ANALES RANM
REVISTA FUNDADA EN 1879

DOI: 10.32440/ar.2021.138.02.rev02
Enviado*: 22.06.21 | Revisado: 28.06.21 | Aceptado: 12.07.21
*Fecha de lectura en la RANM

REVISIÓN

NEUROIMAGING AND NEUROTHERAPEUTICS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

NEUROIMAGEN Y NEUROTERAPIAS EN EL TRASTORNO POR DÉFICIT DE ATENCIÓN E HIPERACTIVIDAD (TDAH)

Katya Rubia
Institute of Psychiatry, Psychology & Neurosciences. King's College London

Keywords:
Attention Deficit Hyperactivity Disorder (ADHD);
Functional magnetic resonance imaging (fMRI);
fMRI-Neurofeedback;
Near infrared spectroscopy (NIRS)-Neurofeedback;
Brain stimulation;
transcranial magnetic stimulation (TMS);
Transcranial direct current stimulation (tDCS);
Trigeminal nerve stimulation (TNS).

Palabras clave:
Trastorno por déficit de atención e hiperactividad (TDAH);
Resonancia magnética funcional (fMRI);
Espectroscopia del infrarrojo cercano (NIRS);
Estimulación magnética transcraneal repetitiva (rTMS);
Estimulación transcraneal con corriente directa (tDCS);
Estimulación del nervio trigémino (TNS).

Abstract
This paper reviews the functional magnetic resonance imaging (fMRI) literature of Attention Deficit Hyperactivity Disorder (ADHD) of the past three decades and the modern neurotherapies that have used these biomarkers as targets for treatment. Meta-analyses of task-based fMRI studies have shown functional abnormalities in different domain-dependent frontal, striatal, parietal, and cerebellar regions in ADHD. Resting state fMRI studies confirm abnormalities in different fronto-striato-parietal cognitive control, dorsal and ventral attention networks. The frontal parts of these networks have been targeted by neurotherapeutics. Only three small-numbered studies so far have applied functional near infrared spectroscopy (NIRS) and fMRI-Neurofeedback to ADHD. Studies have mostly shown feasibility and some promising effects on clinical, cognitive or imaging measures which invite further testing in larger samples. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) or inferior frontal cortex (IFC) has not shown promising effects so far on improving cognition or symptoms. Eighteen studies tested the effects of single or multi-session transcranial direct current stimulation (tDCS) of mostly left DLPFC on mostly cognitive functions with fewer studies targeting right DLPFC or IFC. Our meta-analysis of tDCS studies shows relatively small effects of improvement of cognitive function while insufficient studies have tested clinical efficacy. A proof of concept study of trigeminal nerve stimulation (TNS) showed promising medium size effects for improving clinical symptoms but requires replication in larger samples. In conclusion, neurotherapies are attractive due to minimal side effects and potential longer-term effects on brain plasticity which drugs cannot offer; however, they are still in their infancy. They require systematic testing of optimal protocols in large samples, including optimal site of stimulation/neurofeedback, optimal frequency of treatment sessions, or optimal stimulation amplitude. Importantly, they will need to show potential for individualised treatment by providing understanding of treatment response prediction.

Resumen
Este artículo revisa los trabajos realizados con resonancia magnética funcional (RMf) en el trastorno por déficit de atención e hiperactividad (TDAH) de las últimas tres décadas, así como las neuroterapias modernas que han utilizado los biomarcadores establecidos con RMf como objetivos para el tratamiento. Los meta-análisis de estudios de RMf basadas en tareas cognitivas mostraron anormalidades funcionales en diferentes regiones frontales, estriadas, parietales y cerebrales en el TDAH. Estudios con RMf de estados de reposo confirmaron anormalidades en diferentes redes dorsales y ventrales de atención y en redes estriado-parietales de control cognitivo. Las regiones frontales de esas redes han sido el objetivo de neuroterapias. Sólo tres estudios pequeños hasta ahora aplicaron el neurofeedback usando la espectroscopia del infrarrojo cercano y la RMf al TDAH. Los estudios han mostrado sobre todo viabilidad y algunos efectos prometedores en medidas clínicas, cognitivas o de imagen que invitan a probarlo en estudios más amplios. Estimulación magnética transcraneal repetitiva (rTMS) de la corteza prefrontal dorsolateral (DLPFC) o de la corteza frontal inferior (IFC) no han mostrado efectos prometedores por el momento en la mejora de la cognición o de los síntomas. Dieciocho estudios probaron los efectos de la estimulación transcraneal con corriente directa (tDCS) en sesiones únicas o múltiples de la DLPFC, sobre todo izquierda, en funciones cognitivas, y pocos estudios los hicieron sobre la DLPFC o IFC del lado derecho. Nuestros meta-análisis de tDCS muestran efectos relativamente pequeños de mejora de funciónes cognitivas, mientras no hubo estudios insuficientes que probaron la eficacia clínica. Un estudio

Autor para la correspondencia
Katya Rubia
Department of Child & Adolescent Psychiatry/PO46
Institute of Psychiatry, Psychology & Neurosciences. King's College London
De Crespigny Park. London SE5 8AF
Tlf.: +44 (0)207-8480463 | E-Mail: katya.rubia@kcl.ac.uk

de prueba de concepto de la estimulación del nervio trigémino (TNS) mostró efectos de mejora de síntomas clínicos de tamaño mediano, pero requiere una repetición con muestras mayores. En conclusión, las neuroterapias son atractivas debido a sus efectos secundarios mínimos y efectos potenciales a largo plazo sobre la plasticidad cerebral que los medicamentos no pueden ofrecer; sin embargo, están aún en pañales. Requieren comprobaciones sistemáticas de protocolos óptimos en muestras grandes, incluyendo lugares óptimos para la estimulación/neurofeedback, frecuencia óptima de las sesiones de tratamiento, o amplitud óptima de la estimulación. Es importante recalcar que necesitarán mostrar su potencial en tratamientos individualizados, aportando una comprensión de la predicción de la respuesta individual al tratamiento.

LIST OF ACRONYMS

ADHD: Attention Deficit/Hyperactivity Disorder
DLPFC: dorsolateral prefrontal cortex
EEG: electroencephalography
fMRI: functional magnetic resonance imaging
IFC: inferior frontal cortex
NIRS: near infrared spectroscopy
rIFC: right inferior frontal cortex
rTMS: repetitive transcranial magnetic stimulation
tDCS: transcranial direct current stimulation
TNS: trigeminal nerve stimulation
tRNS: transcranial random noise stimulation

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined in the DSM-5 as a disorder of persisting and impairing symptoms of age-inappropriate inattention, and/or hyperactivity/impulsivity (1). It is one of the most common childhood disorders with a worldwide prevalence of around 7% (2). Problems persist into adulthood in most patients and are associated with comorbidities and poor social and academic outcomes (2).

People with ADHD have deficits in higher-level cognitive functions necessary for mature adult goal-directed behaviors, in so-called "executive functions", that are mediated by late developing fronto-striato-parietal and fronto-cerebellar networks (3). The most consistent deficits are in motor response inhibition, working memory, switching, sustained attention and intraindividual response variability (4), as well as timing functions (5, 6). Children are cognitively more impaired than adults with ADHD (4).

The gold-standard treatment is with psychostimulant medication which enhance catecholamines in the brain, reaching an effect size of ~ 0.8 for parent-ratings of symptoms, with about 70% of patients with ADHD responding to it, followed by second-line treatment with noradrenaline transporter/receptor blockers Atomoxetine and Guanfacine that also enhance brain catecholamines with effect sizes of 0.56 and 0.67, respectively (7). ADHD medications, however, commonly have side effects and longer-term efficacy has not been demonstrated in meta-analyses, observational or epidemiological studies (7, 8), possibly due to brain adaptation (9). Non-pharmacological treatments are hence preferred by parents and children.

FUNCTIONAL NEUROIMAGING MARKERS OF ADHD

Modern neurotherapeutics in the form of neurofeedback -using functional magnetic resonance imaging (fMRI) or near infrared spectroscopy (NIRS)- or brain stimulation have the advantage that they can target directly the key brain function deficits that have been found in ADHD over the past 2.5 decades of fMRI neuroimaging.

These findings of consistent brain structure and function deficits in ADHD has led to ADHD nowadays being considered a neurodevelopmental disorder. Meta- and mega-analyses of structural imaging studies in ADHD have shown reduced grey matter and cortical thickness in frontal, temporal and parietal regions (10-12) as well as reduced grey matter in subcortical regions, most prominently the basal ganglia and insula (10, 12), but also limbic areas such as amygdala and hippocampus (13) (for review see (14)).

fMRI studies have provided consistent evidence for dysfunctions in several brain regions, mostly underactivations relative to healthy controls, involving lateral inferior and dorsolateral prefrontal cortical regions as well as medial frontal, cingulate and orbital frontal regions, basal ganglia and the dissociated fronto-parietal, fronto-striatal, fronto-limbic and fronto-cerebellar networks they form part of (14). Several fMRI meta-analyses have shown cognitive domain-dissociated underactivations in several frontal, striatal, parietal and cerebellar brain regions in ADHD. We replicated the finding of underactivation in ADHD patients relative to controls in right IFC/insula and striatum in 3 meta-analyses of whole-brain fMRI studies of cognitive control (10, 12, 15). Our meta-analysis of fMRI studies of attention tasks showed reduced activation in ADHD patients relative to healthy controls in right DLPFC, right inferior parietal cortex, caudal basal ganglia and thalamus, which are part of the right hemispheric dorsal attention network (15). Other meta-analyses of attention found additional underactivation in

right anterior cingulate (16). Our meta-analysis of fMRI studies of timing functions showed consistently reduced activation in ADHD patients relative to healthy controls in key regions of timing such as left IFC, left inferior parietal lobe and right cerebellum (17). A meta-analysis of fMRI studies of working memory showed that ADHD patients relative to controls had reduced activation in bilateral middle and superior prefrontal cortex and left medial frontal cortex/anterior cingulate (18), as well as right and left IFC (16). We furthermore found in two large comparative fMRI meta-analyses of cognitive control tasks that the right IFC and striatal underactivation is disorder-specific to ADHD relative to obsessive-compulsive disorder and autism (10, 12). Overall, the fMRI meta-analyses suggest that ADHD patients have multisystem functional deficits compromising different fronto-striato-parieto-cerebellar networks that mediate several cognitive domains (14).

ADHD patients have also shown to have abnormally increased activation in areas of the default mode network (15, 17). The default mode network consists of intercorrelated activation of ventromedial frontal cortex, posterior cingulate, precuneus, inferior parietal and temporal regions and is thought to reflect task-irrelevant thoughts, i.e., mind wandering (19). It has been suggested that people with ADHD have less control over their mind-wandering which intrudes into their already weak exteroceptive attention processes, causing inattention. This immature pattern of poor activation of task-relevant networks and of decreased deactivation of the default mode network reflecting more mind-wandering has been suggested to be responsible for the poor performance in ADHD on attention-demanding higher-level cognitive tasks (14).

The most consistently found dysfunctional regions, in particular right IFC, DLPFC and anterior cingulate have been used as targets for neuromodulation studies such as neurofeedback with fMRI or NIRS or brain stimulation.

NEUROTHERAPEUTICS IN ADHD

The last decade of neuroimaging has shown that the brain is highly plastic, not only in the developing brain in childhood and adolescence, but also in adulthood (20). For example, several weeks or months of training of a particular skill in adults, for example, juggling (20), learning to meditate (21) or learning for a medical exam (22) can change the structure of specific brain regions. These insights into the neuroplastic potential of the brain make novel neuromodulation treatments, such as non-invasive brain stimulation or neurofeedback attractive clinical interventions. This applies even more to young people, who have superior neuroplasticity (14).

fMRI studies of ADHD over the past decades have provided good targets for neurotherapeutics. It seems plausible that therapies that aim to reverse these key neurofunctional abnormalities could improve the disorder. FMRI-Neurofeedback or NIRS-Neurofeedback are still very much in their childhood, with too few and very small-numbered studies in ADHD to give evidence for potential clinical effects. Non-invasive brain stimulation studies have been increasing exponentially in ADHD over the past 10 years. The majority of studies, however, have been in relatively small numbers with highly heterogenous study designs. Therefore, the findings have been inconsistent with respect to improving cognition with very little evidence, so far, on improving clinical ADHD symptoms.

fMRI-neurofeedback and NIRS-neurofeedback

Neurofeedback is based on operant conditioning that teaches participants to volitionally self-regulate specific regions or networks using trial and error, through real-time auditive or visual feedback of their brain activation which is typically represented on a PC in the form of a thermometer or with a videogame to make it more attractive for children. Electrophysiology (EEG)- neurofeedback has been tested in ADHD for over 45 years. There are 10 meta-analyses reviewing the evidence with the latest meta-analysis showing small to medium effect size of superiority of EEG-neurofeedback compared to non-active control groups for improving parent rated ADHD symptoms and for improving the inattention subdomain for teacher ratings; however effects are inferior to pharmacotherapy (23).

Real-time fMRI neurofeedback enables participants to self-regulate the blood-oxygen level-dependent response of a targeted brain region, or network, through real-time feedback of their brain activity. fMRI-neurofeedback has superior spatial resolution than EEG-neurofeedback and can target the key cortical and subcortical brain function deficits that have been established in ADHD over the past 26 years of fMRI research (14). fMRI-neurofeedback has shown some promise in improving clinical symptoms and cognition in other psychiatric disorders (24). To date, however, there are only two published fMRI-neurofeedback studies in ADHD.

A small randomised controlled trial in 13 adults with ADHD asked patients to do a mental calculation task with (N = 7) and without (N = 6) fMRI-neurofeedback of the dorsal anterior cingulate in 4 weekly scans of 60 minutes (25). Both groups significantly increased anterior cingulate activation but did not differ in improvements in ADHD symptoms observed in both groups at trend-level. However, only the neurofeedback group showed significant improvement in a sustained attention and working memory tasks, suggesting some positive effects of fMRI-neurofeedback of dorsal anterior cingulate on cognition (25).

A randomised controlled trial from our lab tested fMRI-neurofeedback of the right IFC compared to fMRI-neurofeedback of the left parahippocampal gyrus in adolescents with ADHD (26). Thirty-one boys with a clinical ADHD diagnosis had 4 hourly scans over 2 weeks, in which they did 11 runs of 8.5 min of fMRI-neurofeedback with a rocket

movie as feedback. Eighteen participants learned to self-upregulate the rIFC, while 13 participants self-upregulated a control region, the left parahippocampal gyrus. In both groups, activation of their respective target regions increased progressively across the 11 fMRI-neurofeedback runs. However, only the rIFC-neurofeedback group showed a transfer effect (self-regulation without feedback, as a proxy of transfer to real life) that correlated with reduced ADHD symptoms. There were no group differences in ADHD symptom improvements after the treatment, but both groups improved. However, only the rIFC-neurofeedback group showed a large ADHD symptom reduction at 11 months follow-up, with an effect size of almost 1, compared to an only trend-level reduction in the left parahippocampal gyrus-neurofeedback group. Only the rIFC-neurofeedback group also showed trend-level improvement in a sustained attention task. The rIFC-neurofeedback group also showed increased 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. These connectivity findings suggest that not only the targeted region improved in activation but entire networks that are connected to this region (rIFC) (27). To assess the effects of fMRI-neurofeedback on brain function in ADHD, the participants also performed a motor response inhibition fMRI task before and after treatment. The rIFC-neurofeedback relative to the left parahippocampal gyrus-neurofeedback group showed increased activation after compared to before neurofeedback in the rIFC and parietal regions during inhibition (26) and increased activation in left-hemispheric IFC/insula and striatal regions during performance monitoring, which correlated with ADHD symptom improvements and better performance (28). The increase of activation in IFC and striatal regions were similar to those we observed previously with stimulant medication (29), suggesting that fMRI-neurofeedback of the rIFC has similar brain upregulation effects. Last, there were no group differences in side effects or adverse events. However, when we tested neurofeedback learning capacity, we found that only 48% of patients learned successfully to upregulate their target region with fMRI-neurofeedback -which is similar to the EEG-neurofeedback literature (30). The best predictors of fMRI-neurofeedback learning were not clinical or cognitive data but enhanced fronto-striatal activation in the fMRI Stop task at baseline (30).

The only pilot study that tested NIRS-Neurofeedback trained upregulation of the left DLPFC in 11 hourly sessions over 4 weeks in 9 ADHD children and compared it with EEG-Neurofeedback (N=9) and electromyography-Neurofeedback (N=9). Only NIRS-Neurofeedback showed significant improvements in clinical ADHD symptoms and in performance in inhibition and attention functions, which was, however, not superior to EEG- or electromyography-Neurofeedback (31).

In conclusion, fMRI-Neurofeedback and NIRS-Neurofeedback research is still very new and only 2 small studies have been conducted. Some of the within-group improvement findings of these small proof of concept studies are promising. However, there is a need for larger, double-blind, placebo-controlled randomised controlled trials to more thoroughly assess the potential efficacy of these neurotherapies in ADHD.

Brain stimulation

Non-invasive brain stimulation therapies, specifically repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and trigeminal nerve stimulation (TNS) have been applied to ADHD only very recently, over the past decade. These stimulation techniques are thought to affect cellular and molecular mechanisms involved in use-dependent local and distant synaptic plasticity, i.e. GABA and glutamate-mediated long-term potentiation, which may lead to longer-term brain plasticity (32). In fact, studies in healthy adults and in different patient populations have shown up to 1 year longer-term cognitive effects after stimulation with rTMS or tDCS (33). Furthermore, there is evidence that both techniques can lead to increased levels of catecholamines (33), which are known to be abnormal in ADHD (7). For rTMS and tDCS it seems 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 (33).

Repetitive transcranial magnetic stimulation (rTMS)

rTMS is a relatively safe non-invasive brain stimulation technique that uses brief, intense pulses of electric currents delivered to a coil placed on the subject's head in order to generate an electric field in the brain via electromagnetic induction. Typically, high frequency rTMS promotes cortical excitability, while low frequency rTMS inhibits cortical excitability. rTMS has greater specificity in targeting neural regions than tDCS, but is more expensive and more painful, which makes it less suited for pediatric applications. Side effects are minor and transient, most commonly temporary scalp discomfort underneath the coil due to stimulation of the pericranial muscles and peripheral nerves (33).

Six studies applied between 1-25 rTMS sessions of 20-30 min duration to ADHD, 4 of them in adults with ADHD. Two double-blind, sham-controlled crossover studies stimulated the right DLPFC. One session of 20Hz-rTMS relative to sham significantly improved overall self-rated ADHD symptoms and inattention in 13 ADHD adults but had no effect on hyperactivity (34). Another study showed that 10 daily sessions of 10Hz-rTMS relative to sham had no effect on self-rated clinical symptoms in 9 ADHD adults, nor on EEG measures or cognitive performance (35). A single-blind sham-controlled randomised study showed no effect on self-rated clinical or cognitive measures of sustained attention in 22 ADHD adolescents after 20 daily sessions over 4 weeks of 18Hz deep rTMS over bilateral DLPFC (n = 13)

compared to sham (n = 9) (36). A parallel, semi-blind randomised, active and sham-controlled study found significant improvements in ADHD symptoms in 43 ADHD adults after 15 sessions over 3 weeks of 18 Hz-rTMS of both DLPFC and IFC -combined with a short cognitive training session before and after stimulation- and a 1-month follow-up maintenance session (37). No significant effects were observed on other clinical, cognitive and EEG measures, but EEG measures under the stimulation area correlated with clinical symptom improvements.

In children with ADHD, the first, open label tolerability and safety trial (N = 10) showed fewer teacher-rated inattention and parent-rated hyperactivity/impulsivity symptoms one week after treatment compared to baseline after five daily sessions of 1Hz-rTMS over left DLPFC (38). The second pediatric study in 60 children with ADHD found that 30 daily sessions of 25min of 10Hz rTMS over right DLPFC over 6 weeks combined with Atomoxetine, compared to Atomoxetine (1.2mg/kg) alone of rTMS alone, significantly improved ADHD symptoms but not other clinical or cognitive measures, in which all groups improved (39). Both pediatric studies did not include a sham condition, however, and hence placebo effects cannot be excluded for the improvements within groups.

With respect to safety, one study using rTMS observed a seizure in one patient after 3 sessions (37), but the majority of studies reported no side effects or serious adverse events other than related to transient itching or headache under the stimulation site.

In conclusion, at the current state of the art, there is relatively little evidence that several sessions of rTMS improve ADHD symptoms or cognition. However, studies were relatively underpowered and conducted relatively few session numbers of rTMS with only 2 studies in children without a placebo condition.

Transcranial direct current stimulation (tDCS)

In tDCS, scalp electrodes apply a weak, relatively painless and persistent direct electric current to underlying brain regions with the current passing between a positively charged anode and a negatively charged cathode. The electrical currents lead to increase (anodal stimulation) or decrease (cathodal stimulation) of the excitability of neurons via the generation of subthreshold alterations of neuron membrane potentials that modify spontaneous discharge rates; this can increase or decrease cortical function and synaptic strength. tDCS compared to TMS is much easier to apply, cheaper and less painful and hence more suitable for children. Side effects are minimal and typically transient such as itching and reddening of the scalp site of stimulation in some people (33). Currents are typically applied for 20min in one session, which can be combined with a cognitive paradigm, which can boost the effect (33).

The majority of tDCS studies (12 out of 18), unlike the rTMS studies, were conducted in children rather than adults with ADHD, presumably due to the high tolerability and low side effect profile.

The majority of studies applied 1-5 sessions of about 20 minutes of tDCS in children or adults with ADHD, with the exception of our study which applied 15 sessions. Only 4 studies tested for clinical symptoms, 3 studies after 5 sessions of tDCS of DLPFC and 1 study after 15 sessions of right IFC; two studies in 9 and 15 ADHD patients, respectively, found an improvement with real compared to sham tDCS on clinical inattention symptoms, which persisted 1 or 2 weeks later (40, 41). One study found an improvement with transcranial random noise stimulation (tRNS) of left DPFC and right IFC compared to tDCS of left DLPFC combined with cognitive training on ADHD symptoms in 19 patients (42). However, the largest study that tested 15 sessions of tDCS of right IFC in 50 ADHD patients found no improvement compared to sham in clinical symptoms and even an improvement with sham relative to tDCS (43).

All other studies tested the effects of tDCS on a range of executive cognitive functions and found an improvement on some but not other functions (33) with little consistency in findings between studies, and few of them correcting for multiple testing. Two meta-analyses tested the effects of tDCS on cognitive performance in ADHD. The first meta-analysis included 10 studies in 201 children/adults with ADHD and found that 1-5 sessions of anodal tDCS over mainly left DLPFC significantly improved cognitive performance in inhibition measures (Hedges' g = 0.12) and in n-back reaction times (g = 0.66) (44). However, effect sizes were small and the meta-analysis likely overestimated statistical significance as it did not control for interdependency between measures, and included attention measures within the inhibitory measures (33). Our larger meta-analysis of 12 tDCS studies in a total of 232 children and adults with ADHD found that one to five sessions of anodal tDCS over mainly left DLPFC led to small and only 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) (33). In conclusion, the findings of the use of tDCS to improve ADHD symptoms and cognition are mixed, with only 5 studies testing for clinical effects and meta-analyses showing some positive results on improving cognition, with, however, very small effects sizes.

Very few studies stimulated the right IFC. Most studies tested 1 session and found no significant cognitive improvements (33). We conducted the largest double-blind sham-controlled RCT in 50 children with ADHD where we tested the effects of 15 sessions of 20 min of right IFC stimulation combined with cognitive training in executive function tasks. We found that both groups improved in clinical symptoms and cognitive functions with significantly less improvement in the real versus sham tDCS in primary and secondary clinical outcome measures. There was also no superior effect of real versus sham tDCS on a large battery of executive functions. While side effects did not differ between groups, the real tDCS group had worse adverse events related to mood, sleep and appetite (43).

To conclude, there is large heterogeneity in tDCS studies with respect to study designs, stimulation parameters and site of stimulation which makes comparability between studies difficult. While relatively safe, the larger studies found no clinical effects with multi-session tDCS. Meta-analyses show small effects of improving cognition. However, larger and more homogeneously designed studies using a larger number of sessions of localised tDCS with and without cognitive training are needed to more thoroughly assess clinical and cognitive benefits.

Trigeminal nerve stimulation (TNS)

External trigeminal nerve stimulation (TNS) is another non-invasive intervention with minimal side effects. TNS transmits small electrical currents transcutaneously via a self-adhesive, supraorbital electrode to excite (trigger action potentials) 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 and has widespread connections to the brain, in particular the reticular activation system, locus coeruleus, brain stem, thalamic, frontal and cortical areas (45). It also has effects on dopamine and noradrenaline, which have effects on arousal and attention and been implicated in ADHD (7, 14). Two studies tested the efficacy of TNS in ADHD, which is typically applied every night for several weeks. An 8-week, open trial, pilot feasibility study showed significant reduction in ADHD symptoms in 21 children with ADHD, in depression and in a scale that measures behavioural executive functions in daily life. There were also positive effects on selective attention and inhibitory control. The second study was a blinded, sham-controlled proof of concept study of 4 weeks of TNS in 62 children with ADHD. The active relative to the sham TNS group had a significant reduction in ADHD symptoms and trend-level differential improvement for anxiety but not for depression (46). Quantitative EEG data showed increased power in the active relative to the sham group in right frontal midline and inferior frontal regions after compared to before treatment, which furthermore correlated with improvements in ADHD symptoms. Findings suggest that right frontal upregulation mediates the clinical effects (47). Both trials showed that TNS was well tolerated with no serious adverse events and relatively minor and transient side effects such as headache or fatigue. Based on evidence from this small, underpowered proof of concept study, TNS is now the only brain stimulation technique that is approved for ADHD. More evidence is needed to demonstrate the efficacy of TNS for reducing ADHD symptoms and improving cognition.

CONCLUSIONS

Modern neurotherapeutics is still in its infancy in the field of ADHD. Neurofeedback studies using higher spatially resolved neuroimaging techniques such as NIRS and fMRI have only recently been piloted in ADHD, showing feasibility in relatively small subject numbers, but without the power to demonstrate clinical or cognitive effects. Larger, sham-controlled studies that allow the identification of predictors of neurofeedback learning are necessary to establish whether NIRS or fMRI neurofeedback training has potential as a treatment for some individuals with ADHD.

Several non-invasive brain stimulation studies with heterogeneous study designs have been conducted in small groups of ADHD children and adults, most of them using tDCS in either single or 5 sessions targeting mostly DLPFC with few studies targeting right IFC or other regions. Meta-analyses of tDCS effects mostly of DLPFC show small effect sizes for improving cognitive functions (33, 44). Only 5 studies have tested clinical effects with inconclusive findings. Larger sham-controlled studies are needed to further test the efficacy of tDCS on improving symptoms or cognitive functions.

TNS seems to be promising so far in improving ADHD symptoms based on one sham-controlled study (47), but replication of findings in larger samples is necessary.

For both neurofeedback and brain stimulation studies, far more knowledge is needed on the optimal stimulation protocols for different age and patient subpopulations (i.e., best stimulation/neurofeedback site, intensity of stimulation, duration of stimulation/ neurofeedback, frequency of sessions, electrode size, inter-electrode distance, etc). It is likely that brain stimulation combined with cognitive training has a larger potential to enhance brain plasticity in ADHD than brain stimulation alone. Interindividual baseline differences in brain activation are likely to affect learning of brain self-regulation or stimulation effects. Also, positive or negative side effects of regional fMRI-neurofeedback or stimulation on not self-regulated/non-stimulated regions such as neighbouring regions or homologue regions in the other hemisphere which may be indirectly downregulated needs to be better understood.

In conclusion, the substantial knowledge acquired over 3 decades of fMRI imaging in ADHD has opened up treatment targets for neurotherapeutics which seem attractive for children with ADHD due to their safety and minimal side effects and their potential for longer-term neuroplastic effects, compared to medication treatments. However, neurotherapies need to be more thoroughly tested for their short- and longer-term efficacy, optimal "dose" effects (i.e., optimal target site; intensity of stimulation; frequency of stimulation/neurofeedback sessions), potential costs that may accompany the benefits, and their potential for individualised treatment depending on clinical or cognitive ADHD subtypes. It is likely that different clinical or cognitive subgroups of ADHD patients will benefit from either neurofeedback, brain stimulation or medication with individualised protocols and establishing this knowledge will be crucial to the benefit of individual patients.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 5th ed.; American Psychiatric Publishing, Inc. Washington, DC., 2013. https://doi.org/10.1176/appi.books.9780890425596
2. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics. 2015; 135(4): E994-E1001.
3. Rubia K. Functional Neuroimaging across development: a review. Eur Child Adoles Psy. 2013; 22(12): 719-731
4. Pievsky MA, McGrath RE. The neurocognitive profile of attention-deficit/hyperactivity disorder: a review of meta-analyses. Arch Clin Neuropsych. 2018; 33(2): 1431-1457.
5. Rubia K, Halari R, Christakou A, Taylor E. Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philos Trans R Soc Lond B Biol Sci. 2009; 364(1525): 1919-1931.
6. Noreika V, Falter C, Rubia K. Timing deficits in patients with ADHD. Neuropsychologia. 2013; 51(2): 235-266.
7. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018; 5(9): 727-738.
8. Swanson JM. Debate: are stimulant medications for attention-deficit/hyperactivity disorder effective in the long term? (against). J Am Acad Child Adolesc Psy. 2019; 58(10): 936-938.
9. Fusar-Poli P, Rubia K, Rossi G, Sartori G, Ballotin U. Dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? a meta-analysis. Am J Psychiat. 2012; 169: 264 -272.
10. Norman L, Carlisi CO, Lukito S, et al. Comparative meta-analysis of functional and structural deficits in ADHD and OCD. JAMA Psychiatry. 2016; 73(8): 815-825.
11. Hoogman M, Muetzel R, Guimaraes JP, et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. Am J Psychiat. 2019; 176(7): 531-542.
12. Lukito S, Norman L, Carlisi C, et al. Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. Psychol Med. 2020; 50(6): 894-919.
13. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017; 4(4): 310-319.
14. Rubia K. Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. Front Hum Neurosci. 2018; 12: 1-23.
15. Hart H, Radua J, Mataix D, Rubia K. Meta-analysis of fMRI studies of inhibition and attention in ADHD: exploring task-specific, stimulant medication and age effects. JAMA Psychiatry. 2013; 70(2): 185-198.
16. Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiat. 2012; 169(10): 1038-1055.
17. Hart H, Radua J, Mataix D, Rubia K. Meta-analysis of fMRI studies of timing functions in ADHD. Neurosci Biobehav R. 2012; 36(10): 2248-2256.
18. McCarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. Psychol Med. 2014; 44(4): 869-880.
19. Raichle ME. The brain's default mode network. Annu Rev Neurosci. 2015; 38: 433-447.
20. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training - newly honed juggling skills show up as a transient feature on a brain-imaging scan. Nature. 2004; 427(6972): 311-312.
21. Dodich A, Zollo M, Crespi C, et al. Short-term Sahaja Yoga meditation training modulates brain structure and spontaneous activity in the executive control network. Brain and Behav. 2019; 9(1): e01159.
22. Draganski B, Gaser C, Kempermann G, et al. Temporal and spatial dynamics of brain structure changes during extensive learning. J Neurosci. 2006; 26(23): 6314-6317.
23. Riesco-Matías P, Yela-Bernabé JR, Crego A, Sánchez-Zaballos E. What do meta-analyses have to say about the efficacy of neurofeedback applied to children with adhd? review of previous meta-analyses and a new meta-analysis. J Atten Disord. 2021; 25(4): 473-485.
24. Thibault RT, MacPherson A, Lifshitz M, Roth RR, Raz A. Neurofeedback with fMRI: a critical systematic review. Neuroimage. 2018; 172: 786-807.
25. Zilverstand A, Sorger B, Slaats-Willemse D, Kan CC, Goebel R, Buitelaar JK. fMRI neurofeedback training for increasing anterior cingulate cortex activation in adult attention deficit hyperactivity disorder. an exploratory randomized, single-blinded study. PLoS One. 2017; 12(1): e0170795.
26. Alegria, A.A.; Wulff, M.; Brinson, H.; Barker, G.J.; Norman, L.J.; Brandeis, D.; Stahl, D.; David, A.S.; Taylor, E.; Giampietro, V.; et al. Real-Time fMRI Neurofeedback in Adolescents with Attention Deficit Hyperactivity Disorder. Human Brain Mapping 2017, 38, 3190-3209
27. Rubia K, Criaud M, Wulff M, et al. Functional connectivity changes associated with fMRI neurofeedback of right inferior frontal cortex in adolescents with ADHD. Neuroimage. 2019; 188: 43-58.
28. Criaud M, Wulff M, Alegria AA, Barker GJ, Giampietro V, Rubia K. Increased left inferior frontostriatal activation during error monitoring after fMRI neurofeedback of right inferior frontal cortex in adolescents with attention deficit hyperactivity disorder. Neuroimage Clin. 2020; 27: 102311.
29. Rubia K, Alzamora A, Cubillo A, Smith AB, Radua J, Brammer MJ. Effects of stimulants on brain function in ADHD: a systematic review and meta-analysis. Biol Psychiatry. 2014; 76(8): 616-628.
30. Lam SL, Criaud M, Alegria A, Barker GJ, Giampietro V, Rubia K. Neurofunctional and behavioural measures associated with fMRI-neurofeedback learning in adolescents with Attention-Deficit/Hyperactivity Disorder. Neuroimage Clin. 2020; 27: 102291.

31. Marx A-M, Ehlis A-C, Furdea A, et al. Near-infrared spectroscopy (NIRS) neurofeedback as a treatment for children with attention deficit hyperactivity disorder (ADHD)-a pilot study. Front Hum Neurosci. 2014; 8: 1038.
32. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology. 2013; 64: 566-578.
33. Westwood SJ, Radua J, Rubia K. Non-invasive brain stimulation in attention deficit hyperactivity disorder: a systematic review and meta-analysis. J Psychiatry Neurosci. 2021; 46(1): E14-E33.
34. Bloch Y. Transcranial magnetic stimulation (TMS) as a treatment in ADHD. Isr J Psychiatry Relat Sci. 2012; 49(1): 18.
35. Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP. Transcranial magnetic stimulation (tms) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults a pilot study. J ECT. 2012; 28(2): 98-103.
36. Paz Y, Friedwald K, Levkovitz Y, et al. Randomised sham-controlled study of high-frequency bilateral deep transcranial magnetic stimulation (dTMS) to treat adult attention hyperactive disorder (ADHD): negative results. World J Biol Psychiatry. 2017; 31: 1-6.
37. Alyagon U, Shahar H, Hadar A, et al. Alleviation of ADHD symptoms by non-invasive right prefrontal stimulation is correlated with EEG activity. Neuroimage Clin. 2020; 26: 102206.
38. Gómez L, Vidal B, Morales L, et al. Low frequency repetitive transcranial magnetic stimulation in children with attention deficit/hyperactivity disorder: preliminary results. Brain Stimul. 2014; 7(5): 760-762.
39. Cao P, Xing J, Cao Y, et al. Clinical effects of repetitive transcranial magnetic stimulation combined with atomoxetine in the treatment of attention-deficit hyperactivity disorder. Neuropsychiatr Dis Treat. 2018; 14: 3231-3240.
40. Cachoeira CT, Leffa DT, Mittelstadt SD, et al. Positive effects of transcranial direct current stimulation in adult patients with attention-deficit/hyperactivity disorder: a pilot randomized controlled study. Psychiat Res. 2017; 247: 28-32.
41. Sotnikova A, Soff C, Tagliazucchi E, Becker K, Siniatchkin M. Transcranial direct current stimulation modulates neuronal networks in attention deficit hyperactivity disorder. Brain Topogr. 2017; 30(5): 656-672.
42. Berger I, Dakwar-Kawar O, Grossman ES, Nahum M, Cohen Kadosh R. Scaffolding the attention-deficit/hyperactivity disorder brain using transcranial direct current and random noise stimulation: a randomized controlled trial. Clinical Neurophysiology: Official Journal of the International Federation of Clin Neurophysiol. 2021; 132(3): 699-707.
43. Westwood SJ, Criaud M, Lam S-L, et al. Transcranial direct current stimulation (tDCS) combined with cognitive training in adolescent boys with ADHD: a double-blind, randomised, sham-controlled trial. Psychological Medicine. 2021. doi: https://doi.org/10.1101/2020.12.07.20245456
44. Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. PLoS One. 2019; 14(4): e0215095.
45. Shiozawa P, Silva ME, Carvalho TC, Cordeiro Q, Brunoni AR, Fregni F. Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: a systematic review. Arq Neuro-Psiquiat. 2014; 72(7): 542-547.
46. McGough, J.J.; Loo, S.K.; Sturm, A.; Cowen, J.; Leuchter, A.F.; Cook, I.A. An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. Brain Stimul 2015, 8, 299-304, doi:10.1016/j.brs.2014.11.013.
47. McGough, J.J.; Sturm, A.; Cowen, J.; Tung, K.; Salgari, G.C.; Leuchter, A.F.; Cook, I.A.; Sugar, C.A.; Loo, S.K. Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2019, 58, 403-411.e403.

FINANCIAL DISCLOSURES

KR has received a grant from Takeda pharmaceuticals for other projects and consultancy fees from Lundbeck pharmaceuticals.

ACKNOWLEDGEMENTS

KR has been supported by the Medical Research Council (MRC) (MR/P012647/1); Action Medical Research (AMR; GN2426); the Garfield Weston Foundation for Medical Research; and the UK Department of Health via the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and the Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

CONFLICT OF INTEREST STATEMENT

The author of this article declares not to have any type of conflict of interest with respect to what is stated in this work.

If you want to quote our article:
Rubia K. Neuroimaging and Neurotherapeutics for Attention Deficit Hyperactivity Disorder (ADHD). An RANM. 2021;138(02): 124–131. DOI: 10.32440/ar.2021.138.02.rev02