**Sessions**	**Frequency**	**Duration**	**Clinical**	**Cognitive**
Children									
Cao et al., 2020	Single-blind, randomised, parallel (2 active controls: ATX, ATX-rTMS; no sham)	64 (~20 each)	6-13	R DLPFC[a]	20	18Hz (100% MT)	2000 pulses (4s on, 26s off)	SNAP-IV	CPT; WISC; IGT
Gomez et al, 2014	Open label	10	7 - 12	L DLPFC	5	1Hz (90% MT)	1500 pulses (on, off n/r)	DSM-IV ADHD symptom checklist **(hyperactivity/imp., inattention)**	n/t
Adults									
Bloch et al, 2010	Single-blind, sham-controlled, randomised, crossover	13	NR (adults)	R DLPFC[a]	1	20Hz (100% MT)	1680 pulses (2s on, 30s off)	PANAS (**inattention, total score;** mood, anxiety, hyperactivity); VAS (inattention, mood)[b]	n/t
Paz et al, 2018	Double-blind, sham-controlled, randomised, parallel	A: 13 S: 9	A: 32 S: 30	L DLPFC[c]	20	18Hz (120% MT)	1980 pulses (2s on, 20s off)	CAARS	TOVA

Weaver et al, 2012	Single-blind, sham-controlled, randomised, crossover	9	18	R DLPFC[a]	10	10hz (100% MT)	2000 pulses (4s on, 26s off)	CGI-I scale; ADHD-IV scale	WAIS/WISC-IV; Connors CPT; DKEFS; Buschke Selective Reminding Test; Symbol Digit Coding test; Finger Oscillation tasks
Alyagon et al, 2020	Double-semi-blind, randomised, active and sham-controlled	52 (15, 14,14)	21-46	R IFC & DLPFC	15	18Hz (120% MT)	1440 pulses (2s on, 20s off)	**CAARS** (global **ADHD symptoms; hyperactivity/impul-siveness)** (BAARS-IV **(hyperactivity/impul-siveness)**, BRIEF-A, BDI)	STROOP; STOP

Abbreviations: A, active; BAARS; Barkley Adult ADHD Rating Scale; BRIEF-A; Behavioral Rating Inventory for Executive Functioning ; BDI; Beck Depression Inventory; CAARS, Conners' Adult ADHD Rating Scale; CGI-I, Clinical Global Impression-Improvement Scale; DKEFS, Delis-Kaplan Executive Function System; DLPFC, dorsolateral prefrontal cortex; Hz, number of magnetic pulses per second; IGT: Iowa Gambling task; L, left; MT, motor threshold; n/t, not tested; PANAS, Positive and Negative Affect Schedule; R, right S, sham; SNAP-IV: Clinical rating scale of the severity of ADHD; TOVA, Test of Variables of Attention; VAS, Visual analogue scales; WAIS, Wechsler Abbreviated Scale of Intelligence, selected subtests from the Wechsler Adult Intelligence Scale; WISC-IV, Wechsler Intelligence Scale for Children-IV; [a]5 cm forward to MT point; [b]small change from baseline of .25 and 1.16 out of 5-point Likert scales; [c]6 cm rostral to motor cortex

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Transcranial direct current stimulation (tDCS)

tDCS applies a weak continuous direct electric current to underlying brain areas through via scalp electrodes. The electrical current of 2mA typically passes between a positively charged anode and a negatively charged cathode. These currents can cause plasticity by triggering subthreshold increases with anodal stimulation or decreases with cathodal stimulation in membrane potentials. These membrane potentials then change neuronal discharge and excitability, which can increase or decrease cortical function and synaptic plasticity (Ashkan et al., 2013). tDCS compared to rTMS is cheaper, easier to apply and less painful than TMS and therefore more tolerable for children. Studies have shown very minor side effects in children and adults. The most common side effects are itching and reddening of the stimulation site which typically disappears after a few hours (Krishnan et al., 2015; Zewdie et al., 2020). Combining cognitive training with tDCS (Kuo & Nitsche, 2012) is more effective than each treatment alone (Cramer et al., 2011), presumably via a synergistic effect of plasticity induced by training as well as by stimulation (Ziemann & Siebner, 2008). In other disorders and in healthy controls it has been shown that the effects of tDCS combined with cognitive training can last up to 6 months (Boggio et al., 2012; Kuo et al., 2014) and 1 year (Katz et al., 2017). fMRI studies furthermore show that not only the site of stimulation is modified with tDCS but also areas that are connected to the region that has been stimulated (Polania et al., 2011). This could make it useful for stimulating entire networks in ADHD for example, fronto-striatal networks. Neurotransmitters that are abnormal in ADHD have been implicated in the mechanism of action such as dopamine (Pogarell et al., 2007) and noradrenaline (Kuo, et al., 2017, Mishima et al., 2019). Unlike with rTMS, the majority of tDCS studies (12 out of 18) have been conducted in children with ADHD, presumably due to the high tolerability and relatively low side effect profile of tDCS, which would make it a good treatment option if efficacious. The majority of studies used very small session numbers and tested cognitive

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effects only. Two double-blind, sham-controlled, crossover studies applied single session stimulation over the DLPFC. In 15 adolescents with ADHD, anode-left/cathode-right tDCS over bilateral DLPFC improved WCST completion time, n-back reaction times, and Stroop reaction times and commission errors to incongruent trials but had no effect on n-back accuracy or go/no-go task performance (Nejati, Salehinejad, et al., 2020). In 10 ADHD adolescents, anodal tDCS over the left dlPFC improved n-back accuracy and reaction times compared to both sham and cathodal tDCS; anodal and cathodal tDCS also improved WCST performance, but anodal tDCS led to greater improvement; cathodal tDCS also improved No-Go accuracy, potentially via interhemispheric inhibition increasing right prefrontal activation (Nejati, Salehinejad, et al., 2020), a region associated with motor response inhibition in children and adults (Rubia et al., 2013; Rubia et al., 2003; Rubia et al., 2007). This last finding is in line with a single-blind, crossover study in 21 adolescents with ADHD, which found in a subsample of 7 participants that compared to sham one session of anodal, but not cathodal, tDCS over the right IFC reduced commission errors (trend-level) and reaction time variability in an interference inhibition task (Breitling et al., 2016). Two single-blind, sham-controlled crossover studies conducted in 20 high school students with high ADHD symptoms stimulated left DLPFC or right IFC symptoms. Single session anodal relative to cathodal tDCS over the left DLPFC improved go accuracy while cathodal tDCS relative to anodal tDCS and sham improved no-go accuracy in the go/no-go task, but there was not change in Stroop task performance (Soltaninejad et al., 2019). Anodal tDCS over the rIFC relative to sham improved go accuracy but there were no changes in other go/no-go or Stroop task measures (Soltaninejad et al., 2015). A double-blind sham-controlled RCT in 50 children with ADHD tested the effects of 15 sessions of 20 min of right IFC stimulation combined with cognitive training in executive function tasks. The study found that both groups improved in clinical symptoms and cognitive functions but the improvement in the real versus sham tDCS in primary and secondary clinical

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outcome measures was significantly less pronounced. Groups did not differ in a large battery of executive function cognitive outcome measures nor in EEG measures within a smaller subsample of data collected from 26 participants only. Furthermore, the real tDCS group had worse adverse effects related to mood, sleep and appetite immediately after stimulation (S. J. Westwood et al., 2021).

A double-blind, crossover study applied five daily sessions of anodal or sham tDCS over left DLPFC in 15 adolescents with ADHD, but because of a carry-over and learning effects only the first sessions were analysed thus reducing the sample to 7 to 8 participants per condition (Soff et al., 2017). Compared to sham, anodal tDCS improved parent-rated inattention and cognitive measures of attention (Qb test; which combines cognitive measures of hyperactivity, impulsiveness and inattention in a hybrid n-back/GNG task) one week but not immediately after the last stimulation session, while cognitive measures of hyperactivity on the Qb test were improved immediately after anodal tDCS and seven days later (Soff et al., 2017). Analysis of 13 out of the 15 ADHD adolescents after a single session of anodal tDCS relative to sham showed reduced reaction time variability but increased errors on the QbTest, but this analysis included the carryover effect (Sotnikova et al., 2017). A double-blind, sham-controlled crossover study found that overnight slow-wave oscillatory anodal tDCS over left and right DLPFC, relative to sham, improved declarative memory in 12 ADHD children (Prehn-Kristensen et al., 2014), reaction time and its intra-subject variability on go trials in a go-no-go task in 14 ADHD children (Munz et al., 2015), but had no effects on no-go accuracy, alertness, digit-span, or motor memory. An open label trial in 9 ADHD children found that five daily sessions of anodal tDCS to left DLPFC combined with a picture association cognitive training task reduced errors on attention (omission) and switch tasks but did not improve working memory, while parents, with one exception, reported improvements in some of their children's

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behaviour (Bandeira et al., 2016). In a double-blind, crossover study in 14 children and adolescents with ADHD, the right IFC was stimulated with either conventional tDCS, high definition tDCS (HD-tDCS) or sham while performing a working memory task with inhibitory elements which was repeated after stimulation as outcome measure. HD-tDCS is a 4:1 small electrode array with one electrode encircled by four electrodes of the opposite polarity, which delivers a more spatially restricted and therefore focal stimulation that can reduce side effects from stimulating non-target brain regions. The study found that neither a single session of conventional anodal tDCS nor HD-tDCS over right IFC combined with working memory performance compared to sham had any effect on performance in the n-back task; however, ERP data from 10 participants in ADHD showed elevated N200 and P300 after the two tDCS conditions versus sham and a shift towards the values seen in a healthy control group (Breitling et al., 2020). One study applied one session of anodal tDCS over the right inferior (and some superior) parietal lobe in 17 ADHD children in a single-blind, crossover study. In line with the role of inferior parietal lobe in orienting attention, anodal relative to sham tDCS improved performance in bottom-up orienting attention but deteriorated selective attention as measured in the Stroop interference reaction time and error effects and had no effect on alerting or top-down executive attention as measured in the shifting attention and go/no-go tasks (Salehinejad et al., 2020).

One recent study tested effects of tDCS on reward-related decision making in ADHD (Nejati, Sarraj Khorrami, et al., 2020). Twenty children with ADHD received tDCS in three separate sessions with either anodal tDCS over the left DLPFC and cathodal tDCS over right vmPFC, the reversed montage, and sham stimulation. Anodal tDCS over the right vmPFC, coupled with cathodal tDCS over the left DLPFC, reduced risky decision-making in the Balloon Analogue R Task but had no effect on the key impulsiveness outcome measure in the

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delay discounting task (k mean) but had an effect on some conditions but these were not corrected for multiple testing (Nejati, Sarraj Khorrami, et al., 2020).

Another recent study compared the clinical and cognitive effects of tDCS with tRNS in ADHD. Although similar to tDCS in terms of equipment and setup, tRNS applies an alternating current at random frequencies and/or intensities. The mechanisms by which tRNS influences brain activity are less known but are thought to be different than for tDCS (Fertonani & Miniussi, 2017). The most prevalent explanation for tRNS is stochastic resonance whereby the introduction of an appropriate level of random noise enhances the output of subthreshold signals; thus, the application of weak electric currents amounts to an introduction of neural noise (Fertonani & Miniussi, 2017). Information processing at the neuronal level is sensitive to stochastic resonance (McDonnell & Ward, 2011). The double-blind cross-over study compared 5 sessions of transcranial random noise stimulation (tRNS) over left DLPFC and right IFC with tDCS of left DLPFC combined with executive function training in 19 children with ADHD. Relative to tDCS, tRNS showed a clinical improvement in ADHD rating scale scores from baseline after treatment and one week later. Cognitively, tRNS compared to tDCS improved working memory, but only processing speed during sustained attention. An exploratory moderation analysis predicted a trend-level larger tRNS effect on the ADHD rating scale for those patients who showed the greatest improvement in working memory. tRNS yielded fewer reports of side effects, in line with the literature on adults showing that tRNS is a more comfortable neurostimulation method than tDCS (Berger et al., 2021).

Only four studies have been conducted in adults with ADHD. In a double-blind, parallel study in 60 adults, anodal tDCS over the left DLPFC compared to sham had no effect in two go/no-go tasks or functional cortical network activity based on EEG recordings in a subsample of 50 patients (Cosmo et al., 2015). One single-blind, crossover study applied a single session

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of anodal tDCS over the left and right DLPFC in 20 undergraduate students with ADHD, which, compared to sham, improved in hyperactivity measures (i.e., multiple/random responses) in a sustained attention task but had no effect on omission errors or reaction times (Jacoby et al., 2018). A double-blind, crossover study in 37 adults with ADHD administered three sessions of visual working memory training combined with anodal tDCS of the left DLPFC, and reported that compared to sham, anodal tDCS reduced commission errors in a sustained attention task immediately but not three days after the last stimulation, while there was no effect on omission errors, reaction times, stop task, or visual working memory training performance (Allenby et al., 2018). One double-blind, parallel study in 17 adults with ADHD found that tDCS of anodal right/cathode-left DLPFC (n = 9) versus sham (n = 8) improved inattention but not hyperactivity/impulsive symptoms immediately after 5 daily sessions of stimulation and at a 2-week follow-up, with total ADHD scores also improving at the 2-week follow-up, although group difference disappeared at the 4-week follow-up (Cachoeira et al., 2017). Finally, in a double-blind, crossover study in 37 adults with ADHD, participants were asked to perform a Flanker (n=18) or a Stop task (n=19) before and after receiving a single session of anodal tDCS over the left or right DLPFC relative to sham. In the Flanker task, left but not right DLPFC stimulation reduced reaction times on incongruent but not congruent trials compared to sham and right DLPFC stimulation. This was furthermore correlated with increased left and right P300 increase in EEG measures on incongruent trials after left and right DLPFC stimulation compared to sham, respectively and with reduced N200 amplitude after left compared to right DLPFC stimulation. In the Stop task, there was no effect in inhibitory measures but left DLPFC stimulation relative to sham increased Go reaction time, which was correlated with increased P200 amplitude during go trials (Dubreuil-Vall et al., 2020).

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In conclusion, only 3 out of 17 tDCS studies tested clinical effects. Two studies found that tDCS of left DLPFC improved clinical inattention symptoms while one study found that tRNS compared to tDCS improved ADHD symptoms. With respect to cognition, most studies found effects in the performance of some but not other tasks, with little consistency in findings between studies, and most studies did not correct for multiple testing. Two meta-analyses tested for consistent findings of tDCS on cognition in ADHD. A meta-analysis of 10 studies in 201 children and adults with ADHD found that 1 to 5 sessions of anodal tDCS over mainly left DLPFC significantly improved cognitive performance in inhibitory control measures (Hedges' g = 0.12) and in n-back reaction times (g = 0.66) (Salehinejad et al., 2019). However, effect sizes were small and the meta-analysis likely overestimated statistical significance by not controlling for interdependency between measures, and conflated inhibitory with non-inhibitory cognitive measures (S. Westwood et al., 2021). Addressing these and other limitations, a larger meta-analysis of 12 tDCS studies (232 children/adults with ADHD) found that 1 to five sessions of anodal tDCS over mainly left DLPFC led to small, trend-level significant improvements in cognitive measures of inhibition (g = 0.21) and of processing speed (g = 0.14), but not of attention (g = 0.18) (S. Westwood et al., 2021). To summarise, there have been inconsistent findings of the benefit of tDCS therapy to improve symptoms and cognitive functions in ADHD. Some studies found positive results on improving cognition, with, however, very small effects sizes observed in meta-analyses (see also Table 1). However, comparability of results was hampered by the large heterogeneity in study designs, stimulation parameters and site of anodal and cathodal stimulation. We will need larger sampled tDCS studies that apply more sessions and more comparable study protocols in order to be able to assess whether tDCS with or without cognitive training is a beneficial therapy for ADHD.

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Importantly, for both TMS and tDCS, but also tRNS or tACS, systematic testing is needed to identify the optimal stimulation parameters that can elicit reliable clinical or cognitive effects. Parameters that should be tested include optimal stimulation sites, frequency, duration, and superiority of stimulation effects combined with cognitive training. For tDCS, tRNS and tACS, studies should consider if effects depend on age, electrode size and inter-electrode distance, the focality of stimulation, and antagonistic effects of cathodal stimulation on the desired effect of the anodal stimulation. Because children have thinner skulls and less corticospinal fluid the effects of brain stimulation could be higher than those for adults. For this reason one cannot simply transfer the best dosage form adult to pediatric studies. For example, cathodal tDCS at 1mA, which has excitability-diminishing effects in adults, has shown to have excitatory effects in children and adolescents when applied over the motor cortex (Moliadze et al., 2015). Stronger intensity might be needed for deeper regions, such as IFC, than more superficial regions, such as like DLPFC, which might explain the null findings in studies of stimulation of rIFC in ADHD (Salehinejad et al., 2020). Clear and evidenced dosage guidance is therefore paramount for pediatric studies, especially since stimulation intensity and duration are non-linear (Lefaucheur et al., 2017) and the neuroplasticity changes are strongest during childhood development (Knudsen, 2004). Furthermore, we know very little on the longer-term effects of non-invasive brain stimulation techniques in ADHD. tDCS when combined with cognitive training (Katz et al., 2017) has been shown to have effects up to 1 month in other psychiatric disorders (Kekic et al., 2016; Moffa et al., 2018) while TMS has shown longer-term effects in other psychiatric disorders (Janicak & Dokucu, 2015; Mehta et al., 2019),

Given that tDCS is thought to affect neuroplasticity (Kim et al., 2014; Nitsche et al., 2008), potential longer-term efficacy could be the real advantage of tDCS over stimulant

medication. There is furthermore potential to combine tDCS with pharmacological or non-pharmacological treatments, in particular with cognitive training as mentioned above.

Direct side effects of non-invasive brain stimulation techniques are relatively small and do not last long (Krishnan et al., 2015; Salehinejad et al., 2020). However it is unknown whether they could cause negative effects in children where the brain is still developing. The baseline brain activation is likely to impact upon the effect of stimulation with the ones with lower baseline activation likely to benefit more (Silvanto et al., 2008, Krause et al., 2013a). This suggests that brain stimulation may potentially be ethical in patients who have suboptimal stimulation and where the benefits outweigh the risks, but not for healthy children and adults who have already optimal brain activation (Cohen-Kadosh et al., 2012). It has been shown that differences in traits which are associated with differences in the underlying baseline neural activation, can influence the effects of brain stimulation. For example, people with mathematical anxiety became faster in their reaction time to mathematical tasks after tDCS over DLPFC, while people with low mathematical anxiety became slowed int their reaction times. Also, both groups became impaired in an interference inhibition task (Sarkar et al., 2014), which could suggest that tDCS of DLPFC had a downregulating effect on IFC which mediates interference inhibition. Another study showed that stimulation of DLPFC had a positive effect on learning automaticity but a negative one on numerical learning which is mediated by parietal regions. On the other hand, stimulation of the parietal lobe impaired learning automaticity which is mediated by prefrontal regions but improved numerical learning (Iuculano & Kadosh, 2013). These findings suggest that one will need to take into consideration the differences in baseline brain activation and ideally individualise stimulation treatment based on these baseline activation patterns and the cognitive problems. This is important for ADHD where we know that there is a heterogeneity in cognitive abnormalities with some

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children being normal in cognition (Nigg et al., 2005; Roberts et al., 2017). There is thus worrying evidence that there might be a cognitive cost of tDCS on cognitive functions that are mediated by other brain regions and these need to be systematically studied. Understanding the cost-benefits of brain stimulation in particular in children is therefore crucial. These worries of effects on non-targeted brain regions also applies to the neurofeedback studies. These benefits and costs, however, will still have to be established in ADHD as well as in other childhood disorders.

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Table 2. Clinical and cognitive effects of sham-controlled tDCS studies

				Stimulation protocol					Outcome measures (bold/underlined = improvement; cursive = impairment)	
Study	**Design**	**N**	**Mean age**	**Anode/ Cathode**	**mA**	**Sessions**	**Timing[a]**	**Duration (mins)**	**Clinical**	**Cognitive**
Children										
†Bandeira et al, 2016	Open label	9	11	L DLPFC/ R SOA	2	5	Online	28	**Patient Global Impression of Improvement**	Visual Attention Test (**OM);** NEPSY-II-inhibition (**Switch errors);** Digit Span; Corsi Cubes
Breitling et al, 2016	Single-blind, sham-controlled, randomised, crossover	21	14	R IFC/ L Cheek	1	1	Online	20	n/t	Flanker (Incongruent trials: **COM**[c,d] & **RTV**[c])[e,]
				L Cheek / R IFC	1	1	Online	20	n/t	Flanker
Munz et al, 2015	Double-blind, sham-	14	12	L DLPFC/ R Cheek;	.25	1	Offline	25 (5 on, 1 off)	n/t	Go/No-Go (**Go RT** & **RTV**); Motor memory; Alertness

	controlled, randomised, crossover			R DLPFC/ L Cheek						
Nejati et al, 2020, Exp 1	Double-blind, sham-controlled, randomised, crossover	15	10	L DLPFC/ R DLPFC	1	1	Offline	15	n/t	Go/NoGo; N-back (Acc**, RT**); Stroop (Incongruent trials: **COM & RT)**; WCST (**Completion time)**
Nejati et al, 2020, Exp 2	Double-blind, sham-controlled, randomised, crossover	10	9	L DLPFC/ R SOA	1	1	Offline	15	n/t	Go/NoGo; N-back **(Acc[c], RT)**[d]; WCST (**Total categories completed, total & pers errors**)[d]
				R SOA/ L DLPFC	1	1	Offline	15	n/t	Go/NoGo (NoGo acc)[d]; N-back; WCST (**Total categories completed, total & pers errors**[c])[d]

Prehn-Kristensen et al, 2014	Double-blind, sham-controlled, randomised, parallel	12	12	L DLPFC/ R Cheek; R DLPFC/ L Cheek	.25	1	Offline	25 (5 on, 1 off)	n/t	Declarative Memory (**Acc**); Alertness; Digit Span
Soff et al, 2017	Double-blind, sham-controlled, randomised, crossover	15	14	L DLPFC/ Vertex	1	5	Online	20	FBB-ADHD (**Inattention**[f])[g,h]	QbTest (**Inattention**[f]**; hyperactivity**[i])[g,h]
Soltaninejad et al, 2019	Single-blind, sham-controlled, randomised, crossover	20	16	L DLPFC/ R SOA	1.5	1	Online	15	n/t	Go/NoGo (**Go Acc**)[c,d]; Stroop
				R SOA/ L DLPFC	1.5	1	Online	15	n/t	Go/NoGo (**NoGo Acc**)[c,j]; Stroop
‡Soltaninejad et al, 2015b	Single-blind, sham-	20	16	rIFC/ L SOA	1	1	Online	15	n/t	Go/NoGo (**Go Acc**); Stroop

	controlled, randomised, crossover									
Sotnikova et al, 2017	Double-blind, sham-controlled, randomised, crossover	13	14	L DLPFC/ Vertex	1	1	Online	20	n/t	QbTest (**RT, RTV^{k}**, *OMs, Acc*)[l]
Breitling et al, 2020	Double-blind, sham- and HD-tDCS controlled, randomised, crossover	ADHD: 15 HC: 15	13 (10-16)	R IFC/L SOA	1	3 with CT	Online	20	n/t	WM task; ERPs **N200; P300**
Salehinejad et al., 2020	Single-blind, sham-controlled,	19	9 (8-12)		1	2	Online	23	n/t	**ANT** (orienting); GNG; SAT; *Stroop*

	randomised, cross-over									
† Westwood et al., 2021 *	Double-blind, sham-controlled, randomised, parallel	50	14	R IFC/ L SOA	1	15	Online	20	*ADHD-RS; CPRS*	GNG; Stop; Simon; WCST; CPT; MCT; Verbal Fluency
Nejati et al., 2020	Double-blind, sham-controlled, randomised, cross-over	20	9	L DLPFC/ R vmPFC R DLPFC/ L vmPFC Sham	1	1	Online	20	n/t	**BART; CDDT (k20,k10)**
†Berger et al., 2021	Double-blind, active controlled, randomised, cross-over	19	7-12	L DLPFC (tDCS)/ R SOA L DLPFC/ R IFC (tRNS)	0.75	5	Online	5	n/t	ADHD-RS; Working & short-term memory, Moxo-CPT (all improved with tRNS vs tDCS)

Adults										
†Allenby et al, 2018	Double-blind, sham-controlled, randomised, crossover	37	32	L DLPFC/ R SOA	2	3	Online	20	n/t	Conners CPT (**COM**[m]); Stop Task
Cachoeira et al, 2017	Double-blind, sham-controlled, randomised, parallel	A: 9 S: 8	A: 31 S: 34	R DLPFC/ L DLPFC	2	5	Offline	20	ADHD Checklist **(Inattention, Total)**[n]; SDS **(after tDCS); ADHD total score 2 weeks**	None
Cosmo et al, 2015	Double-blind, sham-controlled, randomised, parallel	A: 30 S: 30	A: 32 S: 33	LDLPFC/ R DLPFC	1	1	Offline	20	n/t	Go/No-Go

Jacoby et al, 2018	Single-blind, sham-controlled, randomised, crossover	20	23	L&R DLPFC/ Cerebellum	1.8	1	Offline	20	n/t	CPT (**multi-button presses**)
Dubreuil-Vall et al 2020	Double-blind, sham-controlled, randomised, crossover	37	18-67	L DLPFC/ R SOA R DLPFC/ R SOA	2	1	Offline	30	n/t	Flanker (**incongruent RT**) N = 18; L **P300;** L *N200*. Stop (**go RTs**); L **P200.** N = 19 Flanker; Stop

Abbreviations: A, active; Acc, accuracy; COMs, commission errors; CPT, continuous performance task; DLPFC, dorsolateral prefrontal cortex; FBB-ADHD, parents' version of a German adaptive Diagnostic Check- list for ADHD; L, left; mA, milliamps; mins, minutes; n/t, not tested; OMs, omission errors; cM, contralateral mastoid relative the other electrode; SOA, contralateral supraorbital area relative the other electrode; IFC, inferior frontal cortex; MCT: Mackworth Clock Task; R, right; RT, reaction time; RTV, reaction time variability or standard deviation of reaction times; S, sham; SAT: Switching attention task; SDS, Sheehan Disability Scale; SSRT, stop-signal reaction time; WCST: Wisconsin task sorting task.

[a]Timing refers to whether cognitive performance was during (online) or after (offline) stimulation; [b]Trend level; [c]Would likely not survive multiple comparison correction; [d]Comparisons between stimulation conditions based on post-hoc LSD tests, which do not correct for multiple comparisons; [e]Based on underpowered analysis focusing on the first session, with seven participants per condition; [f]Improvement only seen seven days after the fifth anodal tDCS session; [g]Did not survive correction for multiple comparisons;

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[h]Based on underpowered analysis focusing on the first five sessions, with seven/eight participants per condition; [il]mprovement seen immediately after the fifth anodal tDCS session and seven days later; [j]Significant in comparison to cathodal tDCS only; [k]Based on a crossover interaction. tDCS reduced RT and RTV in one out of four conditions (2-back tasks), but this did not survive correction for multiple comparisons; [l]Included carryover effect raised by Soff et al (2017); [m]Significant only immediately after anodal tDCS, not significant three days later; [n]Inattention improved immediately after anodal tDCS and after two weeks, while total score improved only after two weeks. †combined stimulation with cognitive training ‡ originally published written in Persian language, but was translated for us by the lead author Dr Zahra Soltaninejad.

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Other stimulation methods

Only one study has compared random noise stimulation (tRNS) to tDCS in ADHD children compared (see above). No studies have been conducted in ADHD with other stimulation methods such as transcranial alternative current stimulation (tACS).

External trigeminal nerve stimulation (eTNS), also known as transcutaneous supraorbital nerve stimulation (tSNS) is another non-invasive intervention with minimal side effects. Small electrical currents are transmitted transcutaneously via a self-adhesive, supraorbital electrode to excite (trigger action potentials) on the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) located under the skin of the forehead. The supraorbital nerve is a branch of the first trigeminal division. The trigeminal nerve has widespread connections to the brain, in particular the reticular activation system, locus coeruleus (LC), brain stem, thalamic, frontal and cortical areas (Shiozawa et al., 2014), as well as effects on dopamine and noradrenaline, all of which have effects on arousal and attention and been implicated in ADHD (Rubia, 2018). Two studies have tested the efficacy of eTNS in ADHD. An 8 week, open trial, pilot feasibility study in 21 children with ADHD between 7-14 years showed significant reduction in the investigator-completed ADHD-IV-Rating scale (ADHD-RS), both for the inattentive and hyperactive/impulsive subscales and the parent completed Conners Global Index and the Clinical Global Impression-Improvement as well as a reduction in the parent completed Behaviour Rating Inventory of Executive Function (BRIEF) that measures executive functions in daily life. Patients with ADHD also improved after treatment in scores of depression, but not of anxiety. Furthermore, they tested performance on a working memory and an attention network tasks, and found improvements in reaction times to interference stimuli, indicating positive effects on selective attention and inhibitory control and a trend-level improvement in response variability that is considered a measure of arousal and attention.

eTNS was well tolerated with few side effects such as eye twitch and headache that were transient (McGough et al., 2015). The second study from the same group was a blinded, sham-controlled pilot study of eTNS in 62 children with ADHD 8-12 years old. The investigator rated ADHD-RS total score was significantly reduced in the active relative to the sham group, as well as the inattentive and hyperactive/impulsive sub-scores and the Clinical Global Impression-Improvement scores. There was furthermore a trend-level differential improvement in the active group for anxiety but not for depression (McGough et al., 2019). There were no serious adverse events and relatively minor and transient side effects such as headache or fatigue. Quantitative electroencephalography (qEEG) data showed increased power in the active relative to sham group in right frontal midline and inferior frontal regions after compared to before treatment, which furthermore correlated with improvements in the ADHD-RS total score and the hyperactive-impulsive subscores, suggesting mediation of clinical effects (McGough et al., 2019). These findings with qEEG are partly consistent with animal and human imaging studies that show that eTNS stimulates the activation of cortical and subcortical structures such as thalamus, amygdala, LC, reticular activation system, prefrontal regions, anterior cingulate and insula (Aston-Jones & Cohen, 2005; Cook et al., 2014). An activation increase in cortical and subcortical regions in ADHD could be the underlying mechanism of action given consistent evidence from us and others of dysfunction in ADHD in fronto-striato-thalamic neural networks (Rubia, 2018). It is hence plausible that eTNS improves ADHD symptoms and cognition by stimulating the activation of dysfunctional fronto-striato-thalamo-cortical systems. Based on evidence from this small, underpowered pilot study, eTNS is now the only brain stimulation technique that is FDA approved for ADHD. More evidence is clearly needed to demonstrate the efficacy and effectiveness of eTNS for reducing ADHD symptoms, to define optimal protocols such as repetition frequency, duration of stimulation, etc, similar to the other neurotherapies, and to understand its currently unknown

underlying mechanisms of action.

Overall conclusions

With the exception of EEG-NF, the other neurotherapeutic treatments are still relatively novel and unexplored in their application to ADHD.

A large number of meta-analyses of randomized controlled trials that applied EEG-NF have shown consistent small to medium effect sizes for the improvement of ADHD symptomatic improvements, but there is controversy regarding to blinded raters (Bussalb et al., 2019; Cortese et al., 2016). Further systematic research needs to focus on the specificity of the effects of EEG-NF as well as on longer-term efficacy. Investigating criteria predicting individual response will be crucial for precision medicine.

Very few recent small studies have used NF with NIRS and fMRI that have better spatial resolution. Most of these studies were only powered to demonstrate study feasibility. However, some findings have emerged that are promising despite the relatively small subject numbers demand further testing. The field will need larger-sampled, sham-controlled RCTs that can also establish predictors of learning in order to establish whether NIRS or fMRI neurofeedback can be used as a treatment for some people with ADHD. Optimal neurofeedback protocols are not known for either NIRS or fMRI and need systematic testing. Potential negative effects on non-regulated brain regions have not been tested in any of the neurofeedback modalities but need to be understood for ethical reasons.

Most non-invasive brain stimulation studies have been conducted in small number of patients, and had heterogeneous study protocols which makes comparability difficult. Most of

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the studies tested rTMS or tDCS in either one to maximum 5 sessions and targeted in their majority the DLPFC or IFC, which are dysfunctional brain regions in ADHD. Studies using TMS have not been promising so far. Meta-analyses of tDCS effects mostly over DLPFC show small effect sizes for improving cognition (Salehinejad et al., 2019; Westwood et al., 2021). Only 3 studies, including a study using tRNS tested for clinical improvements, with inconsistent findings with respect to improvement of inattention. The field will need larger-numbered and sham-controlled studies in order to properly test the potential benefits of tDCS on clinical symptoms of ADHD and on cognitive functions. Studies will also need to assess the potential costs on non-stimulated cognitive or clinical functions. Furthermore, like for fMRI and NIRS-NF, we will need to acquire thorough knowledge on the best stimulation protocols for different patient subgroups of age subgroups such as information on the optimal stimulation site, intensity, frequency, duration, electrode size, or inter-electrode distance. So far, brain stimulation combined with cognitive training seems to have a greater a larger potential to improve ADHD cognition than brain stimulation alone. If used in combination with cognitive training, then we will also need to develop good cognitive training tasks. tDCS or tRNS are promising therapies for childhood onset psychiatric disorders because of the relatively minor side effects and because they could possibly influence abnormal brain development early and with potential plasticity (Krause & Kadosh, 2013). This promise, however, needs to be tested systematically in large RCTs of different protocols. Furthermore, potential costs of brain stimulation on other, non-targeted brain regions and their mediated functions will need to be thoroughly tested before we can apply them in clinical settings. tRNS and TNS have shown promising effects on improving ADHD symptoms in proof-of-concept studies but will need replication.

In conclusion, the substantial knowledge acquired in cognitive neuroscience of ADHD, has led to translational neuroscience studies which try to use the neurofunctional biomarkers of ADHD as treatment targets for neurotherapeutics. Because of their safety and minimal side effects and their potential neuroplastic effects, neurotherapeutics seem attractive for ADHD relative to medication treatments. However, we will need more studies that thoroughly test for their efficacy in the short- and longer-term and for their optimal "dose" effects. Furthermore, we will need to understand whether there are potential costs that may accompany the benefits, and whether they can be used for individualised treatment depending on clinical or cognitive ADHD subtypes. We can expect that different clinical or cognitive subgroups of ADHD patients may benefit from different neurotherapies and it will be crucial to establish this knowledge benefit individual patients.

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