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ROLE OF TRANSCRANIAL MAGNETIC STIMULATION (TMS & rTMS) IN INVESTIGATION AND POSSIBLE TREATMENT OF IMPULSIVITY IN NEUROPSYCHIATRIC DISORDERS WITH ADHD AND BPD AS EXAMPLES

Rashid Zaman

SEPT & Dept of Psychiatry, University of Cambridge, Cambridge, UK

SUMMARY

Pathological Impulsivity is a crucial component of several neuropsychiatric disorders and is cause of significant observed distress and morbidity. Here I will take ADHD and Borderline Personality Disorder (BPD) as examples neuropsychiatric disorders with pathological impulsivity as an important component to describe the usefulness of TMS and repetitive TMS (rTMS) as an investigative tool as well as a potential therapeutic tool.

Key words: *impulsivity – ADHD - borderline personality disorder*

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Impulsivity has been described as "A predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or others" (Moeller 2001).

Impulsivity is equated with impatience and has cognitive, motor and non-planning component. Often there is sudden urge or drive that leads action which though mostly seen as irrational, can however, be beneficial.

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) describes several neuropsychiatric disorders and classifies these as impulse control conditions, which include, Pathological Gambling, Kleptomania, Pyromania, Trichotillomania, Intermittent Explosive Disorder, Impulse Control Disorders NOS, or those which include impulsive symptoms in the diagnostic criteria. Latter include, Attention Deficit Hyperactivity Disorder (ADHD), Antisocial and Borderline Personality Disorders, Bulimia Nervosa, Dementia, Mania, Neurological (Frontal Lobe) syndromes, Obsessive Compulsive Disorder and Substance Abuse Disorders.

Pathological impulsivity in neuropsychiatric disorders described above leads to impairment in quality of life and everyday functioning and therefore without doubt needs to be better understood and appropriately treated.

A number measures have been devised to assess and quantify impulsivity which include, State and Trait Measures, Self-Report rating measures, such as Barratt Impulsiveness Scale (Barratt 1965) and Eysenck Impulsiveness Questionnaire (Eysenck 1977). However, such measures can suffer from individual bias, and are often affected by how individual is feeling at time of being assessed and clearly are hard to relate to the underlying neurobiological basis of impulsivity.

In contrast, more objective computerized cognitive behavioural measures such as Go/No-Go, Stop Signal assessment linked to brain neuroimaging (Matthews 2006) and transcranial magnetic stimulation (TMS) (Sack 2003) are likely give better understanding of neurobiological basis of impulsivity.

Furthermore, selective pharmacological agents can be used to understand the underlying neurochemical basis of impulsivity (Robbins 2005).

Pathological impulsivity clearly plays a significant role in the morbidity associated with numerous neuropsychiatric disorders noted above.

Here I will take ADHD and Borderline Personality Disorder (BPD) as examples neuropsychiatric disorders with pathological impulsivity as an important component to describe the usefulness of TMS and repetitive TMS (rTMS) as an investigative tool as well as a potential therapeutic tool.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a disorder characterized by inattention, hyperactivity and impulsivity of sufficient magnitude to lead to problems both at home and at school (or work in case of adults. Indeed, clinically significant distress or impairment is observed in social, academic, or occupational functioning with long-term consequences that include, lower educational and vocational outcomes, increased risk for antisocial behaviour and drug misuse in adulthood. Not surprisingly, significant a number of young offenders have been found to suffer from ADHD.

ADHD has its origins in complex interplay of genetic and environmental factors. Evidence from imaging studies so far suggests abnormalities in the fronto-striatum- cerebellum circuit, mainly in the right side being responsible for most of the disturbed motor control and the abnormal sensory motor program. The attention deficits, impulsiveness and hyperactivity result from the disordered executive functions.

Some PET and fMRI studies in ADHD have shown atypical function of the fronto-striatal circuit, decreased blood flow in the striatum and prefrontal regions, decreased metabolism of frontal-cerebral circuits. Whilst, Evoked potential studies have shown smaller amplitude and longer latencies, which correlate with attentional dysfunction, steady state visual EP have strongly supported right frontal dysfunction in ADHD.

Alteration in Dopamine appears to be the main neurochemical change underlying these morphologic alterations. Stimulants such as Methylphenidate (MPH) are the most commonly prescribed drug for ADHD with response rate of 80%. MPH increases the striatal and frontal activation capturing DA transporter.

Borderline personality disorder

Borderline personality disorder, a common psychiatric disorder is characterised by a pervasive pattern of instability of mood/affect, poor impulse control, interpersonal relationship difficulties, poor self-image, emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies and brief psychotic episodes, making these patients frequent and often difficult to manage users of mental- health resources.

Neuroimaging studies have revealed presence of dysfunctional network of brain regions that appear to underpin many of the clinical symptoms (such as affective/mood instability and impulsivity) of borderline personality disorder. Dysfunctional fronto-limbic network consisting of the anterior cingulate cortex (ACC), the orbitofrontal and dorsolateral prefrontal cortex, the hippocampus, and the amygdala has been identified. Positron-emission-tomography (PET) studies have shown altered baseline metabolism in prefrontal regions including the ACC (De la Fuente 1997, Soloff 2003, Juengling 2003)

Dysfunctional serotonergic neurotransmission associated with disinhibited impulsive aggression noted in patients with Borderline Personality Disorder has also been described (Soloff 2000).

Jacob and colleagues (2013) by using go/no-go tasks with fMRI after induction of anger, joy or a neutral mood (by presentation of short stories) in patients with BPD, showed disturbance in amygdala-prefrontal network that was compensated by a subcortical loop involving the subthalamic nucleus, leading to normal behavioural inhibition (Jacob 2013).

More recently the dorsomedial prefrontal cortex (DMPFC) that can possibly be targeted with rTMS/rTMS has also been implicated (Downer 2012, 2013) in impulsive behaviour.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) has been established as non-invasive, safe and relatively cheap and accessible tool for investigating pathophysiology of number of neuropsychiatric disorders. Evidence has begun to build up for the detection of clinical and subclinical abnormalities in number of neuropsychiatric disorders including, ADHD and Borderline Personality Disorder (BPD).

TMS findings have demonstrated a delay in the maturation of the cortico-motoneuronal system in patients with ADHD (Ucles 2000). It has been reported that children with ADHD have significantly reduced intra-cortical inhibition (lCl) with normal intra-cortical facilitation when compared to normal controls, which improved with 10mg of MPH (Moll 2000).

Buchmann and co-investigators found that in children with ADHD the intra-cortical silent period (iSP)-latencies were significantly longer and their duration were shorter. They suggested that shortened duration of iSP in ADHD children could be explained by an imbalance of inhibitory and excitatory drive on the neuronal network (Buchmann 2003).

Hoeppner and colleagues (Hoeppner 2008) from their studies suggested that in the disturbed facilitatory and inhibitory motor circuits that were found in ADHD children could not be shown in adults with ADHD. They reasoned this was possibly due to a development-dependent normalization of motor cortical excitability (Hoeppner 2008).

Gilbert and co-investigators compared of the Inhibitory and Excitatory effects of ADHD medications Methylphenidate and Atomoxetine on Motor Cortex. They found, that in healthy adults, both stimulant and non-stimulant medications for ADHD decreased cortical inhibition and increased cortical facilitation and suggested that the cortical inhibition, shown previously to be abnormal in ADHD, was perhaps playing a key role producing behavioral pathology. (Gilbert et al. 2006).

With regards to repetitive TMS (rTMS) as a therapeutic tool, several studies over the last 2 decades have been carried out in depression with many positive results leading to its approval in clinical practice by the FDA in USA, as well as other countries.

Strafella an colleagues have shown that rTMS when applied to the left mid-dorsolateral prefrontal cortex (MDL-PFC) has led to the release of endogenous dopamine from the left caudate nucleaus as a consequence of direct corticostriatal axonal stimulation, increasing the extracellular DA concentration (Strafella 2001).

So far only 2 small studies have been reported where rTMS has been used for therapeutic purpose in ADHD.

Bloch and co-investigators, in their crossover double blind randomized, sham controlled pilot study showed positive effects of high frequency rTMS on attention in 13 adult ADHD patients (Bloch 2010),

Whilst, Niederhofer (2008), reported application low frequency rTMS (1Hz, 1200 stim/daily for five days) on the “impending scalp additional motor area”, in ADHD subjects with results showing a “significant improve-

ment" that lasted for at least 4 week, yet the placebo control did not show any improvement (Niederhofer 2008).

As is the case in ADHD, the number of reported studies utilizing TMS to investigate and rTMS to treat impulsive behaviour in BPD are rather few in number.

Barnow and colleagues (Barnow 2009) investigated different inhibitory and excitatory TMS parameters in 19 matched unmedicated female Borderline Personality Disorder (BPD) patients and 19 healthy control subjects. They found reduction in duration of cortical silent period (CSP) in BPD patients compared with healthy control subjects in the right cortex, suggesting deficit in intracortical inhibitions in BPD patients (Barnow 2009)

As for the use of rTMS to treat of symptoms of BPD, including pathological impulsivity, Arbabi and colleagues (Arbabi 2013), have reported success in one female patient with diagnosis of BPD. The patient received, 10 sessions of high-frequency TMS to left dorsolateral prefrontal cortex (DLPFC) along with pre and post TMS (immediate and one month later) along with functional imaging. They described an association with changes in brain activity with decrease in BPD severity as measured by BPD severity index as well as improvement in severity of depression and in impulsivity (Arbabi 2013).

In a study described as a pilot trial, Caihol and colleagues (Caihol 2014), reported a randomized, controlled study in which 10 BPD patients received series of 10 sessions of high-frequency rTMS to the right DLPFC. The rTMS treated group showed improvements in anger, affective instability, anger and planning (Caihol 2014).

Clearly there is limited published work on the use of TMS and rTMS to explore and treat pathological impulsivity in ADHD and in BPD patients.

Time is ripe for carrying out of well-designed studies combining neuropsychological tests with TMS and rTMS and other imaging modalities that would allow us not only a better understanding of pathological impulsivity but also add an additional therapeutic tool in form of rTMS.

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Correspondence:

Dr Rashid ZAMAN, BSc (Hons) MB BChir (Cantab) DGM MRCGP FRCPsych
Consultant Psychiatrist & Director BCMHR-CU, University of Cambridge,
Charles University, Prague
SEPT & Dept of Psychiatry, University of Cambridge
Cambridge, UK
E-mail: rz218@cam.ac.uk http://www.bcmhr-cu.org