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Invited review

Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders?

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ABSTRACT

Cognitive impairment is a core symptom of many neuropsychiatric diseases and a key contributor to the patient's quality of life. However, an effective therapeutic strategy has yet to be developed. Noninvasive brain stimulation techniques, namely transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are promising techniques that are under investigation for a variety of otherwise treatment-resistant neuropsychiatric diseases. Notably, these tools can induce alterations in neural networks subserving cognitive operations and thus may provide a means for cognitive restoration. The purpose of this article is to review the available evidence concerning cognitive enhancing properties of noninvasive brain stimulation in neuropsychiatry. We specifically focus on major depression, Alzheimer's disease, schizophrenia, autism and attention deficit hyperactivity disorder (ADHD), where cognitive dysfunction is a major symptom and some studies have been completed with promising results. We provide a critical assessment of the available research and suggestions to guide future efforts.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

While the characteristic symptoms and manifestations of the neurological and psychiatric diseases are very different from each other, cognitive impairment remains a core feature shared by a large number of neuropsychiatric disorders and an important indicator of clinical outcome. Because intact cognition is essential for daily functionality and independence, the degree of impairment in higher cognitive functions is a critical factor that has vast impact on the general quality of life and disease related disability. Accordingly, establishment of effective therapies capable of cognitive restoration and enhancement in neuropsychiatric diseases is crucial.

Noninvasive brain stimulation techniques, namely transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), provide means to alter brain activity in specific brain regions and mold plasticity at the network level (Pascual-Leone et al., 2005). Therapeutic utility of these interventions is currently under investigation for several refractory neuropsychiatric diseases with promising results. For example, the Neuronetics TMS device and Neurostar treatment protocol was cleared by the US Food and Drug Administration in October 2008 for the treatment of some patients with medication-resistant depression; the use of TMS for suppression of treatment-refractory auditory hallucinations in schizophrenia has been endorsed by the National Institute of Mental Health (NIMH) Schizophrenia Patient Outcomes Research Team (PORT) (Buchanan et al., 2010); and various companies are actively pursuing the use of TMS or tDCS in Alzheimer's Disease.

Most studies to date have not focused on cognitive restoration or enhancement. However, in most trials cognitive tests were included to assess the safety of noninvasive brain stimulation. Here, we review the cognitive after-effects of noninvasive brain stimulation in a number of neuropsychiatric diseases where cognitive

Abbreviation: NIBS, noninvasive brain stimulation.

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dysfunction is a major symptom, focusing on the question of whether TMS and tDCS can enhance specific cognitive skills. An extensive literature search was conducted in the Web of Science and PubMed databases and the English-language articles were located using the following search terms: 'repetitive TMS' or 'rTMS', 'tDCS', 'transcranial direct current stimulation', 'TBS', 'theta burst stimulation' and 'depression' or 'depressive disorder', 'schizophrenia', 'Alzheimer', 'ADHD', 'attention deficit hyperactivity disorder', 'autism', 'ASD', 'asperger' and 'cognition' or 'cognitive', 'neuropsychological test', 'psychology'. The prospective studies on human subjects until March 2012 were included provided that they performed multiple sessions of rTMS, tDCS or TBS and investigated the cognitive effects of an offline paradigm. We present a comprehensive summary of the identified studies, which provide evidence concerning the ability of noninvasive brain stimulation to act as a cognitive enhancer in these neuropsychiatric disorders, and offer suggestions for future investigations targeting therapeutic neuromodulation of cognition in these patient populations.

2. Noninvasive brain stimulation

2.1. Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a major tool used in the field of non-invasive brain stimulation since its introduction by Barker and colleagues in 1985 (Barker et al., 1985). TMS operates on Faraday's principle of electromagnetic induction by which the transmission of a large, brief pulse of current through loops of copper wire (i.e. magnetic coil) give rise to a fluctuating magnetic field perpendicular to the plane of the coil that subsequently induces an orthogonal electric field. In this way, the magnetic field is used to penetrate highly resistant structures, such as the skull, while the electric field generates secondary currents leading to neuronal activation (Kobayashi and Pascual-Leone, 2003; Hallett, 2007; Wagner et al., 2007). The exact point of stimulation will occur at the location of the maximum spatial derivative of the electric field; i.e. where the intensity of the electric field maximally changes as a function of distance, or where the field encounters a structure with low depolarization threshold (e.g. a bend in the path of neuronal fiber tracts) (Kobayashi and Pascual-Leone, 2003).

TMS provides a means to measure and modulate the excitability of corticocortical and corticospinal pathways (Pascual-Leone et al., 1998; Fitzgerald et al., 2006a) and is commonly applied to the motor cortex of humans to induce target muscle activation that can be electrophysiologically recorded as motor evoked potentials (MEPs). TMS applied as a pair of pulses (paired-pulse TMS) separated by a given time interval further allows for the assessment of more cortical-specific excitability (Chen et al., 1998; Kobayashi and Pascual-Leone, 2003) and several measures probing cortical inhibition, namely short-interval intra-cortical inhibition (SICI) (Kujirai et al., 1993), long-interval intracortical inhibition (LICI) (Valls-Solé et al., 1992) and cortical silent period (CSP) (Cantello et al., 1992), which may provide key information regarding $GABA_A$ and $GABA_B$ functioning. Both single and paired-pulse TMS measures have been evaluated in various neuropathologies, such as epilepsy, stroke, and traumatic brain injury, underscoring their great potential to contribute to the realm of clinical diagnostics (Kobayashi and Pascual-Leone, 2003; Rotenberg, 2010; Demirtas-Tatlidede et al., 2012). TMS not only allows for the assessment of cortical excitability, but when applied in a repetitive paradigm, known as repetitive transcranial magnetic stimulation (rTMS), it can be used to evaluate and guide neuronal plasticity. rTMS enables the use-dependent modulation of brain excitability via mechanisms related to long-term potentiation (LTP) and long-term depression (LTD) (Ziemann et al., 2001; Hoogendam et al., 2009). These effects last beyond the train of stimulation itself and may be affected by the magnitude and duration of stimulation as well as the state of activity in the stimulated brain region (Silvanto and Pascual-Leone, 2008). Presumably, these after-effects represent changes in neuronal plasticity, which can have immense therapeutic potential in neuropsychiatric diseases that feature over- or under-activation of brain regions (Fregni and Pascual-Leone, 2007; Miniussi et al., 2008; Schönfeldt-Lecuona et al., 2010).

Repetitive TMS protocols are defined by the frequency and pattern of stimulation. In most subjects, low frequency (i.e. 0.2–1 Hz) rTMS leads to reduction of excitability in the targeted cortical region, while higher frequency (5–20 Hz) frequently enhances brain excitability (Hallett, 2007). In the context of cognition, it is important to note that high frequency rTMS increases the GABA-mediated cortical inhibition (SICI) and silent period duration (Daskalakis et al., 2006). This neurophysiological effect is proposed to underlie the cognitive facilitating effects of rTMS because mental performance and cognitive functioning have been linked to cortical inhibitory processes and synchrony of the neural activity, which largely depend on GABAergic interneurons. One other form of rTMS, known as theta burst stimulation (TBS), was designed to mimic traditional paradigms of LTP and LTD induction in *ex vivo* models (Huang et al., 2005). TBS consists of 3 pulses at 50 Hz repeated at 200 ms intervals. When applied intermittently (iTBS) cortical excitability can be enhanced, while application in a continuous fashion (cTBS) results in suppression of excitability. These effects of TBS are more prominent and longer lasting than those induced by conventional trains of rTMS.

While the neurobiological substrates of rTMS effects remain insufficiently understood, human and animal models are providing valuable insights. Acute, transient changes in neuronal activity resulting from TMS appear to be secondary to shifts in the ionic equilibrium around cortical neurons or the storage of charge directly from stimulation (Ridding and Rothwell, 2007). More lasting effects, however, are considered to occur via use-dependent mechanisms of plasticity, including synaptic modifications, i.e. LTP and LTD. Huang et al. (2007) demonstrated the occlusion of both the facilitatory and inhibitory forms of TBS with a NMDA receptor antagonist, memantine. Teo et al. (2007) further validated the dependency of TBS after-effects on NMDA receptor activity, when they showed that iTBS effects could be reversed in the presence of the NMDA receptor partial agonist, D-cycloserine (Teo et al., 2007; Cardenas-Morales et al., 2010). However the unpredictable direction of the effects of D-cycloserine in this case suggests that the after-effects of TBS may be the result of simultaneous excitatory and inhibitory processes, which may behave asymmetrically when pharmacologically challenged (Teo et al., 2007). Stagg et al. (2009) subsequently showed, using magnetic resonance spectroscopy, that cTBS induces increased GABAergic interneuronal activity suggesting a process of LTD, dependent upon both NMDA and GABAergic inputs. Further support for the role of GABAergic interneuronal activity comes from the robust effects of iTBS and cTBS on measures of intracortical inhibition; namely, short-interval intracortical inhibition (SICI) (Suppa et al., 2008). It is also interesting to note that the theta-frequency of TBS matches the duration of cortical $GABA_B$ inhibition making it plausible that TBS may promote the up-regulation of excitatory synaptic connections (i.e. LTP) by reducing the efficacy of inhibitory cortical inputs (Thickbroom, 2007). Through animal experiments, Tokay et al., 2009 sought to replicate the classic *in vitro* hippocampal slice preparation for tetanic induction of LTP with the substitution of high-frequency magnetic stimulation (HFMS) for the tetanic electrical stimulus. They found that HFMS was indeed capable of inducing hippocampal LTP, a process reversible by the NMDA antagonist, AP5.

Human studies using rTMS/EEG paradigms have further alluded to the potential mechanisms of rTMS induced long-lasting