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INVESTIGATIVE AND THERAPEUTIC USES OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

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SUMMARY

Attention Deficit Hyperactivity Disorder (ADHD) is a common neuropsychiatric disorder that affects children and young adults. It results in significant impairment of their educational, social and occupational functioning and is associated economic societal burden.

Whilst there are effective medications (such as methylphenidate) as well as some psychobehavioural therapies that can help with management of symptoms of ADHD, the former can have significant cardiac side effects, which limit their use. For number of patients these treatment options lack efficacy or are not acceptable.

There is need to improve our understanding of neurobiology of ADHD as well as explore other treatment options.

Transcranial magnetic stimulation (TMS) and repetitive transcranial magnetic stimulation (rTMS) are safe and non-invasive investigative and therapeutic tools respectively.

In this short paper, I will explore the potential role of TMS and rTMS in further improving our understanding of the neurobiology of ADHD as well as possible treatment option.

Key words: *ADHD – neurobiology – TMS - rTMS*

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INTRODUCTION

It is well recognized that the core features, such as, inattention, hyperactivity and impulsivity of Attention deficit hyperactivity disorder (ADHD) cause significant impairment in individual's social, academic and occupational functioning in childhood as well as in adulthood. The sufferers of ADHD often experiences poor educational and vocational outcomes and have increased risk for antisocial behaviour and drug misuse (Harpin 2005).

Genetics clearly plays a very important role in etiology of ADHD. Although the family studies suggest adult form of ADHD (prevalence of up to 5%) has increased familial liability compared to childhood ADHD, however, when using multiple sources of information it appears that the heritability of clinically diagnosed adult ADHD and childhood ADHD is very similar (Franke et al. 2012).

Attention deficits, impulsiveness and hyperactivity appear to relate to disordered executive functions, disturbed motor control with abnormalities in the fronto-striatal-cerebellar circuits.

PET and fMRI studies suggest atypical function of right fronto-striatal circuits, reduced blood flow in striatum and in frontal-cerebral circuits in individuals with ADHD.

Problems with *attention* in ADHD are common. Meta-analysis of fMRI studies have shown decrease in activity in the attentional networks such as right dorsolateral prefrontal cortex (BA 8, 46), right inferior parietal cortex (BA 40), right precuneus (BA 7), right superior temporal gyrus (BA 42), left putamen, and right thalamus (Hart et al. 2013).

Studies have also shown involvement of the left hemisphere in attentional dysfunction in boys with ADHD with decreased activation of the left DLPFC (middle frontal gyrus, BA 46, 9, 8), superior parietal cortex (postcentral gyrus, BA 6, 4, 2, 1, 7), and subcortical structures involved in fronto-striatal loops (Christakou et al. 2013). Increased DLPFC activation appears to relate to sustained attention.

IMPULSIVITY

Impulsivity in ADHD, although appears to improve with age causes significant emotional and behavioral impairments in children and adults. Impulsivity often leads to poor academic and occupational performance as well as problematic interpersonal relationships. Indeed, it is associated with an elevated risk for substance abuse, cigarette smoking, road traffic accidents and antisocial behaviors and contacts with law enforcement agencies.

The neurobiological basis of impulsivity requires understanding of its association with changes in reward processing and behavioral inhibition. Failure of these processes appear to manifest as impulsivity.

fMRI studies have shown decreased activation of the right inferior frontal gyrus, right supplementary motor area (BA6) and anterior cingulate (BA 32), right fusiform gyrus (BA 19), left caudate head, and right thalamus during motor inhibition tasks (Go-NoGo or Stop signal tasks) in those with ADHD (Hart et al. 2013).

Neural regions activated in inadequate reward processing (involving reward evaluation and decision making) include, medial prefrontal cortex, medial orbitofrontal cortex, anterior cingulate, hippocampus, insula, amygdala, and ventral striatum or nucleus accumbens (Dally et al. 2011).

Individuals with ADHD, have been shown to have decreased activation within this network (Plichta & Scheres 2014).

HYPERACTIVITY

Hyperactivity, a common feature of ADHD, particularly in children, has been shown to be related to abnormalities in the motor systems such as poor motor inhibition. Reduced activity in primary motor cortex (BA4) as well as in sensory cortex during simple motor tasks in individuals with ADHD has been reported (Mostofsky et al. 2006).

Beside the well-known problems with attention, impulsivity and hyperactivity, several other cognitive dysfunctions as well as emotional dysregulation has been described in ADHD sufferers.

Additionally, it has been reported that there is also impairment of number of time-processing mechanisms (ie perceptual and motor timing) in ADHD.

These deficits in time-processing in ADHD are shown through reduced activation of bilateral inferior frontal gyrus, orbitofrontal cortex, SMA, precentral gyrus, insula, and cerebellum (Smith et al. 2008).

Large body of evidence suggests that there is dysregulation of neuromodulators, noradrenaline (NA) and dopamine (DA) in ADHD sufferers (Pliszka 2005).

To date methylphenidate (MPH), one of the commonly prescribed drug for ADHD has shown response rate of up to 80%. MPH increases the striatal and frontal activation capturing DA transporter. Number of other drugs (including, atomoxetine) are also used along with psycho-behavioural therapies for the management of symptoms in both children and adults with ADHD.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive and safe tool to investigate pathophysiological abnormalities in neuropsychiatric disorders. To put it simply, an alternating magnetic field is used to induce electric current, which leads to firing of action potentials in cortical neurons. TMS, first used to successfully modulate the neural activity of the human motor cortex was developed by Barker and colleagues in Sheffield, England in 1985 (Barker et al. 1985).

Within short period, TMS established itself as a useful investigative tool, utilized by neurophysiologists, neurologists and psychiatrists.

With further development, TMS machines were able to deliver repetitive stimulation of low and high frequencies (low frequency: ≤1 Hz, high frequency: >1Hz). Described as repetitive transcranial magnetic stimulation (also known as rTMS), it has led to exploration of therapeutic applications in number of neuropsychiatric disorders including, depression (Loo et al. 2005), bipolar affective disorder (Michael & Erfurth 2004), Obsessive compulsive disorder (Greenberg et 1997) and schizophrenia (Hoffman et al. 2000, Zaman et al. 2008).

The potential therapeutic effects in neuropsychiatric disorders depend upon the cortical regions being stimulated and their interconnectivity with other cortical areas as well as deeper regions of the brain. Furthermore, additional factors play a role which include, frequency and number of stimulations and the length of the period of stimulation.

There have been numerous studies that have yielded positive therapeutic results in treatment depression, which have led to approval of rTMS as clinical treatment by FDA in USA in 2008. Yet despite the fact that TMS was first successfully carried out in Sheffield, UK (Barker 1985), National Institute of Clinical Excellence (NICE) of UK have only very recently (2015) approved its therapeutic use in depression.

The use of TMS and rTMS in ADHD as investigative and therapeutic tool respectively has so far been somewhat limited when compared with its use in other neuropsychiatric disorders such as depression.

As an investigative tool, TMS has been used to demonstrate a delay in the maturation of the cortico-motoneuronal system in children with ADHD (Ucles 2000).

Furthermore, Moll and colleagues reported that ADHD children have significantly reduced intra-cortical inhibition with normal intra-cortical facilitation when compared with normal controls. They also reported this improved with treatment with methylphenidate (Moll et al. 2001).

In a study, comparing 49 children with and without ADHD, Gilbert and colleagues described use of TMS to measure short interval cortical inhibition (SICI) in the motor cortex. They showed reduction of mean SICI by 40% in children with ADHD, as well as a correlation with ADHD severity. These results led to suggestion by the authors that TMS could aid ADHD diagnosis, measure symptom severity as well as reflect upon motor skill development in children (Gilbert et al. 2011).

As described above, our current knowledge of neurobiology of ADHD symptomatology elucidated from the use of various neurophysiological (including TMS) and neuroimaging tools can be utilized to consider various neural circuits as potential target for rTMS in order to alleviate certain symptoms.

However, the published studies in therapeutic use of rTMS in ADHD lag far behind when compared with other neuropsychiatric disorders such as depression. In

addition, there appears to be limited use of current knowledge of neural circuitry involved in ADHD symptomatology partly due to technical difficulties in targeting certain neural regions and circuits.

One of the earliest description of therapeutic use of rTMS for ADHD was by Weaver and colleagues. They described randomized, sham-controlled, crossover study of 9 adolescents and adults with ADHD. The subjects undergoing the study received 10 Hz rTMS, for 10 sessions (2000 stimulation per session) over 2 weeks targeting their right Dorsolateral prefrontal cortex (DLPFC), which led to improvement of clinical global impression and the ADHD-IV scales. However, this positive result applied both to active and sham rTMS, therefore, suggesting that larger controlled studies were needed to see if there was indeed differences in effects of real and sham rTMS (Weaver et al. 2008).

Interestingly in the same year (2008), Niederhofer published a case report. He used low frequency rTMS (1Hz), for five days on the "impending scalp additional motor area", in ADHD subject and reported "significant improvement" that lasted 4 week. However, he also reported that the placebo control did not show any improvement (Niederhofer 2008).

Same author later published another case report, utilizing rTMS (low frequency, 1Hz, 1200 stim/day for five days) also applied on the "impending scalp in the motor additional area" of a patient suffering from combined type ADHD who was also receiving methylphenidate (MPH). Niederhofer reported significant improvement in hyperactivity, lasting for at least three weeks leading to reduction in eventual therapeutic dosage of MPH to 10 mg (Niederhofer 2011).

Bloch and co-investigators, in what was described as crossover, double blind, randomized, sham controlled pilot study evaluated the effect of single session of high frequency rTMS (real and sham) on the right prefrontal cortex of 13 adults with ADHD. They noted improvement in attention after 10 minutes with real rTMS, with no change in anxiety and mood measures. The sham rTMS had no effect (Bloch 2010).

Gomez and colleagues reported preliminary positive results (inattentiveness hyperactivity and impulsivity) having applied 1 Hz rTMS of 90% of the rest motor threshold over the left DLPFC in ten school-aged boys (ages 7–12) suffering from ADHD (Gomez et al. 2014).

It seems to be clear that currently our knowledge concerning the utilization of TMS/rTMS as investigative and therapeutic tool in ADHD is very much in its infancy.

Potentially we can utilise our current knowledge of various neural circuits/networks (such as lateral attentional network, medial reward-related network, and fronto-cerebellar time-processing network) involved in manifestation of common ADHD symptoms. Whilst current rTMS techniques allow access to lateral networks (attention), there are technical difficulties in modulating other networks.

Possible targets for modulation by rTMS include, dorsolateral prefrontal cortex (improving attention, emotional dysregulation and impulsivity), inferior frontal gyrus (improving behavioral inhibition and time estimation) and cerebellum (improving time processing, cognitive and affective symptoms), though stimulation of latter causes problems with tolerability due to neck muscles stimulation. Recent technical advances in rTMS have improved the possibility of stimulating medial cortical areas, thus potentially aiding improvement of impulsivity in ADHD.

CONCLUSIONS

Given above, there is great potential to use TMS as an investigative tool either on its own (for example as a diagnostic tool) or in combination with other tools (for example EEG, MRI, fMRI, DTI etc) in order improve our understanding of the neurobiology of ADHD.

As for further exploring the potential of rTMS as a therapeutic tool in ADHD, there is little doubt, that there is need for larger studies, utilizing standardised protocols (such as cortical regions being targeted, frequency of stimulation, number and length of stimulation sessions) as has been the case in many depression studies. Only then we could be in position to draw more satisfactory conclusions concerning the use of rTMS as potentially effective therapeutic option for ADHD.

Furthermore, studies are also needed to explore whether rTMS could also be used to augment current and newer ADHD medications in individuals described as treatment resistant.

Indeed, rTMS could also be used as an alternative treatment in those who either can not take medications (due to intolerance or serious side-effects) or in those who are not suitable for stimulant medications such as those with risk of abuse.

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