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## Letter to the Editor

# Low-frequency repetitive transcranial magnetic stimulation (rTMS), a new treatment option in neuropsychiatry

Repetitive transcranial magnetic stimulation (rTMS) has appeared as a potential new non-invasive method, for treating a number of psychiatric as well as neurological diseases (1). The method is based on the principle of electromagnetic induction and implies non-convulsive focal stimulation of the brain through a time-varying magnetic field. The mechanism of action is unclarified. However, simplistically it appears that the method probably works by modulating a disturbed balance between excitatory and inhibitory circuits in neural networks between cortical and deep brain structures. This probably involves different neuronal tracks and brain areas depending on the type of the neuropsychiatric disorder and model of stimulation.

During the last decades, a large number of studies have been carried out to elucidate the potential of rTMS in the treatment of a growing palette of different psychiatric and neurological disorders. A tremendous number of publications report rTMS to have an advantageous side-effect profile limited to discomfort owing to tactile sensations and muscle twisting during stimulation, and a very low risk of eliciting an epileptic seizure from high-frequency stimulation. The symptom-relieving effect of the method has been variating and most promising in the treatment of depression and Parkinson's disease (PD).

Zhu et al. (2) has recently reported the result of a meta-analysis covering eight high-quality randomised clinically controlled trials ($n = 319$) examining the efficacy of low-frequency rTMS on Parkinson motor function. The main conclusion was that low-frequency rTMS had a significant effect on PD motor signs indicating that low-frequency simulation owing to a more advantageous side-effect profile might be a more appropriate choice of treatment model in the treatment of PD than high-frequency rTMS. Owing to the limited number of trials included, this study is not definite conclusive but it emphasises the significance of the frequency of stimulation in relation to the outcome in a clinical setting.

The matter is complicated. The impact of rTMS on brain function depends on a couple of stimulus variables (frequency, intensity, location of the coil, number and timing of the stimulus trains, etc.), which gives rise to a tremendous number of different combinations. We do not know the optimal combination of these variables in relation to treatment outcome (1). The stimulus frequency has been suggested to play a key role in the mechanisms of action of rTMS. Previous animal studies have demonstrated that low-frequency rTMS is associated with long-term inhibition of neuronal activity (long-term depression), whereas high-frequency stimulation is followed by prolonged activation (long-term potentiation) (3). However, this dichotomy theory on the pathophysiological effect of different frequency levels is probably too simplistic to explain the outcome of clinical studies. Both high-frequency and low-frequency rTMS seem to have mixed excitatory and inhibitory effects.

Much of our experience on the issue derives from clinical research on the antidepressant efficacy of the method. The majority of these studies have used high-frequency stimulation of the left prefrontal cortex supporting the antidepressant efficacy of this treatment model, which has been approved by the US FDA (4) and later in EU for the treatment of depression. Fewer studies have used right prefrontal low-frequency rTMS, though this model of stimulation obviously has fewer side effects such as local discomfort and a lower risk of releasing epileptic seizures, than high-frequency stimulation. The issue has given rise to an increasing number of studies emphasising the antidepressant efficacy of low-frequency rTMS (5,6). Both stimulus models has been shown to have a modest, statistically significant antidepressant effect (4–6) at the same level. The issue indicates that low frequency owing to the more advantageous side-effect profile may be the stimulus



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model of choice for the treatment of depression in a clinical setting.

The study by Zhu et al., which point to at similar issue concerning the potential of rTMS in the treatment of PD, is supported by another recent meta-analysis by Chou et al. (7). In all, 20 sham-controlled randomised controlled trials with a total of 470 patients were included. In this study, no significant differences were found in effect size between high- and low-frequency rTMS. However, the outcome was detailed by showing a significant difference in effect size among different combinations of rTMS and the choice of stimulus site. High-frequency rTMS targeting the primary motor cortex as well as low-frequency rTMS applied over other frontal regions was found significantly more efficacy with respect to symptom-relieving effect compared with sham. The outcome of the opposite combinations of stimulus frequencies and sites of stimulations were insignificant. A couple of other stimulus variables are obviously of significance for the outcome of rTMS in the treatment of PD. Thus, additional high-quality RCT's taking account for these variables are needed to find further support for low-frequency rTMS as first line choice in the treatment of PD.

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