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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

after-effects with cortical oscillations playing an important role. Cortical oscillatory activity occurs in a number of frequency bands, including delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz) (Sokhadze et al., 2009). This activity can be evaluated via measures of event related power, a function of regional oscillatory activity, and event related coherence, a reflection of interregional connectivity. These synchronized oscillations are molded by GABAergic interneurons, which play key role in sustaining the control of the neural cell firing and the gating of information. A number of reports have shown acute alterations in this cortical oscillatory activity in the setting of rTMS. Fuggetta et al. (2008) showed that 5 Hz rTMS applied to the left primary motor cortex could achieve synchronization of cortical oscillations in the alpha and beta frequency domains. This work served as a demonstration of the effect of rTMS on regional and interregional synaptic transmission via the induction of cortical oscillations. More recent work by Azila Noh and Fuggetta (in press) demonstrated broader effects of high frequency rTMS (11 Hz) on theta, mu, and beta frequency bands. Sokhadze et al. (2009) further applied these techniques to demonstrate the potential therapeutic benefit of rTMS in autism to provide a means of altering neuronal plasticity through a presumed mechanism of enhanced cortical gamma oscillations. Altogether these findings support TMS as a tool for *in vivo* real-time evaluation and manipulation of neuronal plasticity via mechanisms of LTP and LTD.

Extensive research in the last decade has provided considerable evidence that rTMS is reasonably safe with mild side effects when performed in compliance with the recommended safety guidelines (Wassermann, 1998; Rossi et al., 2009). Most frequent side effects include mild headache responsive to common analgesics, local pain or paresthesias in the stimulated region, neck pain, tooth pain, transient changes in audition and syncope (Machii et al., 2006). Induction of a seizure is a possible serious adverse effect, but is a very rare phenomenon when the investigators strictly adhere to the recommended guidelines (Machii et al., 2006; Rossi et al., 2009).

The heterogeneity of individual responses to TMS appears certainly multifactorial, but has interestingly been linked to some genetic polymorphisms in genes crucial to the processes of neuronal plasticity. Kleim et al. (2006) looked at healthy subjects with a Val66Met polymorphism (rs6265) in the brain-derived neurotrophic factor (BDNF) gene, which leads to reduced BDNF expression, and found reduced motor cortical plasticity in response to training (Bramham and Messaoudi, 2005). It is possible that these polymorphisms may also lead to maladaptive plasticity in development, aging, and neuronal injury (Pascual-Leone et al., 2011). Another candidate, which may influence the network plasticity is the apolipoprotein E susceptibility gene located on chromosome 19. As we gain further insight from pharmacogenomic studies the refinement of therapeutic interventions based upon genetic screening may soon be commonplace.

### 2.2. Transcranial direct current stimulation (tDCS)

Another major tool in the realm of non-invasive brain stimulation is tDCS. tDCS modulates brain excitability via the application of low-amplitude (0.5–2 mA) direct current through scalp electrodes (Wagner et al., 2007; Nitsche et al., 2003a). This current, through its effects on resting membrane potentials, can lead to increased or decreased neuronal excitability depending upon the polarity and spatial arrangement of the electrodes. Earlier reports by Nitsche and colleagues demonstrated the capacity of tDCS to modulate motor cortical excitability (Nitsche and Paulus, 2000). Anodal tDCS is capable of enhancing excitability as evaluated by TMS-elicited MEP amplitudes. Generally, cortical excitability is increased under the tDCS anode and decreased under the cathode. tDCS provides a unique stimulation paradigm that influences spontaneous neuronal activity as opposed to directly causing neuronal activation as with TMS and transcranial electrical stimulation (TES) (Wagner et al., 2007). The duration of tDCS after-effects outlasts the stimulation and is largely a function of the intensity and duration of tDCS application (Nitsche and Paulus, 2001). Additional reports suggest that weekly repeated tDCS sessions might further increase the duration of its effects on behavioral outcomes (Boggio et al., 2007a).

Short-term effects of tDCS are thought to occur via non-synaptic mechanisms by depolarization of resting membrane potentials (Nitsche et al., 2003a; Priori, 2003). Long-term effects are believed to occur through NMDA-dependent mechanisms, similar to LTP and LTD. Liebetanz et al. (2002) tested the dependence of tDCS on glutamatergic signaling and changes in membrane potential. They found that dextromethorphan, a NMDA antagonist, could occlude the after-effects of either polarity of stimulation while carbamazepine, a sodium channel blocker, impaired only the anodal effects, suggesting a more specific reliance upon membrane potential depolarization for the tDCS under the anode (Liebetanz et al., 2002; Priori, 2003). Together these data suggest that the after-effects of tDCS may be consistent with use-dependent synaptic plasticity; i.e. LTP and LTD. Furthermore, reports have demonstrated its utility in the facilitation of several cognitive domains, such as implicit motor learning and visuo-motor learning (Antal et al., 2004; Nitsche et al., 2003b), indicating its potential for modulation of behavior through modulation of neurotransmitter-dependent plasticity on the network level.

The safety profile of tDCS is quite favorable, as many studies have failed to demonstrate lasting adverse effects. Nitsche and Paulus measured neuron specific enolase (NSE), a marker of neuronal injury, following up to 13 min of 1 mA tDCS and demonstrated no change in NSE levels (Nitsche and Paulus, 2001). Commonly reported adverse effects include fatigue (35%), mild headache (11.8%), nausea (2.9%), and a transient tingling, itching, and/or redness in the region of stimulation (Nitsche et al., 2003c; Poreisz et al., 2007). Measurements related to the safety of electrical stimulation include the current density ($A/cm^2$), total charge ($C/cm^2$), charge per phase ($\mu C$), and charge density ($\mu C/cm^2$). However, without an established criterion specifically for maximum stimulation amplitude, the establishment of an objective safety threshold has been difficult to define.

Combination of tDCS with other interventions can be achieved with relative ease given the highly portable nature of tDCS devices and simplicity of application. To date, a number of studies have looked at the utility of tDCS-induced neuronal modulation coupled with physical and occupational rehabilitation (Lindenberg et al., 2010). Overall, tDCS has a number of properties that make it well suited for translational clinical applications in cognitive rehabilitative settings. As we gain further insight into its actions on neuronal plasticity and its underlying pharmacology, tDCS holds great potential to enhance functional improvements beyond our current means when integrated with traditional methods for rehabilitation, cognitive therapy, psychotherapy, or computer-based and gaming interventions.

## 3. Noninvasive brain stimulation for cognitive enhancement in neuropsychiatric disorders

### 3.1. Depression

Major depression is a mood disorder characterized by affective, behavioral and cognitive dysfunction. Functional neuroimaging studies in depression generally demonstrate reduced activity in prefrontal cortex, especially in, left more so than right, Brodman

areas BA 9 and BA 46 (Fitzgerald et al., 2006b), and abnormal activation in a cortico-subcortical network, which comprises the subgenual and anterior cingulate cortices. As such, the rationale of initial rTMS studies was to increase the activity over the left dorsolateral prefrontal cortex (DLPFC) using high frequency rTMS (Pascual-Leone et al., 1996). The acute and long-term antidepressant efficacy of this approach has been subsequently confirmed by numerous trials (O'Reardon et al., 2007; Demirtas-Tatlidede et al., 2008; for a review see Schönfeldt-Lecuona et al., 2010). Further, decreasing right DLPFC activity via low frequency rTMS has also been tested and found to be effective, presumably due to increased activity in the left DLPFC by way of transcallosal connections. These two approaches presently appear to promote the reestablishment of the balance in malfunctioning bi-hemispheric networks.

A number of randomized, sham-controlled trials (RCT), which primarily aimed to investigate the antidepressant efficacy of rTMS, also looked into the effects of rTMS on cognitive performance (Avery et al., 1999, 2006; Padberg et al., 1999; Loo et al., 2001; Moser et al., 2002; Höppner et al., 2003; Loo et al., 2003; Hausmann et al., 2004; Mosimann et al., 2004; Januel et al., 2006; Janicak et al., 2008; Mogg et al., 2008; Schutter et al., 2010) (Table 1). Among these 13 trials, 8 did not report significant differences between active- and sham-rTMS groups in regards to cognitive functions (see table for details of the rTMS protocols). Of note, one of these trials (Avery et al., 1999) reported improvement in several of the administered cognitive tasks, however, the sample size was very small and none of these effects reached statistical significance.

Two RCTs studies reported improvements in verbal memory (Padberg et al., 1999; Hausmann et al., 2004). Padberg et al. (1999) compared the efficacy of high frequency and low frequency rTMS over the left DLPFC with sham controls and the cognitive improvement was detected following high frequency stimulation of the DLPFC. Hausmann et al. (2004) also reported an improvement in verbal memory after pooling two active treatment groups (left DLPFC 20 Hz rTMS, and left 20 Hz combined with right 1 Hz DLPFC rTMS).

Moser et al. (2002) conducted a RCT specifically focused on cognition with the hypothesis that active rTMS would result in significant changes in executive function compared to sham rTMS in patients with depression. Elderly patients with a mean age of 60 underwent 5 consequent sessions of 20 Hz rTMS targeting the anterior portion of the middle frontal gyrus using neuronavigation. The real rTMS group showed a significant improvement in a specific aspect of executive functioning (Trail making-B) regardless of changes in mood. Höppner et al. (2003) used the other approach and found a main effect of real TMS condition vs. sham on psychomotor speed and concentration when stimulation was applied at 1 Hz over the right DLPFC.

More recently, Schutter et al. (2010) used a different paradigm in a double-blind, sham-controlled study and tested the efficacy of 10 sessions of 2-Hz rTMS over the right parietal cortex in patients with depression. Real rTMS resulted in significantly higher sensitivity for recognizing angry facial expressions over sham rTMS. Further, this effect showed correlation with the percentage decrease in depression scores, providing support for the cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment.

Regarding depression in the context of other neurological diseases, two randomized, sham-controlled studies have been performed. Jorge et al. (2004) investigated the effects of 10 sessions of 10 Hz rTMS applied over the left DLPFC in patients with post-stroke depression. While the authors reported a trend towards general cognitive improvement, there were no significant effects between active and sham groups. In the same way, Boggio et al. (2005) performed 10 sessions of rTMS over the left DLPFC to treat depression in patients with Parkinson's disease, and specifically investigated the cognitive effects. The authors compared the effects of real 15 Hz rTMS and placebo drug with sham TMS and fluoxetine. Both groups showed antidepressant benefits, and improvements in executive functions and visuospatial ability domains and no difference were detected between the two groups. The authors concluded that rTMS could improve cognitive functions similar to fluoxetine in Parkinson's disease.

ECT is a well-established therapy for medication-resistant depression, which may result in cognitive worsening, especially in the domain of memory. Five studies compared the cognitive side effects of rTMS and ECT in patients with refractory depression and all these studies applied 10 Hz rTMS to the left DLPFC between 90 and 110% MT intensities (O'Connor et al., 2003; Schulze-Rauschenbach et al., 2005; Rosa et al., 2006; Eranti et al., 2007; McLoughlin et al., 2007). Three of these studies found no deleterious effect of rTMS on cognitive functions (Rosa et al., 2006; Eranti et al., 2007; McLoughlin et al., 2007). The remaining studies reported cognitive improvements. O'Connor et al. (2003) detected mild improvements in working memory and retrograde memory in the rTMS group. Schulze-Rauschenbach et al. (2005) reported cognitive improvements in measures of long-term memory recall or recognition and the subjective memory rating following rTMS, while no changes were present for non-memory measures. Specifically, this study performed two or three rTMS sessions per week with a mean of 10.8 treatments, in an attempt to make ECT and rTMS frequencies comparable.

With respect to non-controlled studies, we identified 2 intra-individual cross-over studies, both of which specifically focused on the cognitive side effects of 10 consecutive sessions of 20 Hz rTMS and 1 Hz rTMS over the left DLPFC (Little et al., 2000; Speer et al., 2001). No cognitive decline was present in either study. Little et al. (2000) reported an improvement in list recall following both 20 Hz and 1 Hz rTMS stimulation, whereas Speer and colleagues did not find any significant differences between 20 Hz, 1 Hz and sham stimulation. A randomized double-blind study by Fitzgerald et al. (2009) compared the antidepressant effects of high frequency rTMS over the left DLPFC and low frequency rTMS over the right DLPFC. The authors applied 15 sessions of rTMS over three weeks with an option to cross over to the other treatment type if the antidepressant effect was $<30\%$; 8 patients crossed over to the other active treatment. They reported an improvement in immediate verbal memory and verbal fluency, independent of the type of TMS received. In another randomized double-blind study, Shajahan et al. (2002) investigated the cognitive effects of 20 Hz, 10 Hz and 5 Hz rTMS applied over the left DLPFC. Following 10 days of stimulation, the pooled data revealed improvements in digit span forward and a sub-item of Test of Everyday attention.

With regard to open studies, all of the open studies investigating the cognitive effects of rTMS in depression stimulated the left DLPFC via high frequency rTMS (Triggs et al., 1999; Martis et al., 2003; Fabre et al., 2004; O'Connor et al., 2005; Kuroda et al., 2006; Bloch et al., 2008; Vanderhasselt et al., 2009; Holtzheimer et al., 2010; Harel et al., 2011, in press; Leyman et al., 2011). Notably, most of these trials reported improvements in one or more cognitive domains. These domains comprise verbal fluency (Triggs et al., 1999; Fabre et al., 2004), attentional control (Vanderhasselt et al., 2009), reaction time (O'Connor et al., 2005; Bloch et al., 2008; Vanderhasselt et al., 2009), executive functions/working memory (Martis et al., 2003; Bloch et al., 2008), procedural learning (O'Connor et al., 2005), language (Triggs et al., 1999), memory (Triggs et al., 1999; Martis et al., 2003; Fabre et al., 2004; Kuroda et al., 2006,), motor speed (Martis et al., 2003), global cognitive functioning (Holtzheimer et al., 2010) and emotional processing (Leyman et al., 2011) (see Table 1 for details).

Finally, in regards to tDCS, five studies have searched for long-term cognitive effects in patients with depression. Fregni et al. (2006) administered 5 daily sessions of tDCS at 1 mA with the

**Table 1**
Noninvasive brain stimulation studies investigating cognitive after-effects in depression.

| Study | N<br>design | Stimulation site | Stimulation intensity/frequency | # Sessions/time | Cognitive measures | Cognitive enhancement |
|---|---|---|---|---|---|---|
| *rTMS* | | | | | | |
| Avery et al., 1999 | 4/2<br>RCT | L DLPFC | 1. 80% MT, 10 Hz | 10/16 days | Digit span, digit symbol, RVLT, COWAT, TMT A/B, Stroop | No effect |
| Padberg et al., 1999 | 6/6/6<br>RCT | L DLPFC | 1. 90% MT, 10 Hz<br>2. 90% MT, 0.3 Hz<br>3. Sham | 5/1 week | Verbal learning task, three (simple, choice, paradoxical choice) reaction tasks | Verbal memory (verbal learning task, 10 Hz group) |
| Triggs et al., 1999 | 10<br>open | L DLPFC | 1. 80% MT, 20 Hz | 10/2 weeks | HVLT, Digit span F/B, COWAT, BNT | Verbal fluency (immediate and at 3 months); language, memory (3 months) |
| Little et al., 2000 | 10<br>crossover | L DLPFC | 1. 80% MT, 20 Hz<br>2. 80% MT, 1 Hz | 10/2 weeks | BSRT, Colorado Neuropsychological battery, CPT | Verbal recall (in both groups) |
| Loo et al., 2001 | 9/9<br>RCT | L DLPFC | 1. 110% RMT, 10 Hz<br>2. Sham | 10/2 weeks<br>20/4 weeks | RVLT, Verbal fluency, VPAL, MMSE, TOL, Digit span F/B, AMI | No effect |
| Speer et al., 2001 | 18<br>crossover | L DLPFC | 1. 100% MT, 20 Hz<br>2. 100%, 1 Hz<br>3. Sham | 10/2 weeks | Verbal fluency, CPT, Colorado Neuropsychological battery, BSRT | No effect |
| Moser et al., 2002 | 9/10<br>RCT | Ant. middle frontal gyrus | 1. 80% MT, 20 Hz<br>2. Sham | 5/1 week | TMT A/B, Digit symbol, Stroop, COWAT, BNT, RVLT, JLO | Executive function (TMT B) |
| Shajahan et al., 2002 | 15<br>RDB | L DLPFC | 1. 80% MT, 20 Hz<br>2. 80% MT, 10 Hz<br>3. 80% MT, 5 Hz | 10/2 weeks | AVLT, Digit span F/B, Digit symbol, Verbal fluency, Test of everyday attention, Traffic lights test | Attention (test of everyday attention, digit span F) |
| Höppner et al., 2003 | 10/10/10<br>RCT | L DLPFC<br>R DLPFC | 1. 90% MT, 20 Hz<br>2. 110% MT, 1 Hz<br>3. Sham | 10/2 weeks | d2 test | Concentration, psychomotor speed (1 Hz group) |
| Martis et al., 2003 | 15<br>open | L DLPFC | 1. 110% MT, 10 Hz | 10/2 weeks<br>20/4 weeks | Reaction time (simple, choice), Stroop, Verbal fluency, Letter-number span, Visual reproduction/ logical memory (WMS-R), Grooved pegboard, Squire | Working memory-executive function, objective memory, fine motor speed |
| Loo et al., 2003 | 9/10<br>RCT | L&R DLPFC | 1. 90% RMT, 15 Hz<br>2. Sham | 15/3 weeks | MMSE, VPAL, RVLT, TOL, COWAT, Expanded paired association test | No effect |
| O'Connor et al., 2003 | 14/14<br>open | L DLPFC | 1. 90% MT, 10 Hz<br>2. ECT | 10/2 weeks | Letter-number, RVLT, TNET | Working memory, retrograde memory |
| Fabre et al., 2004 | 11<br>open | L DLPFC | 1. 100% MT, 10 Hz | 10/2 weeks | GBVL, Verbal fluency, TMT A/B, Hive test, Digit span F/B, MMSE | Verbal fluency, visual learning (Hive test delayed recall) |
| Jorge et al., 2004 | 10/10<br>RCT | Left PFC (middle frontal gyrus) | 1. 100% MT, 10 Hz<br>2. Sham | 10/2 weeks | MMSE, TMT A/B, Stroop, COWAT, RVLT, BVRT, BNT, Token Test, Block design, Line Bisection Test | No effect |
| Hausmann et al., 2004 | 12/13/13<br>RCT | L DLPFC<br>L DLPFC&R DLPFC | 1. 100% MT, 20 Hz<br>2. 100% MT, 20Hz + 120% MT, 1 Hz<br>3. Sham | 10/2 weeks | MVG, TMT A/B, Stroop, COWAT, Verbal fluency | Verbal memory encoding (pooled active groups) |
| Mosimann et al., 2004 | 12/12<br>RCT | L DLPFC | 1. 100% MT, 20 Hz<br>2. Sham | 10/2 weeks | MMSE, Verbal learning task, Verbal fluency, TMT A/B, Stroop | No effect |
| Schulze-Rauschenbach et al., 2005 | 16/14<br>SB | L DLPFC | 1. 100% MT, 10 Hz<br>2. ECT | 2–3 per week, Total #: 10.8 | AVLT, Memory for Persons Test, AMI, Four-card task, Squire, MMSE, TMT A/B, Digit span F/B, Letter-number span, Verbal fluency | Memory (improvement in long-term memory recall and recognition) |
| O'Connor et al., 2005 | 19<br>open | L DLPFC | 1. 110%, 10 Hz | 10/2 weeks | SRTT | Response speed, procedural learning |
| Boggio et al., 2005 | 13/12<br>RCT | L DLPFC | 1. 110%, 15Hz + placebo drug<br>2. Sham rTMS + fluoxetine | 10/2 weeks | TMT B, WCST, COWAT, Stroop, HVOT, colored progressive matrices, Digit span F/B | Executive functions, visuospatial ability (Stroop, WCST, Hooper, both groups) |
| Avery et al., 2006 | 35/33<br>RCT | L DLPFC | 1.110%, 10 Hz<br>2. Sham | 15/4 weeks | RVLT, Digit Symbol Test, Digit span F/B, TMT A/B, MMSE, COWAT, Stroop, GOAT | No effect |
| Kuroda et al., 2006 | 9<br>open | L DLPFC | 1. 100%, 10 Hz | 10/2 weeks | MMSE, visual memory, verbal memory, TMT A/B | Verbal memory |

**Table 1** (*continued*)

| Study | N<br>design | Stimulation<br>site | Stimulation<br>intensity/frequency | # Sessions/time | Cognitive measures | Cognitive enhancement |
|---|---|---|---|---|---|---|
| Rosa et al., 2006 | 20/15<br>RSB | L DLPFC | 1. 100%, 10 Hz<br>2. ECT | 20/4 weeks | Vocabulary, cubes (WAIS-R), Digit span F/B, Rivermead Behavioral Memory Test | No effect |
| Januel et al., 2006 | 11/16<br>RCT | R DLPFC | 1. 90%, 1 Hz<br>2. Sham | 16/4 weeks | GBVL, Stroop, TMT A/B, Auditory visual attention span, Verbal fluency | No effect |
| Eranti et al., 2007 | 24/22<br>RSB | L DLPFC | 1. 110%, 10 Hz<br>2. ECT | 15/3 weeks | CAMCOG | No effect |
| McLoughlin et al., 2007 | 24/22<br>RSB | L DLPFC | 1. 110%, 10 Hz<br>2. ECT | 15/3 weeks | CAMCOG | No effect |
| Janicak et al., 2008 | 1. 165/160, RCT<br>2. 92, open<br>3. 53, open | L DLPFC | 1. 120% RMT, 10 Hz<br>2. Sham | 1. 26.3/6 weeks<br>2. 28.5/6 weeks<br>3. 19.9/6 weeks | MMSE, BSRT, AMI | No effect |
| Bloch et al., 2008 | 9<br>open | L DLPFC | 1. 80%, 10 Hz (circular coil) | 14/3 weeks | CANTAB | Reaction time (immediate and at 1 month), planning (at 1 month) |
| Mogg et al., 2008 | 29/30<br>RCT | L DLPFC | 1. 110%, 10 Hz<br>2. Sham | 10/2 weeks | CAMCOG, MMSE, Digit span F/B, Digit symbol modalities, Grooved pegboard | No effect |
| Fitzgerald et al., 2009 | 16/11<br>RDB | L DLPFC<br>R DLPFC | 1. 100%, high frequency<br>2. 110%, low frequency | 15/3 weeks<br>20/4 weeks | Brief Visuospatial Memory Test, HVLT, digit span F/B, COWAT | Immediate verbal memory, verbal fluency |
| Vanderhasselt et al., 2009 | 15<br>crossover/open | L DLPFC | 1. 110%, 10 Hz (open) | 10/2 weeks | Task switching paradigm | Increased attentional control (decreased RT, open phase) |
| Schutter et al., 2010 | 14/14<br>RCT | R parietal cx | 1. 90%, 2 Hz<br>2. Sham | 10/2 weeks | Emotional facial recognition task | Higher sensitivity for angry facial expressions |
| Holtzheimer et al., 2010 | 14<br>open | L DLPFC | 1. 100%, 20 Hz | 15/2 days | Repeatable Battery for the Assessment of Neuropsychological Status | Global cognitive functioning (at 6 weeks) |
| Harel et al., 2011 | 19<br>open | L DLPFC | 1. 120%, 20 Hz | 20/4 weeks | CANTAB | No effect |
| Leyman et al., 2011 | 14<br>open | L DLPFC | 1. 110%, 10 Hz | 10/2 weeks | Negative affective priming task | Improved inhibitory control for negative information |
| Harel et al., in press | 29<br>open | L DLPFC | 1. 120%, 20 Hz | 20/4 weeks<br>18 weeks F-UP | CANTAB | No effect |
| *tDCS* | | | | | | |
| Fregni et al., 2006 | 9/9<br>RCT | *Anode:* L DLPFC (F3), *Cathode:* contralateral supraorbital region | 1 mA, 20 min | 5/1.5 weeks (alternate days) | MMSE, Symbol digit modalities, Digit span F/B, Stroop, 5 point test | Digit span F/B |
| Boggio et al., 2007b | 12/7/7<br>RCT | *Anode:* L DLPFC *Cathode:* right supraorbital region | 2 mA, 20 min | 10/2 weeks | Affective Go-no-go task | Greater number of correct responses for emotional content |
| Ferrucci et al., 2009 | 14<br>open | *Anode:* L DLPFC, *Cathode:* R DLPFC | 2 mA, 20 min | 10/2 weeks | Sternberg task<br>Word recognition task<br>Posner paradigm | No effect |
| Loo et al., 2010 | 20/20<br>RCT | *Anode:* L DLPFC, *Cathode:* lat. contralateral orbit | 1 mA, 20 min | 5 + 5/1.5 weeks (alternate days) | RVLT, TMT A/B, Digit span F/B, COWAT, SDMT | No effect |
| Loo et al., 2012 | 33/31<br>RCT | *Anode:* L DLPFC, *Cathode:* lat. contralateral orbit | 2 mA, 20 min | 15/3 weeks | RVLT, Digit Span F/B, Stroop, COWAT, Letter −Number Sequencing, SDMT, RT (simple and choice) | Attention, working memory (SDMT, acute effects after the first active tDCS, no after-effects following 3 weeks) |

**Abbreviations:** rTMS: repetitive transcranial magnetic stimulation, RCT: randomized sham-controlled trial, L: left, R: right, DLPFC: dorsolateral prefrontal cortex, MT: motor threshold, RVLT: Rey Auditory Verbal Learning Test, COWAT: Controlled Oral Word Association Test, TMT A/B: Trail making tests A and B, HVLT: Hopkins Verbal Learning Test, F/B: forward, backward, BNT: Boston naming test, BSRT: Buschke selective reminding test, CPT: continuous performance test, VPAL: visual paired associates learning, Squire: Squire Subjective Memory Questionnaire, MMSE: mini mental state examination, TOL: Tower of London, AMI: Autobiographical Memory Interview, JLO: Judgment of Line Orientation, RDB: randomized double-blind trial, AVLT: Auditory Verbal Learning Test, WMS-R: Wechsler memory scale-Revised, RVLT: Rey Auditory Verbal Learning Test, ECT: electroconvulsive therapy, GBVL: Grober and Buschke verbal learning, BVRT: Benton Visual Retention Test, TNET: Transient news events test, MVG: Muenchner Verbaler Gedaechtnistest, SB: single-blind trial, AMI: Autobiographical Memory Interview, SRTT: Serial reaction time task, WCST: Wisconsin card sorting test, HVOT: Hooper Visual Organization Test, GOAT: Galveston Orientation and Amnesia Test, RSB: randomized single-blind trial, WAIS-R: Wechsler intelligence scale-Revised, CAMCOG: Cambridge cognition examination, RT: reaction time, F-UP: follow-up, CANTAB: Cambridge Neuropsychological Test Automated Battery, tDCS: transcranial direct current stimulation, lat: lateral, SDMT: Symbol Digit Modalities Test.

anode placed over the left DLPFC. Upon the completion of 5 sessions, the authors reported an improvement in working memory as indexed by digit span-forward and -backward tests. Similarly, Boggio et al. (2007b) applied 10 sessions of tDCS at 2 mA with anodal stimulation placed over the left DLPFC. The authors tested an affective go-no-go task and reported an improved performance with increased correct responses for figures of positive emotional content. More recently, Loo et al. (2010) conducted two larger scale studies of tDCS in depression. The first one included 10 sessions of tDCS applied at 1 mA with anode placed over the left DLPFC in 40 patients with depression. The authors administered an inclusive neuropsychological battery comprising multiple domains and observed no change in cognitive performance after 10 sessions. In their second study, Loo et al. (2012) performed 15 sessions of tDCS in a series of 64 patients and used 2 mA using the same electrode positions. The authors reported an acute effect of tDCS on attention and working memory while no effect was detected upon completion of the sessions suggesting that administration of multiple tDCS sessions may not result in cumulative cognitive enhancing effects.

On the whole, the vast majority of the identified studies in depression were centered over the DLPFC. The initial choice of stimulating the Brodmann area 9/46 was based on the pathophysiological processes underlying the depressive symptoms (i.e. reduced cortical metabolism and/or abnormal neurotransmission), which may also interfere with cognition (Pascual-Leone et al., 1996; Fitzgerald et al., 2006b). This proposed location found wide acceptance by many others pursuing research on neuropsychiatric disorders, as abnormal functioning of the frontal-subcortical networks is consistently implicated in the majority of the neuropsychiatric diseases. Indeed, DLPFC is a critical region for cognition that is neuroanatomically connected with all other heteromodal regions of the cerebral cortex, unimodal areas in all the major sensory modalities and many paralimbic sectors (Mesulam, 2000a). Accordingly, DLPFC is involved in a large variety of cognitive domains comprising attention, memory, executive functions, psychomotor speed, and social cognition, making it a favorable therapeutic target with remarkable potential impact on cognition. Given these features, one would anticipate enhancement of several of these cognitive domains following excitatory stimulation of this region. However, the reviewed studies do not demonstrate such a substantial effect in all domains relevant to the function of DLPFC. Rather, improvements in verbal memory were more consistently reported than the others. It appears that specific neuropsychological realms (i.e. verbal learning, verbal memory and psychomotor speed) may be more closely related to clinical improvement than the other domains (Douglas and Porter, 2009). As such, verbal memory might be more responsive to rTMS-induced clinical improvement in depression and this effect might partly reflect normalization of the cortical metabolism or abnormal neurotransmission following the left DLPFC stimulation. The findings from the present review also suggest more variable improvements in psychomotor speed, attention, verbal fluency, executive function and working memory domains.

In the light of the presented data, noninvasive brain stimulation can be regarded as a valuable and promising technique for cognitive enhancement in depression. However, there are various unsettled factors, which will require considerable amount of systematical effort in the future work. While high frequency rTMS applied to the DLPFC currently appears to be the most promising cognitive enhancing technique, the application of different stimulation parameters (i.e. stimulation intensity, frequency and duration), possible differences in targeting and positioning of the coil, the use of limited neurocognitive measures and the open nature of most positive studies makes it difficult to draw clear indications from these reports as well as guide future study design and implementation. Additionally, factors affecting the individual response to noninvasive brain stimulation, such as the BDNF gene polymorphisms and the state-dependent modulation of stimulation (metaplasticity) have not been studied in any of these trials and will need to be considered in the future. The possibility to perform deeper cortical and subcortical stimulation, with specially designed coils, might enable the investigation of innovative stimulation paradigms pertinent to the pathophysiology and neurobiology of the cognitive decline. As such, neuronavigation may improve the efficacy and reproducibility of the induced cognitive effects. In general, benefits of noninvasive brain stimulation strategies may be optimized by successful incorporation of cognitive training and application of individually tailored therapies with the help of functional neuroimaging techniques. Further large-scale, sham-controlled trials should systematically investigate the duration and real-time utility of the induced cognitive improvements using more sensitive neurocognitive measures.

### 3.2. Schizophrenia

Schizophrenia is a disabling mental disorder that results in decreased daily functionality and poor quality of life due to the impairments in realms of reality, emotional functioning and multiple domains of cognition. Besides the characteristic positive (delusions, hallucinations, thought disorder, disorganized behavior) and negative (anhedonia, apathy, social withdrawal) symptoms of schizophrenia, profound cognitive deficits constitute a core disability. In fact, cognitive deficits may be predictors of outcome and particularly early indicators of disease, detectable even in individuals at risk (Green, 1996; Gold, 2004). The neural mechanisms underlying the cognitive deficits are still largely unknown and development of effective treatment alternatives to enhance cognition appear critical for patients with schizophrenia.

Initial rTMS studies in schizophrenia were primarily focused on the clinical efficacy of rTMS on the positive and negative symptoms of the disease. For positive symptoms (specifically auditory hallucinations), the goal was to inhibit the left temporoparietal cortex via 1 Hz rTMS, based on the rationale that increased temporal activity correlates with positive symptoms (for a review see Freitas et al., 2009). In regards to negative symptoms, numerous studies attempted to increase the activity in the left prefrontal region via high-frequency rTMS as this might regulate the dopamine release and ameliorate the negative symptoms. The cognitive effects of these approaches were investigated in several of these studies as a safety or secondary outcome measure.

Among numerous studies that targeted the negative symptoms, only five RCT assessed the cognitive effects (Novák et al., 2006; Mogg et al., 2007; Fitzgerald et al., 2008; Schneider et al., 2008; Mittrach et al., 2010) (Table 2). One of these studies reported a significant effect of rTMS in cognitive functions (Mogg et al., 2007). Mogg et al. applied 10 consecutive daily sessions of 10 Hz rTMS to the left DLPFC and reported a significant improvement in verbal learning in a series of patients with prominent negative symptoms.

In addition, two intra-individual crossover studies applied 10 sessions of 20 Hz rTMS to the left DLPFC (Rollnik et al., 2000; Huber et al., 2003) and tested 12 patients (8 male, 4 female). The authors initially failed to detect a significant effect of rTMS on cognition (Rollnik et al., 2000). However, when analyzed stratifying for gender, an improvement of visuomotor tracking was observed in females (Huber et al., 2003).

In regards to open studies, Sachdev et al. applied 20 sessions of 20 Hz rTMS to the left DLPFC and detected no improvement in cognitive functions (Sachdev et al., 2005). Two open studies targeted deeper frontal regions using special TMS coils. Cohen et al.

**Table 2**
Noninvasive brain stimulation studies investigating cognitive after-effects in schizophrenia.

| Study | N design | Stimulation site | Stimulation intensity/frequency | # Sessions /weeks | Cognitive measures | Cognitive enhancement |
|---|---|---|---|---|---|---|
| *rTMS* | | | | | | |
| Cohen et al., 1999 | 6 open | Bilateral PFC | 1. 80% MT, 20 Hz (butterfly coil) | 10/2 weeks | Block design, TMT A/B, verbal fluency, visual memory, verbal paired associates (WMS), WCST | Delayed visual memory |
| Rollnik et al., 2000 | 12 crossover | Dominant DLPFC | 1. 80% MT, 20 Hz 2. Sham | 10/2 weeks | Number connection test | No effect |
| d'Alfonso et al., 2002 | 9 open | 2 cm above T3 | 1. 80% MT, 1 Hz | 10/2 weeks | Auditory imagery test, RVLT, Token Test, verbal fluency, JLO, Line Bisection Test, Benton Visual Retention Test, Test for Facial Recognition | Auditory imagery test |
| Huber et al., 2003 | 12 crossover | Dominant DLPFC | 1. 80% MT, 20 Hz 2. Sham | 10/2 weeks | Number connection test | Visuomotor integration /psychomotor speed (NCT) in females |
| Sachdev et al., 2005 | 4 open | L DLPFC | 1. 90% MT, 15 Hz | 20/4 weeks | MMSE, Digit Span F/B, TMT A/B, Symbol-Digit coding, Verbal Fluency, WCST | No effect |
| Fitzgerald et al., 2005 | 17/16 RCT | Auditory TPC (TP3) | 1. 90% MT, 10 Hz 2. Sham | 10/2 weeks | HVLT, Verbal Fluency, Digit Span F/B, BVMT-R, Visuospatial Digit Span | No effect |
| Novák et al., 2006 | 8/8 RCT | L DLPFC | 1. 90% MT, 20 Hz 2. Sham | 10/2 weeks | AVLT, TMT A/B, ROCF, CPT | No effect |
| Mogg et al., 2007 | 8/9 RCT | L DLPFC | 1. 110% MT, 10 Hz 2. Sham | 10/2 weeks | Stroop, HVLT, COWAT, Grooved pegboard | Verbal learning, at 2 week follow-up |
| Fitzgerald et al., 2008 | 10/10 RCT | Bilateral DLPFC | 1. 110% MT, 10 Hz 2. Sham | 15/3 weeks | Stroop, COWAT, TMT A/B | No effect |
| Schneider et al., 2008 | 17/17/17 RCT | L DLPFC | 1. 110% MT, 10 Hz 2. 110% MT, 1 Hz 3. Sham | 20/4 weeks | WCST | No effect |
| Mittrach et al., 2010 | 20/15 RCT | L DLPFC | 1. 110% MT, 10 Hz 2. Sham | 10/2 weeks | TMT A/B, WCST, D2 attention task, KAI | No effect |
| Demirtas-Tatlidede et al., 2010 | 8 open | Cerebellar vermis | 1. 100% AMT, iTBS | 10/1 week | Verbal Fluency, symbol coding, TMT A/B, Auditory CPT, Letter-Number Span, Spatial Span, WCST, proverbs test, CVLT-II, ROCF, Grooved pegboard | Working memory (auditory CPT, spatial span), visual learning (ROCF, delayed organization), at 1 week follow-up |
| Levkovitz et al., 2011 | 15 open | Bilateral PFC (L > R) | 1. 120% MT, 20 Hz (H coil) | 20/4 weeks | CANTAB | Executive functions (SOC, spatial span, spatial working memory), sustained attention (rapid visual information processing, maintained after 2 weeks) |

**Abbreviations:** rTMS: repetitive transcranial magnetic stimulation, L: left, R: right, PFC: prefrontal cortex, MT: motor threshold, TMT A/B: Trail making tests A and B, WMS: Wechsler memory scale, WCST: Wisconsin card sorting test, DLPFC: dorsolateral prefrontal cortex, RVLT: Rey Auditory Verbal Learning Test, JLO: Judgment of Line Orientation, NCT: Number connection test, RCT: randomized sham-controlled trial, TPC: temporoparietal cortex, MMSE: mini mental state examination, F/B: forward, backward, HVLT: Hopkins Verbal Learning Test, BVMT-R: Brief Visuospatial Memory Test Revised, AVLT: Auditory Verbal Learning Test, ROCF: Rey-Osterrieth Complex Figure, CPT: Continuous Performance Test, COWAT: Controlled Oral Word Association Test, KAI: short test of general intelligence, iTBS: intermittent theta burst stimulation, AMT: active motor threshold, CVLT: California Verbal Learning Test, CANTAB: Cambridge Neuropsychological Test Automated Battery.

(1999) stimulated the PFC bilaterally with 20 Hz using a double-cone coil, a special coil considered to stimulate deeper brain regions compared to standard figure-of-eight coil. Following 10 sessions of rTMS, the authors reported an improvement in visual memory. In a recent study, Levkovitz et al. performed bilateral deeper stimulation of the prefrontal cortex (L > R) using an H-coil and applied 20 sessions of 20 Hz rTMS. The authors reported improvement in executive functions, spatial working memory, attention, and rapid visual information processing.

Regarding studies targeting positive symptoms, we identified only two studies, which looked into the cognitive effects of rTMS. In a RCT, Fitzgerald et al. (2005) applied 10 sessions of 1 Hz rTMS over the left temporoparietal region (TP3) and did not detect any cognitive effects related to real rTMS condition. In an open study, d'Alfonso et al. (2002) stimulated the left auditory cortex (T3) with 1 Hz rTMS on 10 consecutive days and reported an improvement in an auditory imagery test performance.

Finally, in an open-safety study, we introduced a novel approach and attempted to excite the cerebellar vermis using an intermittent TBS paradigm (Demirtas-Tatlidede et al., 2010). Following 10 sessions of stimulation in 5 days (twice per day with a minimum gap of 4 h), we observed an improvement in working memory and visual learning domains while no significant decline was found. The direction of improvement in the 70% of the neuropsychological variables suggested a trend toward improvement in cognition. A double-blind, sham-controlled Phase-II study is currently underway.

The cognitive restoration in schizophrenia is in need of productive lines of research leading to new promising directions. It

has recently been demonstrated that rTMS may lower the excessive gamma oscillatory activity (a finding associated with higher cognitive processes) in schizophrenia when applied bilaterally over the DLPFC and significantly improve working memory (Barr et al., 2011). Accordingly, this approach may prove effective for improvement of some cognitive functions in schizophrenia. In fact, one RCT and two open studies have searched for the cognitive effects of bilateral stimulation of the DLPFC in schizophrenia (Fitzgerald et al., 2008; Cohen et al., 1999; Levkovitz et al., 2011). Fitzgerald et al. (2008) reported negative results of bilateral high frequency rTMS applied over the DLPFC for three consequent weeks. On the other hand, two open studies, which performed deeper stimulation via the use of double-cone and H-coils reported improvement of several cognitive domains (Cohen et al., 1999; Levkovitz et al., 2011). Future randomized sham-controlled studies assessing the effects of bilateral deep DLPFC stimulation should reveal whether deep rTMS is more effective than standard rTMS for cognitive improvement in schizophrenia. Another interesting target location, which could potentially affect the gamma activity via rTMS is the cerebellar vermis (Schutter et al., 2003). This location is further supported by the recent evidence stressing GABAergic dysfunction in cerebellum of patients with schizophrenia in addition to the previously demonstrated deficits in the prefrontal and cingulate cortices (Fatemi et al., 2011; Marín, 2012). Consequently, in the light of our preliminary findings on cognition (Demirtas-Tatlidede et al., 2010), this novel location merits further testing, perhaps with deep stimulation techniques.

### 3.3. Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia characterized by memory dysfunction secondary to the degeneration in the limbic system. The range of cognitive impairment increases with time, as the disease progresses to include the neocortex. Current medical therapeutic approaches offer very limited improvement in cognitive and behavioral symptoms and there is a global effort dedicated to the investigation of new strategies, which may slow the progression of the disease.

In regards to noninvasive brain stimulation, presently only a few trials have been conducted (Table 3). Two RCTs have been published and both reported positive changes following consecutive sessions of rTMS application. Cotelli et al. (2011) applied 20 sessions of 20 Hz rTMS over the left DLPFC and performed a series of language tests in patients with moderate AD. The authors reported a significant effect of rTMS on auditory comprehension. Secondly, Ahmed et al. (2012) tested the effects high and low frequency rTMS applied over the bilateral DLPFCs. A significant improvement in global cognitive functioning was reported following 5 consecutive sessions of bilateral high-frequency stimulation and this effect was maintained for 3 months.

In an open trial, Bentwich et al. (2011) tested the effects of 10 Hz rTMS together with cognitive training in patients with AD. This combined therapy was applied for 6 weeks while the authors stimulated 6 different locations (Broca, Wernicke, right and left DLPFC, right and left parietal somatosensory association cortices) with an aim to cover the cognitive domains affected by the disease. A significant improvement in the primary outcome measure, Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog), was detected at 6 weeks and 4.5 months. MMSE revealed a significant change at 6 weeks only. A double-blind, multiple site European study is under way to confirm these promising findings.

We identified only one tDCS study exploring for the long-term effects of tDCS in patients with AD. In this cross-over study, patients received 5 daily sessions of anodal tDCS over the bilateral temporal lobes for 30 min (Boggio et al., in press). The authors reported an improvement in visual recognition memory, which persisted for 4 weeks.

AD is characterized by impaired synaptic plasticity ultimately leading to the failure of plasticity mechanisms (Mesulam, 2000b). Indeed, we have recently provided evidence on the abnormal hypoplastic state in patients with mild AD (Pascual-Leone et al., 2011). This feature makes noninvasive brain stimulation particularly relevant and intriguing in this case as both rTMS and tDCS allow for the facilitation of the neuronal plasticity by induction of long-lasting after-effects. The few trials conducted to date reveal positive effects and provide initial evidence on the potential of

**Table 3**
Noninvasive brain stimulation studies investigating cognitive after-effects in Alzheimer's disease.

| Study | N design | Stimulation site | Stimulation intensity/frequency | # Sessions/weeks | Cognitive measures | Cognitive enhancement |
|---|---|---|---|---|---|---|
| *rTMS* | | | | | | |
| Bentwich et al., 2011 | 8 open | Broca, Wernicke, R DLPFC, L DLPFC, R PSAC, L PSAC | 1. 90% MT, 10 Hz (+cognitive training) | 30/6 weeks | ADAS-cog MMSE | Memory, language, praxis (ADAS-cog, at 6 weeks and 4.5 months) Global cognitive functioning (MMSE, at 6 weeks only) |
| Cotelli et al., 2011 | 5/5 RCT | L DLPFC | 1. 100% MT, 20 Hz 2. Sham | 20/4 weeks 10/2 weeks | SC-BADA, picture naming task, Aachener Aphasie test, serial curve position, cognitive estimation test, MMSE | Language (auditory sentence comprehension subtest (SC-BADA), at 2 weeks and 8 weeks) |
| Ahmed et al., 2012 | 15/15/15 RCT | R and L DLPFC (bilateral stimulation) | 1. 90% MT, 20 Hz 2. 100% MT, 1 Hz 3. Sham | 5/1 week | MMSE | Global cognitive functioning (MMSE, in 20 Hz group, maintained for 3 months) |
| *tDCS* | | | | | | |
| Boggio et al., in press | 15 crossover | Anode: bilateral temporal, Cathode: right deltoid | 1. 2 mA, 30 min 2. Sham | 5/1 week | Adas-Cog, Visual Recognition Task, Visual Attention Task, MMSE | Visual recognition memory test (persisted for 4 weeks) |

**Abbreviations:** rTMS: repetitive transcranial magnetic stimulation, tDCS: transcranial direct current stimulation, RCT: randomized controlled trial, R: right, L: left, DLPFC: dorsolateral prefrontal cortex, PSAC: parietal somatosensory association cortex, MT: motor threshold, Adas-Cog: Alzheimer's Disease Assessment Scale-cognitive sub scale, SC-BADA: Battery for Analysis of Aphasic Deficits.

noninvasive brain stimulation for cognitive enhancement in AD. However, these studies have not been replicated and the evidence remains preliminary. While the initial target in patients with mild cognitive impairment and mild AD should be to halt the progression of the disease, cognitive enhancement strategies in moderate to severe AD should target multiple cognitive domains in conjunction with cognitive training in order to achieve a clinically meaningful effect. Further systematically designed, sham-controlled trials will establish whether noninvasive brain stimulation might prove an effective cognitive enhancing strategy for this implacable disease.

### 3.4. Attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by hyperactivity and incapability to focus. The neurobiology appears to include noradrenalin and dopamine dysfunction (Pattij and Vanderschuren, 2008) and dopamine reuptake inhibition is the current evidence-based strategy to manage the disease. Neuroimaging reveals abnormalities in the fronto-striato-cerebellar network (Epstein et al., 2007) and dorsal part of anterior cingulate cortex (Bush et al., 2008).

No off-line noninvasive brain stimulation trials have yet been published on ADHD and cognitive functions. The only available publication reports a case, in which benefits were realized after five consecutive sessions of 1 Hz rTMS applied over the motor areas (Niederhofer, 2008). In a recent cross-over study by Bloch et al. (2010), a single session of 20 Hz rTMS over the right DLPFC was found to be beneficial on attention (as revealed by the PANAS attention score, a self-report measure) in patients with ADHD and was considered a preliminary step which may be useful for future studies.

Theoretically, targeting the dysfunctional fronto-striato-cerebellar network using noninvasive brain stimulation coupled with cognitive training could lead to cognitive improvements in ADHD. However, further experimental data is needed to clarify the rationales and possible translational therapeutic applications before large-scale randomized trials are initiated.

### 3.5. Autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by impaired social cognition, constrained, repetitive and ritualistic behavioral patterns, restricted interests, and variable degrees of abnormalities in communication and motor functioning. Network abnormalities in the frontal and temporal lobes, cerebellum, brain stem and the amygdala, and increase in white matter connectivity have been implicated (Konrad and Eickhoff, 2010). Histology characteristically points to changes in cerebral cortical minicolumns and cell sizes and a decrease in the number of cerebellar Purkinje cells (Courchesne and Pierce, 2005).

It has been suggested that rTMS might be a candidate tool that may improve the symptoms of ASD (Tsai, 2005; Hoppenbrouwers et al., 2008). The candidate genes in ASD are involved in synaptic development and plasticity (Pascual-Leone et al., 2011). Indeed, aberrant mechanisms of plasticity can be demonstrated using TMS in patients with ASD for both LTP- and LTD-like plasticity (Pascual-Leone et al., 2011; Enticott et al., 2010; Fatemi et al., 2009a, 2009b). Further, enhanced indiscriminative gamma band power has been observed during visual processing of individuals with ASD. This might be related to reduced GABAergic inhibitory processing, and appears to improve following application of low frequency rTMS over the DLPFC (Baruth et al., 2010). This neurophysiologic improvement was accompanied by positive changes in behavioral questionnaires.

With this rationale, Sokhadze et al. (2012) focused on the executive function deficits and searched whether error monitoring and post-error response correction could be improved via inhibitory rTMS in high-functioning patients with ASD. Twelve sessions of rTMS were performed weekly for 12 weeks over the DLPFC (6 sessions over the right and 6 sessions over the left DLPFC) at 1 Hz with a total of 150 pulses/day. The authors reported improvement in error monitoring and correction while no changes were detected in the wait-list group. The authors suggested that TMS might have the potential to become a valuable therapeutic tool in treatment of ASD.

Overall, noninvasive brain stimulation techniques may have the potential to modulate the hyperexcitable, hyperplastic state in autism while available evidence regarding its possible cognitive implications is yet very sparse. In addition to the prefrontal regions, cerebellar stimulation using excitatory rTMS might theoretically regulate the hyperexcitable cortex as well as abnormal gamma activity (Brighina et al., 2006; Schutter et al., 2003). Further, defective GABA inhibition in autism, which might explain some of the cognitive difficulties, appears to be located extensively in cerebellum along with BA9 and BA40 (Fatemi et al., 2009a, 2009b). Hence, cerebellum may be another candidate location to target for cognitive improvement in autism (for a review see Hoppenbrouwers et al., 2008). Future research employing these and newly-developed neurocognitive approaches guided by EEG and functional neuroimaging techniques may be able to elucidate whether noninvasive brain modulation might result in clinically significant cognitive improvements in ASD.

## 4. Conclusions and future directions

Overall, the number of reliable studies primarily focusing on the cognitive enhancing properties of noninvasive brain stimulation in neuropsychiatry is limited. Available data is promising but presents no conclusive evidence regarding the efficacy of noninvasive brain stimulation on the restoration of cognitive deficits as a rehabilitation strategy. Further, the heterogeneity of cognitive impairment across the neuropsychiatric diseases stands out as a major challenge for future research in this field. While the neural networks affected by impaired cortical function differ between the neuropsychiatric disorders, there might be common pathophysiologic substrate and shared aspects regarding plasticity, which can be linked to reestablish neural functioning and improve neurocognitive deficits. For instance, recent work highlights specific deficits in cortical inhibitory neurotransmission as a common pathophysiology shared by a variety of neuropsychiatric diseases comprising depression (Möhler, 2012; Smith and Rudolph, 2012), schizophrenia (Nakazawa et al., 2012; Lewis et al., 2005), autism (Marín, 2012; Hines et al., 2012) and AD (Luchetti et al., 2011a, 2011b), and this GABAergic pathology has particularly been linked to intellectual disabilities and cognitive deficits related to the neuropsychiatric diseases (Rao et al., 2000; Pouget et al., 2009; Paine et al., 2011). In this context, noninvasive brain stimulation might offer a promising role in the restoration of the GABAergic interneuron dysfunction through its potential to modulate GABA-mediated cortical inhibition and inhibitory/excitatory balance in support of neural plasticity. Through testing of current and new hypotheses, future systematic and reproducible trials combining brain stimulation and neural training strategies with proper experimental design will enable gaining further insights and will establish the potential of noninvasive brain stimulation as a cognitive enhancer in neuropsychiatric disorders.

## Conflict of interest disclosures

APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Allied Mind, Neosync, and Novavision,

and is an inventor on patents and patent applications related to noninvasive brain stimulation and the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

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