Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 265-275 *Conference paper*

NEUROSTIMULATION IN TREATING ADHD

Heng Chun Wong[1] & Rashid Zaman[2,3,4]

[1]University of Cambridge, School of Clinical Medicine, Cambridge, UK
[2]Centre for Mental Health Research in association with University of Cambridge (CMHR-CU), Cambridge, UK
[3]Hertfordshire Partnership University NHS Foundation Trust, UK
[4]Department of Psychiatry, University of Cambridge, Cambridge, UK

SUMMARY

Background: *Neurostimulation techniques are potential methods of treating ADHD, involving stimulation of brain areas showing abnormal activity in ADHD. They are associated with benefits that last longer with fewer side effects. This literature review will evaluate the effectiveness of these methods.*

Subjects and methods: *A literature search using scientific databases including PubMed and the Cochrane Library, using "ADHD" and "Attention Deficit Hyperactivity Disorder" combined with "Transcranial Magnetic Stimulation", "TMS", "Transcranial Direct Current Stimulation", "tDCS", "Vagus Nerve Stimulation", "VNS", "Trigeminal Nerve Stimulation", "TNS", "Deep Brain Stimulation", "DBS", "Electroconvulsive Therapy", "ECT", "Ultrasound stimulation" as keywords was conducted, yielding 417 references, 30 of which are used in this paper.*

Results: *Mixed results have been found in the effectiveness of neurostimulatory methods in treating ADHD.*

Conclusions: *Neurostimulation techniques have potential in treating ADHD, with some studies having positive results. More research using greater sample sizes and standardised outcome measures could be done to verify the results of previous studies.*

Key words: *Attention Deficit Hyperactivity Disorder (ADHD) - Transcranial Magnetic Stimulation (TMS) - Transcranial Direct Current Stimulation (tDCS) - Trigeminal Nerve Stimulation (TNS)*

* * * * *

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by persistent patterns of inattentive, hyperactive and impulsive behaviour in an individual, inappropriate for their developmental stage and causing functional problems in the academic, social and occupational domains of their life, present before 12 years of life and not being explained by other psychiatric or personality disorder (1). Individuals with the condition could present with predominantly inattentive symptoms, predominantly hyperactive/impulsive symptoms or both.

ADHD has a prevalence of 7.2% (Thomas et al. 2015) and is associated with significant economic costs (Matza et al. 2005), academic underachievement (Barbaresi et al. 2007), comorbid psychiatric conditions like oppositional defiant disorder (Barkley et al. 2002) and epilepsy (Tan et al. 2005) and social rejection (Hoza 2007), making it an important problem to be addressed in psychiatry.

The exact pathophysiology of ADHD is unknown, though past studies have pointed to a neurochemical and neuropsychological basis for the disease. Association studies of candidate genes have found significant associations in the DRD4, DRD5, DAT, DBH, 5HTT, HTR1B, SNAP25, MAOA, TPH2 and ADR2A, genes associated with the dopaminergic, noradrenergic and serotonergic systems (Faraone et al. 2005, Gizer et al. 2009). Stimulants like amphetamine and methylphenidate, drugs that increase levels of noradrenaline and dopamine via inhibition of reuptake, seem to work, again pointing to the involvement of these neurotransmitters in the pathophysiology of ADHD. Neuropsychological theories of ADHD suggest a primary deficit in executive function (Willcutt et al. 2005), supported by imaging studies showing impairments in several networks associated with cognitive control, attention, timing and working memory, as well as poor deactivation of the default mode network (Rubia 2018).

Current Treatments for ADHD

Current treatments for ADHD have focused on rectifying the neurochemical abnormalities present in ADHD pharmacologically through the use of methylphenidate, amphetamine, atomoxetine and clonidine, with help via psychosocial methods including cognitive behavioural therapy, behaviour parent training, classroom modifications and psychoeducation.

Current treatments seem to be effective, as suggested by reviews on the topic. Randomised control trials have found amphetamines and methylphenidate improved clinicians' and teachers' ratings of symptom severity (Cortese et al. 2018), while psychosocial treatments were considered efficacious once all studies were considered, as reviewed by (Fabiano et al. 2016), and are associated with sustained long-term gains (Lopez-Pinar et al. 2018).

Problems, however, have been associated with the use of pharmacotherapy in treating ADHD. Various side effects including decreased appetite, stomach pain, sleep disturbances, headaches, labile mood, growth suppression and possible sudden cardiac death have been asso-

ciated with pharmacotherapy (Cortese et al. 2013, Dalsgaard et al. 2014), with no reduction in symptom severity following extended use (Swanson et al. 2017). Misperceptions of ADHD medication have resulted in the formation of stigmatising beliefs and the association of it with costs rather than benefits in children with ADHD (Harpur et al. 2008) and possibly lowered self-esteem in children who take the medication (Davis-Berman and Pestello 2010). Pharmacotherapy is also known not to work in a significant minority cases of ADHD, leading to the need for new methods of treating ADHD to be found.

Neurostimulation in Treating ADHD

Given the problems of current methods of treating ADHD, new methods of treating the condition have been explored, with neurostimulation being one of them. Neurostimulation involves the electrical or magnetic stimulation of the brain to cause long term changes in excitability or neurochemical activity, allowing for the rectification of key problems seen in neuropsychiatric conditions. This stimulation could be used to affect focal areas of the brain (eg. Using transcranial magnetic stimulation, transcranial direct current stimulation, ultrasound stimulation and deep brain stimulation), the whole brain (eg. Using electroconvulsive therapy) or neurochemical pathways via ascending connections of the areas stimulated (eg. Using vagus nerve stimulation and trigeminal nerve stimulation). Given the pathophysiology of ADHD, this represents a new method of treating the condition while bypassing the problems of current treatment methods.

This review will describe each of these methods, describe the trials investigating the effectiveness of these methods, and evaluate these trials.

SUBJECTS AND METHODS

Literature Search

A literature search for this paper was conducted on 16 March 2019 using scientific databases including PubMed and the Cochrane Library, using “ADHD” and “Attention Deficit Hyperactivity Disorder” combined with “Transcranial Magnetic Stimulation”, “TMS”, “Transcranial Direct Current Stimulation”, “tDCS”, “Vagus Nerve Stimulation”, “VNS”, “Trigeminal Nerve Stimulation”, “TNS”, “Deep Brain Stimulation”, “DBS”, “Electroconvulsive Therapy”, “ECT”, “Ultrasound stimulation” as keywords. This produced 417 references, 30 of which are included in this paper.

RESULTS

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation is a non-invasive method of neurostimulation that is able to depolarise or hyperpolarise cortical neurons (George et al. 2003). It involves the placement of an electromagnetic coil against the scalp of the subject, which delivers brief, powerful magnetic pulses which induce electrical activity in neuronal membranes, stimulating them. Different coil types are able to produce different magnetic field patterns, changing the area of the cortex stimulated. Figure-eight coils, for instance, produce a more focal pattern of stimulation, while H-coils activate deeper areas of the brain.

Repetitive TMS (rTMS), the application of successive trains of such pulses, has been found to cause long-term effects on the excitability of cortical areas, depending on the frequency used – Low frequency rTMS (of 5 Hz of less) reduces neuronal excitability and cerebral blood flow of the area stimulated, while high frequency rTMS (of above 5 Hz) increases neuronal excitability and cerebral blood flow of these areas. The intensity of rTMS stimulation is measured in terms of motor threshold (MT), the intensity of stimulation of the motor cortex producing the smallest reproducible activation of a muscle (normally the abductor pollicus brevis muscle). Due to the possibility of inducing epileptic activity as a result of continuous stimulation, trains of pulses are interspersed with intervals of varying times, with the total dose of an rTMS session ultimately being dependent on the number of pulses (a function of the frequency and the time stimulated) and the intensity of rTMS stimulation.

The side effects of rTMS tend to be mild, ranging from transient headaches to scalp discomfort (Janicak et al. 2008), with a very low incidence of seizures and hypomania (Loo et al. 2008), making it a promising new method of treating neuropsychiatric conditions. Its therapeutic use has been investigated in a wide range of neuropsychiatric disorders, including, depression (George et al. 2007), OCD (Zaman and Robbins 2017) and schizophrenia (Aleman et al. 2007) as well as ADHD.

12 studies analysing the effects of rTMS on ADHD symptoms were found, mostly focusing on the stimulation of the dorsolateral prefrontal cortex (DLPFC), an area associated with executive control.

Niederhofer described a case of a 42-year-old female with ADHD with mainly hyperactive symptoms, who was treatment resistant to methylphenidate, which was stopped 2 months prior to the trial. A 5-day course of rTMS of the motor additional area, given at a frequency of 1 Hz, totalling to 1200 pulses per day given over an hour was administered. ADHD symptoms on the Connor’s rating scale (CSRS) for adults before the treatment and after the treatment, as well as after a course of sham stimulation (with the application of the coil without any pulses delivered) four months after the course of active rTMS. Some improvement in her hyperactive symptoms was found after active stimulation, lasting for at least 4 weeks, with no such improvement seen after the sham stimulation. However, no improvement of in her inattentive symptoms were seen

(Niederhofer 2008). A further study by Niederhofer examined the effectiveness of rTMS in a similar patient, stimulating at the same frequency and pulse rate, but over the right motor area for 21 days, while the patient was on methylphenidate. Again, the CSRS for adults was used to assess symptomatology before and after treatment. Clinical improvement of symptoms was seen after the first 5 days of the experiment, prompting Niederhofer to lower the patient's dose of methylphenidate to 10 mg daily (from an original dose of 20 mg daily). Again, improvement was seen in the patient's hyperactive symptoms, with no difference in inattention, with the effect lasting at least 3 weeks (Niederhofer 2011).

Bloch and colleagues described a double-blind crossover trial involving 13 patients with ADHD. Participants were exposed to 1 session of active Fig8 rTMS (involving 42 cycles of 20 Hz stimuli for 2 s, followed by 30 s intertrain intervals over the right DLPFC at 100% MT, found via measuring 5 cm anterior to the motor threshold) and 1 session of sham rTMS (whereby patients were subjected to rTMS with 1 wing of the Fig8 being in contact with the scalp at 45 degrees, causing no active stimulation), scheduled a week apart, with half the participants having the active rTMS session first while the other half having the sham rTMS session first.

Scores on the Positive and Negative Affect Scale (PANAS), Visual Analogue Scales (VASs) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) were assessed before and after each trial. Significantly higher attention scores on the PANAS and VAS were found post-active rTMS, with no such difference being seen post-sham rTMS, though no difference in ADHD symptoms was seen, as assessed by the Adult ADHD Self Report Scale (ASRS), Wender-Utah adult ADHD scale (WUAAS) and clinical evaluation (Bloch et al. 2010).

Weaver and colleagues described a randomised sham-controlled crossover study involving 9 adolescents with ADHD, aged 14 to 21. Participants were made to stop all stimulant medications 2 weeks before randomisation, before having 2 weeks each of active Fig8 rTMS (involving 50 cycles of 10 Hz stimuli for 4 s, followed by 26 s intertrain intervals, for 5 sessions per week of the right DLPFC at 100% MT, found via measuring 5 cm anterior to the motor threshold) and sham rTMS (involving the coil being tilted at 90 degrees, with a week of no stimulation between the phases of the experiment. Significant changes were seen in the Clinical Global Impression of Improvement scale (CGI-I) and the ADHD-IV scale, though significant differences in scores between the active and sham conditions were only seen in the CGI-I scale, and not the ADHD-IV scale (Weaver et al. 2012).

Ustohal and colleagues described a case report of a 36-year-old man diagnosed with ADHD in childhood, unresponsive to atomoxetine, with comorbid depressive disorder. After five sessions of 10 Hz stimulation of the left DLPFC at 120% MT, with 10 s of stimulation followed by 30 s intertrain interval, for a total of 1500 stimuli per session, the patient showed improvement in attention, assessed via the d2 Test of Attention. Of note, though, was that the patient also showed an improvement after sham stimulation, and showed adverse effects of dysphoria, inability of respond emotionally, hypobulia, tension and impaired attention after a single session of stimulation of the right DLPFC (done after the 5 sessions of left DLPFC stimulation), and showed improvements in attention after sham stimulation (done before the 5 sessions of left DLPFC stimulation) (Ustohal et al. 2012).

Gomez and colleagues described a trial of 1 daily session of 1 Hz rTMS over the left DLPFC, with 1500 stimuli given per session at 90% MT over 5 consecutive days, administered to 10 boys aged 7 to 12 with ADHD, resistant to conventional therapy. ADHD symptoms were assessed via a symptoms check list filled in by parents and teachers before and 1 week after the rTMS sessions, and found that the inattentiveness symptoms at school and hyperactivity/impulsivity symptoms at home improved after treatment (Gomez et al. 2014).

Shahar and colleagues conducted a double-blind randomised control study of 15 sessions of high frequency rTMS using either deep, Fig8 or sham coils over the right prefrontal cortex on 20 adults with ADHD, and found improvements in the attention measures using the Conner's Adult ADHD Rating Scales (CAARS) and response inhibition using the Stop Signal Reaction Time (SSRT) test (Shahar et al. 2014).

Paz and colleagues conducted a double-blind placebo-controlled trial of H-coil rTMS on 22 adults with ADHD. Participants were subject to either 4 consecutive weeks of rTMS sessions, of 5 days per week, with 55 cycles of pulses at 18 Hz, lasting 2 s per train, followed by 20 s intertrain interval at 120% MT of both prefrontal cortices, or sham rTMS. While improvements were seen in both the CAARS and the Tests of Variables of Attention (TOVA) scores, no differences were seen between the active and sham groups (Paz et al. 2017).

Harmelech and colleagues conducted a blinded sham-controlled trial of H-coil rTMS on 34 adults with ADHD, with participants randomised to receive either right, left or sham DLPFC rTMS after cognitive training, for 15 sessions spread over 3 weeks. Improvements were seen in the CAARS inattention subscale and the attention and executive function scores of the Mindstreams cognitive assessment battery for the group with right DLPFC stimulation, with increased activation of that area during a working memory task, as measured via fMRI (Harmelech et al. 2018).

Finally, Cao and colleagues conducted 2 trials examining the effects of rTMS on ADHD symptoms. 64 children with ADHD, aged 6 to 13, were assigned randomly to 3 groups, receiving 6 weeks of either

atomoxetine, rTMS (using a Fig8 coil, 5 sessions per week, of 25 minute sessions of 50 cycles of 4 s of 10 Hz stimulation followed by 26 s intertrain interval at 100% MT, totalling to 2000 pulses per session, of the right DLPFC, measured via moving 5 cm forward from the motor threshold), or both. Significant improvements were seen in the attention deficit, hyperactive/impulsive and oppositional defiance subscales of the SNAP-IV questionnaire, with a non-significant difference between the group treated with atomoxetine and the group treated with rTMS in the attention deficit and hyperactive/ impulsive subscales, and non-significant differences between all 3 groups in the oppositional defiance subscale. Improvements were also seen in hot and cold executive functions, measured using the subscales of arithmetic, digit span and coding of the continuous performance test (CPT) and Weschler Intelligence Scale for Children (WISC), and the Iowa Gambling Task (Cao et al. 2018). A further study by Cao and colleagues had 66 patients with ADHD randomly divided to receive 6 weeks of either rTMS (using a Fig8 coil, 5 sessions per week, of 30 minute sessions of 60 cycles of 4 s of 10 Hz stimulation followed by 26 s intertrain interval at 100% MT, totalling to 2400 pulses per session of the right DLPFC, found via moving 5 cm forward from the motor threshold), sham rTMS (with the coil placed perpendicular to the scalp), atomoxetine (0.5 mg/kg/d, increased to 1.2 mg/kg/d after 3 days) or a placebo. Again, significant improvements were seen in the attention deficit, hyperactive/impulsive and oppositional defiance subscales of the SNAP-IV scale, with rTMS being almost as effective as atomoxetine, with no improvements seen in the sham rTMS and placebo groups (Cao et al. 2019).

Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS) is another method of neurostimulation, using direct current passed through the scalp to stimulate brain areas. Current is passed through electrodes placed on the scalp, flowing from the anodal electrode to the cathodal electrode, with anodal stimulation depolarising neuronal membranes while cathodal stimulation hyperpolarising neuronal membranes. This causes long term changes in cortical excitability, with effects persisting post-stimulation, making it another method to treat neuropsychiatric conditions such as ADHD.

tDCS treatments normally involve a ramping up period, whereby current is slowly raised to the desired level, before being maintained at that level for the period of stimulation. Sham conditions normally involve having this ramping up period, but have the current turned off directly after the peak level has been reached. The dose of tDCS given during each course of treatment is dependent on the energy supplied per unit surface area, which is turn is affected by the intensity of stimulation, duration of stimulation and the surface area of electrodes used.

Much like with rTMS, the side effects of tDCS tend to be mild, mainly being skin lesions similar to light burns on areas where electrodes were placed, with a low incidence of mania or hypomania in depressed patients (Matsumoto and Ugawa 2017). Its therapeutic use has been investigated in different conditions including depression (Bennabi and Haffen 2018), schizophrenia (Agarwal et al. 2013) and ADHD 13 studies examining the effects of tDCS on ADHD symptoms were found, again mostly focusing on the DLPFC.

Cosmo and colleagues described a randomised control trial of 60 patients with ADHD aged 18 to 65. Participants were split into groups of 30, receiving a single session of either active tDCS (with anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC, using electrodes of 5 x 7 cm, with 30 s ramping up time followed by 20 minutes of 1 mA stimulation, and 30 s ramping down time) or sham tDCS (with no stimulation apart from the initial 30 s ramping up time). No differences were found between the groups in changes in performance in the Go/NoGo task, with the effect size of group differences in changes in scores being small (Cosmo et al. 2015).

Soltaninejad and colleagues conducted a single-blinded crossover sham-controlled study of 20 high school students with ADHD symptoms, aged 15 to 17. Participants were rotated through 3 phases of the experiment, receiving a single session of either anodal stimulation (with the anode over the left DLPFC and cathode over the right supraorbital, electrodes of 7 x 5 cm, 15 s ramping up time followed by 15 minutes of 1.5 mA stimulation and 15 s ramping down time), cathodal stimulation (with the same conditions as the anodal stimulation, but with the cathode over the left DLPFC and anode over the right supraorbital instead) or sham stimulation (with no stimulation apart from the 15 s ramping up time). Participants were also made to perform the Go/NoGo task followed by the Stroop test after 8 minutes of stimulation in each condition, for the remaining period of stimulation. An interval of 72 h was given between phases. Anodal stimulation showed no effect on interference inhibition (as measured by the Stroop test), though an increased proportion of correct responses was seen in the Go portion of the Go/NoGo test. Cathodal stimulation, on the other hand, increased inhibition accuracy of the inhibition stage of the Go/NoGo task compared to sham stimulation (Soltaninejad et al. 2015).

Breitling and colleagues described a trial of 21 male patients with ADHD, matched with 21 healthy controls, aged 13 to 17. Participants were rotated through 3 phases of the experiment, receiving single sessions of either anodal stimulation (with the anode over the right inferior frontal gyrus and cathode posterior to the left mastoid, electrodes of 7 x 5 cm, with 30 s ramping up time followed by 20 minutes of stimulation at 1 mA and 30 s ramping down time), cathodal stimulation (with the same conditions as the anodal stimulation, but with the

anode posterior to the left mastoid and the cathode over the right inferior frontal gyrus) and sham stimulation (with 30 s of ramping up time followed by 30 s stimulation at 1 mA and

30 s ramping down time, electrode positions as per anodal stimulation). Participants were also made to perform the Flanker task after 5 minutes of stimulation, for the remining period of stimulation. An interval of 1 week was given between phases. Due to a significant learning effect being observed between sessions, only the first session was taken into account. Improved interference control was observed in ADHD patients receiving anodal stimulation to almost comparable levels to controls, with impaired performance observed in ADHD patients receiving either cathodal or sham stimulation (Breitling et al. 2016).

Bandeira and colleagues described a trial of tDCS on 9 patients with ADHD, aged 6 to 16. 7 x 5 cm electrodes were used for both cathodal and anodal stimulation, with the cathode being placed over the right supraorbital area and the anode being placed over the left DLPFC. Stimulation was held at 1 mA for the 1st minute, before being increased to 2 mA for the 2nd to 29th minute, before being reduced to 1 mA for the final minute of stimulation before the end of the trial. Participants were made to play the game "Super Lynx", a game stimulating the DLPFC, during stimulation. 5 sessions were conducted over consecutive days for the trial. Participants showed an improvement in the selective attention part of the visual attention test (TAVIS-3), along with improvements in some stages of the Neuropsychological Development Assessment (NEPSY-II), namely the time to check information and the frequency of errors in the alternating attention task after stimulation. No improvements were seen in digit span (measured using the WISC-III) and visual working memory (using the Corsi cubes test), though (Bandeira et al. 2016).

Cachoeira and colleagues described a randomised, double blind, placebo-controlled trial of tDCS on 17 adults with ADHD aged 18 to 45 were randomised to receive either active or sham tDCS treatment, with anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC, using electrodes of 7 x 5 cm. 2 mA of current was applied for 20 minutes per day for 5 consecutive days for the active tDCS condition, with the device being turned off 1 minute after the start of stimulation in the sham tDCS condition. Participants were instructed to relax, read, listen to music or sleep while being stimulated. Improvements were seen in the self-report ASRS scale in both the sham and active tDCS condition, with the improvement being greater in the active condition, though not significantly different from that of the sham condition. Closer examination of ASRS scores, however, revealed significant differences in the inattention subscale between active and sham conditions. Sheehan Disability Scales were also seen to be significantly lower in the active compared to the sham condition. These effects did seem to decrease with time, though (Cachoeira et al. 2017)

Soff and colleagues described a double-blinded randomised sham-controlled crossover study of 15 adolescents with ADHD, aged 12 to 16 years. Participants received either 5 sessions of active tDCS with anodal stimulation of the left DLPFC (involving a round anode of surface area 314 mm2 and a cathode surface area of 1250 mm^2 over the vertex, with a ramping up period of 8 s before 20 minutes of stimulation at 1 mA, followed by 8 s ramping down period) or 5 sessions of sham tDCS (involving the same electrodes and placement, but with a ramping up time of 8 s followed by only 5 s of 1 mA stimulation before another 8 s ramping down), before 2 weeks of washout before receiving the other stimulation. Each stimulation session occurred while participants were in an MRI scanner, to record fMRI activity, as well as having a resting state fMRI scan directly after stimulation. Additionally, participants were made to do the n-back working memory paradigm before and during each session of stimulation. Active tDCS showed a significant reduction in clinical symptoms of inattention and impulsivity (assessed by the FBB-ADHD, filled in by parents) compared to the sham tDCS condition, and also showed a significant reduction in inattention and hyperactivity, measured by the QbTest. These effects were more pronounced 7 days after the end of stimulation (Soff et al. 2017).

Sotnikova and colleagues described a similar experiment using the same paradigm as (Soff et al. 2017), except using cathodes of 35 cm2 and anodes of 13 cm^2. fMRI scans done found increased activation in the left DLPFC, left premotor cortex, left supplementary motor cortex and precuneus after active tDCS stimulation, with strengthened DLPFC connectivity outlining the working memory network 20 minutes after stimulation. Improvements in reaction time variability was also seen in active tDCS stimulation but not in sham stimulation (Sotnikova et al. 2017).

Nejati and colleagues conducted a randomised double-blind sham-controlled trial involving 25 children with ADHD, having moderate to severe SNAP-IV scores. 15 participants received either active stimulation (with anodal stimulation of the left DLPFC and cathodal stimulation of the right DLPFC, using 25 cm2 electrodes, with a ramping up period of 30 s followed by 15 minutes of stimulation at 1 mA and 30 s ramping down period) or sham stimulation (with no stimulation apart from the 30 s ramping up period, with electrodes placed in the same position), followed by a 72 h washout period and reception of the other condition. Participants were made to perform the Go/NoGo task, n-back task, Wisconsin Card Sorting Task (WCST) and Stroop task after stimulation in each condition. No differences were observed in performance in the Go/NoGo and WCST tasks, with no improvements in working memory (measured by the n-back task), though reaction time was reduced and performance on the Stroop task improved in the active condition compared to the sham condition.

10 participants were instead rotated through 3 phases, consisting of anodal stimulation (with the anode over the left DLPFC and cathode over the right orbitofrontal cortex, using the same electrode size and stimulation protocol as the other group), cathodal stimulation (with the same protocol, but with the cathode over the left DLPFC and anode over the right orbitofrontal cortex) or sham stimulation (with electrode placement as per anodal stimulation, but with only 30 s ramping up time followed by no stimulation). Significant increases in NoGo accuracy was observed after cathodal stimulation compared to sham stimulation. Both anodal and cathodal stimulation reduced perseverative errors and total errors while increasing completed categories in the WCST, with anodal stimulation being more effective in doing so than cathodal stimulation. Accuracy and reaction time in the n-back task was seen to improve following anodal stimulation (Nejati et al. 2017).

Aycicegi-Dinn and colleagues described a study involving 53 university students with or without elevated scores on a measure of ADHD. Participants received a single tDCS session with anodal stimulation of the left DLPFC and cathodal stimulation of the frontopolar region, at an intensity of 2 mA for 20 minutes or sham tDCS. Participants receiving active tDCS did not obtain higher scores on measured of executive control and working memory, with no differences seen in performance in the California Verbal Learning Test (CVLT) and Rey Complex Figure Test (RCFT). That said, male participants receiving active tDCS were found to have higher scores on the CVLT compared to males in the sham group, a difference not seen in female participants (Aycicegi-Dinn et al. 2018).

Jacoby and Lavidor described a double-blind sham-controlled crossover study involving 20 adults with ADHD and 15 healthy controls, aged 19 to 29. Participants were rotated between single sessions of either double anodal bilateral tDCS (with anodes placed over the right and left DLPFC and cathode over the cerebellar cortex 1 cm below the inion, anode surface area 3 x 3 cm, cathode surface area 5 cm x 7 cm, 30 s ramping up period followed by 20 minutes stimulation at 1.8 mA and 30 s ramping down period) or sham stimulation (with the same electrodes and placement but no stimulation other than the initial ramping up period), with a 1 week period between each session. Participants were made to perform the MOXO-CPT test 20 minutes after each session, as well as the PANAS. Hyperactivity, as assessed by the MOXO-CPT, improved following active stimulation compared to sham stimulation in ADHD patients but not in controls, with all other measures assessed by the MOXO-CPT (impulsivity, reaction time and attention) showing only a learning effect (Jacoby and Lavidor 2018).

Allenby and colleagues conducted a double-blind sham-controlled crossover study involving 37 adults with ADHD, aged 18 – 65. Participants were rotated through 2 phases of the experiment, each consisting 3 sessions (conducted on alternating days) of either active tDCS (with the anode placed over the left DLPFC, cathode over the right supraorbital area, 5 x 5 cm electrodes, 30 s ramping up period followed by 19 minutes of stimulation at 2 mA and 30 s ramping down time) or sham tDCS (with the same electrodes and placement but with a 30 s ramping up period immediately followed by a 30 s ramping down period at the beginning and end of the session instead), with a 2 week washout period between each phase of the experiment. Participants were made to perform a fractal n-back training task during each session. Participants were also made to do the Conners Continuous Performance Task and stop signal reaction time task 3 days after the final stimulation sessions of each phase of the experiment. Participants receiving active tDCS made fewer false positive errors compared to baseline, though no improvement was seen in true positive errors, response time or SSRT scores, and the effect on false positive errors did not persist at follow-up (Allenby et al. 2018).

2 studies were found analysing the effects of transient oscillating DCS (toDCS) on sleep in patients with ADHD, another function affected in the condition. Prehn-Kristensen and colleagues conducted a trial of toDCS on 12 boys with ADHD and 12 healthy boys aged 10 – 14. Electrodes were placed over the DLPFC and mastoids of participants, with current intensities ranging from 0 to 250 uA at a frequency of 0.75 Hz, initiated 4 minutes after participants fell into stage 2 non-REM sleep, for 5 cycles of 5 minutes of stimulation followed by 1-minute intervals free from stimulation. Participants were made to play the card game "Concentration", involving an encoding session just before sleep and a retrieval session upon waking up. Memory loss in children with ADHD was worse than healthy controls, but this difference vanished after the toDCS session, with slow oscillation power in stage 4 non-REM being enhanced after toDCS (Prehn-Kristensen et al. 2014). Munz and colleagues performed a similar experiment involving 14 boys aged 10 to 14 with ADHD. The same protocol as (Prehn-Kristensen et al. 2014) was used, with cognitive performance assessed using the Go/NoGo task, the alertness subtest of the KiTAP and a finger sequence tapping task. Reaction times and variability, as assessed by the Go/NoGo task, were found to be shorter after the night of stimulation. No differences were found in alertness, though, and participants showed a gain in speed in the finger tapping task regardless of stimulation (Munz et al. 2015).

Vagus Nerve Stimulation (VNS)/ Trigeminal Nerve Stimulation (TNS)

Other methods of neurostimulation have focused on remedying the neurochemical deficits present in

patients with ADHD. Vagus nerve stimulation (VNS) is one such method, involving the electrical stimulation of the vagus nerve via a surgically-implanted electrode, delivering pulses at a programmable frequency, charge, duration and active period. It is currently used to treat treatment-resistant epilepsy. The exact mechanism of VNS is unknown, though it has been found that chronic VNS increases locus coeruleus (LC) activity in rats, as measured through direct recordings of neural activity (Groves et al. 2005) and via measurements of c-fos levels in the LC post-VNS (Naritoku et al. 1995). This seems to increase noradrenaline levels in the hippocampus and prefrontal cortex, measured via microdialysis (Roosevelt et al. 2006, Follesa et al. 2007).

Trigeminal Nerve Stimulation (TNS) works similar to VNS, using a small stimulator worn during sleep, emitting mild electrical signals which are conducted via adhesive electrode pads worn on the forehead over the trigeminal nerve. Again, through its connections with the LC (De Cicco et al. 2018), it could increase noradrenaline levels much like VNS, but without the potential side effects of vocal cord palsy and postoperative haematoma (Revesz et al. 2016).

Given the possible involvement of the noradrenergic system in ADHD (Pliszka 2005), VNS and TNS could represent a new method of treating ADHD. No studies have been done to assess the effects of VNS on patients with ADHD directly, though trials on healthy controls have yielded some positive results – VNS has been seen to enhance post-error slowing (Sellaro et al. 2015), which is deficient in patients with ADHD (Balogh et al. 2016); VNS is also seen to have a positive effect on response inhibition as measured by a stop-signal task (Schevernels et al. 2016), another deficit in patients with ADHD.

2 studies examining the effects of TNS on patients with ADHD were found. McGough and colleagues described an 8-week trial of TNS on 21 children with ADHD, aged 7 to 14. TNS was administered to children, at a frequency of 120 Hz, 250 us pulse width, and a duty cycle of 30 s on and 30 s off, with bilateral stimulation of the V1 branches of the trigeminal nerve for 7-9 h per night. Symptoms of inattention and hyperactivity / impulsivity, measured by the ADHD-RS were found to improve after the treatment, with reductions in CGI-I scores as well. Parental reports using the Behaviour Rating Inventory of Executive Functioning (BRIEF), showed improvements as well. Improvements were also seen in the Attention Network Task (ANT) incongruent reaction times, alongside improvements in sleep anxiety and sleep problems, as measured by the Children's Sleep Habits Questionnaire (CSHQ) (McGough et al. 2015). A further sham-controlled double-blind study by McGough and colleagues involving 62 children with ADHD aged 8 to 12 was done. Participants were randomised, receiving either active or sham TNS, with bilateral stimulation of the V1 branch of the trigeminal nerve for 8 h per night for 4 weeks, with the active TNS group receiving stimulation of 2–4 mA, with the same protocol as the earlier study by the same group. ADHD-RS scores of both groups showed improvements during the first week, with improvements in subsequent weeks seen only in the group having active stimulation. The group receiving active stimulation also showed significantly improved CGI-I scores compared to the group receiving sham stimulation. No differences were seen between groups in CSHQ scores, though (McGough et al. 2018).

Other methods

Other methods of treating neuropsychiatric conditions using neurostimulation include deep brain stimulation (DBS), ultrasound stimulation and electroconvulsive therapy (ECT).

Deep Brain Stimulation (DBS) is the surgical implantation of an electrode in an area of the brain, allowing for the delivery of electrical stimuli which disrupt abnormal patterns of neural signalling or stimulate the area of the brain which the electrode is implanted. DBS is currently used to treat Parkinson's disease (PD), essential tremor, dystonia, epilepsy, Tourette syndrome, chronic pain, depression and obsessive-compulsive disorder (Delaloye & Holtzheimer 2014, Martinez-Ramirez et al. 2018, Laxatives et al. 2014). Similar to tDCS and rTMS, it could be used to directly stimulate areas of the brain that show abnormal activity in patients with ADHD, albeit being an invasive procedure. No trials have been conducted to treat ADHD with DBS. Much like with VNS, the invasive nature of the procedure would make it unlikely to be approved for treatment of ADHD.

Ultrasound stimulation another possible method of noninvasively stimulating focal areas of the brain, making it a possible treatment for ADHD, given the specificity of brain regions affected in the condition. Low intensity focused ultrasound is used to stimulate areas of the brain with greater resolution and depth (Bystritsky et al. 2011). Current research in its use in medicine has focused on mental states (Hameroff et al. 2013) and diagnosis of psychiatric conditions (Drepper et al. 2017), with no research conducted on its therapeutic use in ADHD.

Electroconvulsive Therapy (ECT) is a method of neurostimulation involving the passage of electrical current to induce a seizure in patients (when under general anaesthesia), causing relief of neuropsychiatric symptoms. It has been used in the treatment of depression, catatonia and schizophrenia (Weiner and Reti 2017), with high remission rates (Kellner et al. 2010) though it has been associated with memory loss and cognitive deficits (Sackheim et al. 2007). Again, as yet no studies analysing the effects of ECT on ADHD symptoms have been done.

DISCUSSION

As seen above, some studies have been done analysing the effect of rTMS on ADHD symptoms, mostly focusing on stimulation of the DLPFC, with some investigating the stimulation of other areas, including the PFC (Paz et al. 2017, Shahar et al. 2014) and the motor areas (Niederhofer 2008, Niederhofer 2011). The studies investigating the effects of rTMS on DLPFC stimulation mostly agreed with each other – increasing the excitability of the right DLPFC through high frequency rTMS and decreasing the excitability of the left DLPFC through low frequency rTMS improve ADHD symptoms (Weaver et al. 2012, Bloch et al. 2010, Gomez et al. 2014, Harmelech et al. 2018 and Cao et al. 2018), albeit with (Ustohal et al. 2012) reporting the worsening of depression in a patient with right DLPFC stimulation, with improvements in ADHD symptoms in left DLPFC and sham stimulation. The studies on PFC stimulation have had mixed results, with (Shahar et al. 2014) reporting improvements in ADHD symptoms while (Paz et al. 2017) reporting no differences in results between active rTMS and sham rTMS.

That said, there are problems with these studies – most of them have small sample sizes, all of them except (Cao et al. 2018, Cao et al. 2019) having less than 30 participants, decreasing the power of the studies. Study populations have been heterogenous, with some recruiting children while others recruiting adults. This could be a problem if rTMS works differently at different ages. Further, the determination of the area of stimulation in the studies have generally been via usage of approximations, via moving the stimulator 5 cm anterior from the area where the motor threshold is determined, which could raise questions on the precision of stimulation target. Perhaps more accurate ways of determining the location of the DLPFC could be made (eg. Through the use of infrared neuronavigation or correlational fMRI). Finally, outcome measures have been rather heterogenous, with different scales being used, ranging from the CGI-I, CSRS, ADHD-IV and SNAP-IV to task performance in the IGT, CPT TOVA and SSRT. Standardisation of outcome measures and sample populations could be done perhaps using a single agreed ADHD symptom scale and the use of multiple tasks to judge the efficacy of treatment on different groups of patients, even following their symptoms through time via having follow-up studies on the same population.

Studies analysing the effect of tDCS and toDCS on ADHD symptoms have mostly focused on stimulation of the right DLPFC and inhibition of the left DLPFC or the reverse, with a study focusing on the inferior frontal gyrus (Breitling et al.2016) and 2 studies investigating the effect of toDCS.

Studies investigating the effect of right DLPFC stimulation and left DLPFC inhibition have yielded mixed results, with (Cosmo et al. 2015) finding no differences in test performance, while (Cachoeira et al. 2017) finding improvements in the ASRS and (Soltaninejad et al. 2015) noting improvements in inhibition accuracy in the Go/NoGo task. Studies investigating the effect of left DLPFC stimulation have yielded more positive results, patients having left DLPFC stimulation had an increased proportion of correct responses in the Go portion of the Go/NoGo task (Soltaninejad et al. 2015), improvements in selective attention in the TAVIS, improvements in time to check information and reduced errors in the alternating attention task in the NEPSY (Bandeira et al. 2016), reduced clinical symptoms of inattention and impulsivity, as reported by parents as well as through the QbTest (Soff et al. 2017), reduced reaction time in the Stroop test, reduced preserverative errors and total errors in the WCST, improved accuracy and reaction time in the n-back test (Nejati et al. 2017), improvements in the CVLT (Aycicegi-Dinn et al. 2018) and fewer false positive errors in the CPT test (Allenby et al. 2018). One study focused on IFG stimulation, reporting increased interference control in the flanker task (Breitling et al. 2016). toDCS also seems to show results, with improvements in memory (Prehn-Kristensen et al. 2014) and reaction times and variability in the Go/NoGo test (Munz et al. 2015) being reported.

However, the same problems can be seen in these studies as with the studies on rTMS – all of the studies have small sample sizes of less than 60, with some having as few as 9. Study populations are again heterogenous, with participants coming from different age groups and having different inclusion criteria. Outcome measures are again heterogenous, with multiple different tasks being used, making it difficult to compare results. All in all, a trial of tDCS with more participants, standardised outcome measures and inclusion criteria could be done, perhaps through multicentre trials.

The invasive nature of VNS implantation and its potential associated side effects could make VNS unlikely to be approved for the treatment of ADHD, given the other less invasive methods of stimulation, including TNS. That said, a study analysing the effects of VNS on ADHD symptoms could be done, given the increased incidence of ADHD in epileptics (Williams et al. 2016) and its use to treat symptoms of epilepsy. This could allow the indirect observation of the effects of VNS on ADHD symptoms, albeit in a select group of patients with the condition.

As seen through the 2 studies analysing the effects of TNS on ADHD symptoms, TNS seems to be a promising new method of treating ADHD, with both studies showing improvements in ADHD symptoms, as measured through different tasks, including the ANT, ADHD-RS and CGI-I. That said, more studies could be done with larger sample sizes to confirm these findings, as well to assess the safety and compliance of patients for this method of treatment.

No studies have been done analysing the effects of DBS on ADHD symptoms, with the procedure being unlikely to be approved for the treatment of ADHD, given its invasive nature. Ultrasound, on the other hand, could represent a potentially new method of treating ADHD, given its specificity in targeting brain areas while being non-invasive in nature. Studies could be done focusing on stimulation of the DLPFC or the IFG, areas known to be affected in ADHD, to study its effects on ADHD symptoms.

No studies have been done analysing the effects of ECT on ADHD symptoms, though much like with VNS, studies could be done to indirectly observe the effects of ECT on ADHD symptoms in patients with comorbid depression or schizophrenia being treated using ECT.

CONCLUSION

In conclusion, research suggests that in ADHD, there is underlying disturbance in neurotransmitter pathways and select regions of the brain, ultimately manifesting as significant problems with inattention, hyperactivity and impulsivity. Current methods of treating the condition mainly with pharmacotherapy has been associated with side effects and indeed fail to work in a significant minority of patients. Given this situation, Neurostimulation could be a promising new method of treating ADHD, with fewer side effects. Many studies analysing effects of Neurostimulation such as rTMS and tDCS on ADHD symptoms has yielded generally positive results. However, more studies with greater sample sizes, standardisation of treatment parameters and outcome measures are needed to confirm these findings. Other methods of neurostimulation, including, ultrasound stimulation and electroconvulsive therapy could represent new ways of treating ADHD, though their effects have not been studied directly.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Heng Chun Wong carried out the literature search and analysis and wrote the first draft of the manuscript.

Rashid Zaman conceived and supervised the project, carried out literature search and revised the manuscript.

References

1. *Agarwal S, Shivakumar V, Bose A, Subramaniam A, Nawani H, Chhabra H, Venkatasubramanian G: Transcranial direct current stimulation in schizophrenia. Clinical psychopharmacology and neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology 2013; 11:118-25*
2. *Aleman A, Sommer I & Kahn R: Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. The Journal of clinical psychiatry 2007; 68:416-21*
3. *Allenby C, Falcone M, Bernardo L, Wileyto E, Rostain A, Ramsay J, Loughead J: Transcranial direct current brain stimulation decreases impulsivity in ADHD. Brain Stimulation 2018; 11:974-981*
4. *Aycicegi-Dinn A, Goral F, Adigüzel S, Karamürsel S & Dinn W: TDCS and memory function among individuals with or without elevated ADHD symptoms. 2017*
5. *Balogh L & Czobor P: Post-Error Slowing in Patients with ADHD. Journal of Attention Disorders 2016; 20:1004-1016*
6. *Bennabi D & Haffen E: Transcranial Direct Current Stimulation (tDCS): A Promising Treatment for Major Depressive Disorder? Brain sciences 2018; 8*
7. *Bystritsky A, Korb A, Douglas P, Cohen M, Melega W, Mulgaonkar A, Yoo S-S: A review of low-intensity focused ultrasound pulsation. Brain Stimulation 2011; 4:125-136*
8. *Cortese S, Adamo N, Giovane D, Mohr-Jensen C, Hayes A, Carucci S, Cipriani A: Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. 2018; 5. www.thelancet.com/psychiatry*
9. *Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Sergeant J: Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. Journal of Child Psychology and Psychiatry 2013; 54:227-246*
10. *Dalsgaard S, Kvist A, Leckman J, Nielsen H & Simonsen M: Cardiovascular Safety of Stimulants in Children with Attention-Deficit/Hyperactivity Disorder: A Nationwide Prospective Cohort Study. Journal of Child and Adolescent Psychopharmacology 2014; 24:302-310*
11. *Davis-Berman J & Pestello F: Medicating for ADD/ADHD: Personal and Social Issues. International Journal of Mental Health and Addiction 2010; 8:482-492*
12. *De Cicco V, Tramonti Fantozzi M, Cataldo E, Barresi M, Bruschini L, Faraguna U & Manzoni D: Trigeminal, Visceral and Vestibular Inputs May Improve Cognitive Functions by Acting through the Locus Coeruleus and the Ascending Reticular Activating System: A New Hypothesis. Frontiers in Neuroanatomy 2018; 11:130*
13. *Delaloye S & Holtzheimer P: Deep brain stimulation in the treatment of depression. Dialogues in clinical neuroscience 2014; 16:83-91*
14. *Drepper C, Geißler J, Pastura G, Yilmaz R, Berg, D, Romanos M & Gerlach M: Transcranial sonography in psychiatry as a potential tool in diagnosis and research. The World Journal of Biological Psychiatry 2018; 19:484-496*
15. *Fabiano G, Schatz N, Aloe A, Chacko A & Chronis-Tuscano A: A systematic review of meta-analyses of psychosocial treatment for attention-deficit/hyperactivity disorder. Clinical child and family psychology review 2015; 18:77-97*
16. *Faraone S, Perlis R, Doyle A, Smoller J, Goralnick J, Holmgren M & Sklar P: Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry 2005; 57:1313-1323*

17. Follesa P, Biggio F, Gorini G, Caria S, Talani G, Dazzi L, Biggio G: Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. Brain Research 2007; 1179:28-34
18. George M, Nahas Z, Borckardt J, Anderson B, Foust M, Burns C, Short E: Brain stimulation for the treatment of psychiatric disorders. Current Opinion in Psychiatry 2007; 20:250-254
19. Gizer I, Ficks C & Waldman I: Candidate gene studies of ADHD: a meta-analytic review. Human Genetics 2009; 126:51-90
20. Groves D, Bowman E & Brown V: Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. Neuroscience Letters 2005; 379:174-179
21. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace M, Boyle P, Badal J: Transcranial Ultrasound (TUS) Effects on Mental States: A Pilot Study. Brain Stimulation 2013; 6:409-415
22. Harpur R, Thompson M, Daley D, Abikoff H & Sonuga-Barke E: The Attention-Deficit/Hyperactivity Disorder Medication-Related Attitudes of Patients and Their Parents. Journal of Child and Adolescent Psychopharmacology 2008; 18:461-473
23. Jacoby N & Lavidor M: Null tDCS Effects in a Sustained Attention Task: The Modulating Role of Learning. Frontiers in psychology 2018; 9:476
24. Janicak P, O'Reardon J, Sampson S, Husain M, Lisanby S, Rado J, Demitrack M: Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. The Journal of clinical psychiatry 2008; 69:222-32
25. Kellner C, Knapp R, Husain M, Rasmussen K, Sampson S, Cullum M, Petrides G: Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. British Journal of Psychiatry 2010; 196:226-234
26. Laxpati N, Kasoff W & Gross R: Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials. Neurotherapeutics 2014; 11:508-526
27. Loo C, McFarquhar T & Mitchell P: A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. International Journal of Neuropsychopharmacology 2008; 11:131-147
28. López-Pinar C, Martínez-Sanchís S, Carbonell-Vayá E, Fenollar-Cortés J & Sánchez-Meca J: Long-Term Efficacy of Psychosocial Treatments for Adults With Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Frontiers in psychology 2018; 9:638
29. Martinez-Ramirez D, Jimenez-Shahed J, Leckman J, Porta M, Servello D, Meng F-G, Okun M: Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome. JAMA Neurology 2018; 75:353
30. Matsumoto H & Ugawa Y: Adverse events of tDCS and tACS: A review. Clinical Neurophysiology Practice 2017; 2:19-25
31. McGough J, Loo S, Sturm A, Cowen J, Leuchter A & Cook I: An Eight-week, Open-trial, Pilot Feasibility Study of Trigeminal Nerve Stimulation in Youth With Attention-deficit/Hyperactivity Disorder. Brain Stimulation 2015; 8:299-304
32. McGough J, Sturm A, Cowen J, Tung K, Salgari G, Leuchter A, Loo S: Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for ADHD. Journal of the American Academy of Child & Adolescent Psychiatry 2019
33. Munz M, Prehn-Kristensen A, Thielking F, Mölle M, Göder R & Baving L: Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. Frontiers in cellular neuroscience 2015; 9:307
34. Naritoku D, Terry W & Helfert R: Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. Epilepsy research 1995; 22:53-62
35. Nejati V, Salehinejad MA, Nitsche MA, Najian A & Javadi A-H: Transcranial Direct Current Stimulation Improves Executive Dysfunctions in ADHD: Implications for Inhibitory Control, Interference Control, Working Memory, and Cognitive Flexibility (n.d.)
36. Prehn-Kristensen A, Munz M, Göder R, Wilhelm I, Korr K, Vahl W, Baving L: Transcranial Oscillatory Direct Current Stimulation During Sleep Improves Declarative Memory Consolidation in Children With Attention-deficit/hyperactivity Disorder to a Level Comparable to Healthy Controls. Brain Stimulation 2014; 7:793-799
37. Révész D, Rydenhag B & Ben-Menachem E: Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. Journal of Neurosurgery: Pediatrics 2016; 18:97-104
38. Roosevelt R, Smith D, Clough R, Jensen R & Browning R: Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. Brain Research 2006; 1119:124-132
39. Rubia K: Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and Its Clinical Translation. Frontiers in human neuroscience 2018; 12:100
40. Sackeim H, Prudic J, Fuller R, Keilp J, Lavori P & Olfson M: The Cognitive Effects of Electroconvulsive Therapy in Community Settings. Neuropsychopharmacology 2007; 32:244-254
41. Schevernels H, van Bochove M, De Taeye L, Bombeke K, Vonck K, Van Roost D, Boehler C: The effect of vagus nerve stimulation on response inhibition. Epilepsy & behavior, E&B 2016; 64(Pt A):171-179
42. Sellaro R, van Leusden J, Tona K-D, Verkuil B, Nieuwenhuis S & Colzato L: Transcutaneous Vagus Nerve Stimulation Enhances Post-error Slowing. Journal of Cognitive Neuroscience 2015; 27:2126-2132
43. Shoirah H & Hamoda H: Electroconvulsive therapy in children and adolescents. Expert Review of Neurotherapeutics 2011; 11:127-137
44. Soff C, Sotnikova A, Christiansen H, Becker K & Siniatchkin M: Transcranial direct current stimulation improves clinical symptoms in adolescents with attention deficit hyperactivity disorder. Journal of Neural Transmission 2017; 124:133-144
45. Sotnikova A, Soff C, Tagliazucchi E, Becker K & Siniatchkin M: Transcranial Direct Current Stimulation Modulates Neuronal Networks in Attention Deficit Hyperactivity Disorder. Brain Topography 30:656-672

46. Weiner R & Reti I: Key updates in the clinical application of electroconvulsive therapy. International Review of Psychiatry 2017; 29:54-62
47. Willcutt E, Doyle A, Nigg J, Faraone S & Pennington B: Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Biological Psychiatry 2005; 57:1336-1346
48. Williams A, Giust J, Kronenberger W & Dunn D: Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges. Neuropsychiatric disease and treatment 2016: 12:287-96
49. Zaman R, Robbins TW: Is there potential for repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment of OCD? Psychiatr Danub 2017; 29(Suppl 3):672-678
50. Zervas I, Theleritis C & Soldatos C: Using ECT in schizophrenia: A review from a clinical perspective. The World Journal of Biological Psychiatry 2012; 13:96-105

Correspondence:

Rashid Zaman, BSc (Hons), MB BChir (Cantab), DGM MRCGP FRCPsych
Department of Psychiatry, University of Cambridge
Cambridge, UK
E-mail: rz218@cam.ac.uk http://www.cmhr-cu.org/