Can the ‘yin and yang’ BDNF hypothesis be used to predict the effects of rTMS treatment in neuropsychiatry?

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Summary Repetitive transcranial magnetic stimulation (rTMS) is a novel technique of non-invasive brain stimulation which has been used to treat several neuropsychiatric disorders such as major depressive disorder, chronic pain and epilepsy. Recent studies have shown that the therapeutic effects of rTMS are associated with plastic changes in local and distant neural networks. In fact, it has been suggested that rTMS induces long-term potentiation (LTP) and long-term depression (LTD) – like effects. Besides the initial positive clinical results; the effects of rTMS are still mixed. Therefore new tools to assess the effects of plasticity non-invasively might be useful to predict its therapeutic effects and design novel therapeutic approaches using rTMS. In this paper we propose that brain derived neurotrophic factor (BDNF) might be such a tool. Brain-derived neurotrophic factor is a neurotrophin that plays a key role in neuronal survival and synaptic strength, which has also been studied in several neuropsychiatric disorders. There is robust evidence associating BDNF with the LTP/LTD processes, and indeed it has been proposed that BDNF might index an increase or decrease of brain activity - the ‘yin and yang’ BDNF hypothesis. In this article, we review the initial studies combining measurements of BDNF in rTMS clinical trials and discuss the results and potential usefulness of this instrument in the field of rTMS.

Introduction The field of neuromodulation has grown significantly in the past decade. Recent developments and studies in this field have increased our understanding on the physiological effects of neuromodulation; but at the same time, several questions have been raised. One neuromodulatory tool that has been increasingly used is repetitive transcranial magnetic stimulation (rTMS). We propose in this article that brain derived neurotrophic factor (BDNF) might be used to understand and predict the effects of rTMS.

TMS is a novel non-invasive brain stimulation therapy in which a strong magnetic field induces...
an electric current in a cortical focal brain area. Because TMS can interrupt brain activity transiently, it was initially used to induce "virtual brain lesions", thus exploring the brain-behavior relationship [1]. Later on, it was found that if TMS is applied repeatedly, it can change and modulate focal activity beyond the stimulation period [2]. Therefore, researchers started to explore its neuromodulatory effects in different neuropsychiatric disorders such as major depression, Parkinson’s disease, chronic pain, and epilepsy. However, as stated by Ridding and Rothwell [3], rTMS produces a mixture of excitatory and inhibitory effects and it is still unknown how rTMS modifies brain activity and induces long-term, therapeutic effects.

BDNF is a neurotrophin related to neuron survival, synaptic signaling and synaptic consolidation [4]. The main breakthrough in this field was the association of BDNF with brain plasticity; particularly with the phenomenon of long term potentiation and depression (LTP and LTD), which is a property of hippocampus neurons to increase or decrease synaptic strength due to a remote, past stimulus. Here an important difference between mature and precursor BDNF (m- and proBDNF) needs to be underscored. Mature BDNF plays a key role in all stages of LTP, being implicated in early and late LTP; also inducing dendritic and axonal growth and de novo gene expression - for a detailed review, see Bramhman and Messaoudi [5]. In contrast, proBDNF, which has affinity to p75NTR death receptors [6], is associated to LTD.

Based on these observations, Lu, Pang and Woo [7] proposed the ‘yin and yang’ hypothesis for proBDNF and mBDNF; in which mBDNF might be associated with an increase in brain activity and excitability and proBDNF might be associated with an opposite effect: a decrease in brain activity and excitability. Interestingly, both neuropeptides (proBDNF and mBDNF) are in extracellular equilibrium; therefore, for instance, an excessive increase in proBDNF might induce secondarily an increase in mBDNF due to peptide cleavage; thus, resulting in a homeostatic effect.

Therefore, mBDNF expression would be desirable in conditions in which an increase in cortical activity is needed, such as major depression; and proBDNF expression, on the other hand, would be useful in conditions in which an inhibition of cortical excitability is desirable, such as epilepsy.

Similarly, rTMS also induces opposite effects according to the parameters of stimulation. For instance, high frequency (HF) rTMS increases motor cortical excitability and decreases cortical inhibition, and low frequency (LF) rTMS decreases motor cortical excitability [8]. Although, this evidence is supported by electrophysiological measurement methods in healthy subjects; the understanding of the mechanism of action of TMS in other conditions or in other central nervous system (CNS) areas is mainly empirical [3]. In addition, rTMS effects in healthy subjects show a significant variability, such as that up to 20% of subjects receiving LF rTMS have an increase in cortical excitability and similar effects are seen for HF rTMS [9].

Given that rTMS appears to induce LTP and LTD-like effects [3] and BDNF appears to be intimately correlated with these effects [5] we propose to use BDNF as a biological marker to quantify rTMS effects. We further selected three rTMS clinical models to use as a framework to test this ‘yin and yang’ BDNF hypothesis model.

Clinical models

Major depressive disorder

Based on earlier neuroimaging studies suggesting a left prefrontal lobe dysfunction [10,11]; researchers hypothesized that rTMS would be an ideal tool to revert this dysfunction. Pascual-Leone et al. [12] were the first to demonstrate in a randomized clinical trial that HF rTMS of the left prefrontal cortex is effective to ameliorate major depression. Since then, several clinical studies have been designed — initially with mixed results, probably due to the heterogeneity of stimulation parameters; though more recent studies with different parameters have presented better results [13].

Recent BDNF studies showed that BDNF levels are decreased in MDD subjects [14] and antidepressant treatment leads to an increase in BDNF levels [14]. Similarly, two clinical trials have demonstrated an increase in BDNF levels following rTMS therapy [15,16], whereas one clinical trial demonstrated no significant increase in BDNF levels after rTMS therapy [17]. Nonetheless, these studies were limited by small samples, absence of a control group and previous use of antidepressants in the treatment group. Despite these limitations, these results are in accordance with our hypothesis as HF rTMS that is associated with an increase in cortical excitability increased BDNF levels.

Another interesting, unexplored issue is the potential difference between left and right hemisphere activity in MDD. There are no definite conclusions on this hypothesis, and, in fact, some authors suggested a general prefrontal hypoactivity in MDD [10,18]; however there are studies demonstrating a differential left and right prefrontal activation [19], which seems to be reverted after
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condition which appears to be associated with overall increased central nervous system activity. Repetitive TMS for epilepsy is still in its infancy, as BDNF role in epileptogenesis. Nevertheless, mutual research could lead to appealing results.

One major contemporary limitation of BDNF application in rTMS field is that, currently, only BDNF blood levels can be easily assessed, which translate the overall BDNF net effect in the CNS. Mapping BDNF expression along the CNS with noninvasive techniques needs to be further explored.

The combination of repetitive TMS in the clinical field and BDNF assessment seems to be promising. BDNF expression is very dynamic, being up- and down-regulated at the same time along the brain and; hence, BDNF might provide insights not only of the local but also of distant network effects associated with the use of rTMS.

References