Clinical Psychology Review 41 (2015) 61–69

Contents lists available at ScienceDirect

Clinical Psychology Review

Neurostimulation as an intervention for treatment resistant depression: From research on mechanisms towards targeted neurocognitive strategies

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HIGHLIGHTS

- The efficacy of neurostimulation for treatment resistant depression could not be sufficiently demonstrated.
- Research on the working mechanisms of neurostimulation is important to develop new neurocognitive interventions.
- A combination of neurostimulation and cognitive interventions holds promise to treat treatment resistant depression.

ARTICLE INFO

Article history:
Received 1 March 2014
Received in revised form 17 August 2014
Accepted 13 October 2014
Available online 4 November 2014

Keywords:
Treatment resistant depression
tDCS
rTMS
Neurocognitive training
Neurostimulation
Cognitive control

ABSTRACT

Despite the fact that several interventions for major depression have proven efficacy, a substantial number of patients are or become treatment resistant to various forms of pharmacotherapy and psychotherapy. Biological interventions that directly target brain activity such as electroconvulsive therapy are used to treat these patients, but some of these interventions are unlikely to be easily accepted because of their more invasive nature or side-effects. The efficacy of non-invasive neurostimulation with a favorable side effect profile, such as repetitive Transcranial Magnetic Stimulation, could not be sufficiently demonstrated for treatment resistant depressed patients (TRD). We argue that research on the working mechanisms of these neurostimulation techniques is necessary to develop more efficient treatment protocols. After an overview of current neurostimulation approaches to treatment resistance and the introduction of a neurobiological and a cognitive framework of depression, we provide an integrative review of research on both the neurobiological and cognitive working mechanisms of neurostimulation in TRD, with a specific emphasis on the work of our lab. Thereafter, we describe our own studies and studies from other labs on new neurocognitive interventions. Finally we discuss how all this knowledge can be used to further develop new strategies to deal with treatment resistance, in combining neurostimulation and cognitive interventions.

Contents

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http://dx.doi.org/10.1016/j.cpr.2014.10.006
0272-7358/

1. Introduction

Major depressive disorder (MDD) is highly prevalent and is associated with serious personal suffering and societal costs (Kessler et al., 2010). The conceptualization of MDD as a psychological disorder has inspired the development of various forms of psychotherapy such as Cognitive Behavior Therapy (CBT), whereas the conceptualization of depression as a disorder of the brain has stimulated the use of different forms of pharmacotherapy such as Selective Serotonin Reuptake Inhibitors (SSRI). Many of these interventions have proven efficacy (Cuijpers et al., 2013) but relapse or recurrence rates are very high (Beshai, Dobson, Bockting, & Quigley, 2011). Moreover, in spite of the correct use of pharmacological or psychotherapeutic approaches, a substantial number of patients become treatment resistant (up to 15%) (Burrows, Norman, & Judd, 1994; Fava, 2003). Neurobiological interventions that directly target brain activity such as *Transcranial Magnetic Stimulation* (TMS) are frequently used when patients do not respond to pharmacological interventions or psychotherapy. However, an important question is whether there is enough evidence to justify the application of these interventions for treatment resistant depression (TRD). We argue that research on the working mechanisms of neurostimulation may be necessary for the development of more efficient treatment protocols. After an overview of current neurostimulation approaches to treatment resistance and the introduction of a neurobiological and a cognitive framework of depression, we provide an integrative review of research on both the neurobiological and cognitive working mechanisms of neurostimulation in TRD, with a specific emphasis on the work of our lab. Thereafter, we describe our own studies and studies from other labs on new neurocognitive interventions. Finally we discuss how all this knowledge can be used to further develop new strategies to deal with treatment resistance, in combining neurostimulation and cognitive interventions.

2. Neurostimulation approaches to treatment resistance

Electroconvulsive Therapy (ECT) is a biological intervention that has been used for several decades to treat patients with TRD (Kosel, Frick, Lisanby, Fisch, & Schlaepfer, 2003). In ECT, generalized seizures are electrically induced by electrodes focally placed on the scalp. ECT revealed to be a possible alternative for pharmaco-resistant patients, but during the course of such treatment general anesthetics have to be administrated multiple times, and in particular bi-temporal ECT may cause memory and learning impairments (Rami-Gonzalez et al., 2001). Although ECT has proven efficacy at the short term, based on a meta-analysis, it has been shown that despite continuation therapy with pharmacotherapy, the risk of relapse within the first year following ECT is substantial (>50%), with the greatest risk for relapse within the first 6 months (>37%) (Jelovac, Kolshus, & McLoughlin, 2013).

A variant of ECT is *Magnetic Seizure therapy* (MST). In MST, which has fewer cognitive side effects, focal seizure activity is induced by TMS (Lisanby, Luber, Schlaepfer, & Sackeim, 2003). In a small open label pilot clinical trial (N = 13), 38.5% of the depressed patients showed clinical response at the end of the study (Fitzgerald et al., 2013). This procedure may hold promise, but research on the use of MST is still very scarce and more research is needed to determine its antidepressant properties and its utility for TRD (Wani, Trevino, Marnell, & Husain, 2013).

A considerable amount of research has been performed using TMS, a non-invasive neurostimulation technique that is increasingly used. Electrical stimulation is delivered by an electromagnetic coil placed above the scalp in which a high-intensity current is rapidly turned on and off, producing a time-varying magnetic field. This magnetic field passes freely through the skin, muscle and skull to the surface of the brain, where it induces weak electric currents to flow in the underlying neurons. These neurons will be induced to fire if stimulation is provided above a given threshold. Delivering trains of high-frequency (HF) (≥1 Hz) repetitive TMS (rTMS) pulses produces an increase in local cortical excitability *after* stimulation, whereas low-frequency (LF) stimulation (0.1–1.0 Hz) decreases cortical excitability (Fitzgerald, Fountain, & Daskalakis, 2006). Although rTMS has been investigated as a treatment tool for various psychiatric disorders, most research has been done in major depression. Treatment protocols for depression consist mostly of 5–25 sessions of HF-rTMS to the left dorsolateral prefrontal cortex (DLPFC) or LF-rTMS applied to its right counterpart. A meta-analysis of 34 studies comparing rTMS to sham treatment showed a moderate effect size of 0.55 on depressive symptoms (Slotema, Blom, Hoek, & Sommer, 2010), whereas another meta-analysis of 30 HF-rTMS studies found an effect size of 0.39 (Schutter, 2009). Although these effect sizes are comparable to psychotherapy and pharmacotherapy (Roshanaei-Moghaddam et al., 2011), it is important to consider long term effects and treatment resistance to psychotropic agents.

Disappointing effects of TMS on remission are illustrated by the results of a well-designed large scale (N = 190) prospective, multisite, randomized, sham-controlled, duration-adaptive intention-to-treat study in depressed patients. In a first phase, 3 weeks of daily weekday treatment (left DLPFC, 10 Hz) was followed by continued blinded treatment for up to another 3 weeks in improvers (patients who did not achieve full remission but a 30% reduction on the Hamilton Scale for Depression (HAM-D)) (George et al., 2010). The primary efficacy analysis of the initial intervention of 3–6 weeks revealed a significant effect of treatment, but the number of remitters was modest (14.1% in the active and 5.1% in the sham condition), and importantly most remitters were not treatment resistant in the past. The latter is consistent with the results of another trial also suggesting that patients who have repeatedly failed other treatments tend to be less responsive to rTMS (Lisanby et al., 2009). In the open-label follow-up second phase of 3–6 weeks treatment in patients who did not achieve a 30% reduction on their HAM-D score after the initial 3 week period of phase 1, only 30% remitted. The investigators correctly concluded that, although this kind of treatment produced a statistically significant effect on remission, the overall number of remitters and responders was less than one would like with a treatment requiring a daily intervention for 3 weeks or more. Moreover, few studies have assessed the long term effects of rTMS. In a large retrospective naturalistic study (Cohen, Boggio, & Fregni, 2009), a group of patients who remitted after both high and low frequency rTMS treatment were further followed up to 6 months. During this period there were no further rTMS sessions, and medication was never introduced or changed after rTMS treatment. Event-free remission was 75.3% at 2 months, 60.0% at 3 months, 42.7% at 4 months, and only 22.6% at 6 months. To summarize, although rTMS produces