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The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: A controlled comparison with standard techniques

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Background
Repetitive transcranial magnetic stimulation (rTMS) treatment of depression utilizes numerous predetermined patterns of stimulation. As an alternative to using invariant stimulus timing parameters, the interactive technique delivers individual stimuli based on the background electroencephalogram (EEG) activity.

Objective
This study examines the use of an EEG-dependent technique as a means to enhance the efficacy of rTMS in the treatment of depression.

Methods
Forty-four patients with treatment-refractory major depression were treated, in a randomized, doubleblind, 4-week trial, with two different rTMS stimulus timing techniques (left dorsolateral prefrontal cortex). Standard rTMS utilized 10-Hz stimuli, whereas interactive rTMS applied individual stimuli in response to a selected pattern of background EEG activity analyzed in real time. Hamilton

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Depression Rating Scale (HDRS) and the Beck's Depression Inventory-II (BDI) scores were recorded at baseline, 2 weeks and after the final treatment.

Results

The interactive group showed a trend toward greater efficacy than the standard group in both absolute ($t = -1.68$; $P = .100$) and percentage ($t = -1.74$; $P = .090$) change in scores on HDRS (and similarly BDI). The response rate (>50% reduction) for the interactive technique of 43% (9/21) was also different to that of the standard technique (22%; 5/23; odds ratio: 2.70).

Conclusions

The use of EEG-based TMS stimuli has been shown to be feasible in an rTMS clinical trial in treatment-resistant depression. The EEG-based interactive technique was associated with an indication of a trend toward a greater clinical effect than the standard rTMS technique. The interactive technique thus has the potential to refine the rTMS methodology and to enhance efficacy in the treatment of depression.

Keywords rTMS; depression; interactive stimulus; EEG

Repetitive trancranial magnetic stimulation (rTMS) has been widely proposed as a treatment for major depression.[1-3] It is the most studied magnetic stimulation application in psychiatry, but meta-analyses have reported inconsistent results between studies,[4,5] leading to skepticism about its clinical use.[6,7] The most recent meta-analysis was more positive,[8] possibly reflecting an improvement in methodology,[9] or varying selection criteria.[10] Although the exact mechanism of action is unclear, it is accepted that the therapeutic effect of (subconvulsive) stimuli probably depends on the combined timing effects (stimulus and train) of repeating trains of repetitive stimuli.[2]

That the physiologic effects of TMS stimuli are dependent on generic (pertaining to all stimuli) stimulus timing parameters have already been reported from pharmacological studies.[11] Fixed-frequency exemplars in depression[2,12] have used "fast" stimuli (5 Hz,[13] 10 Hz,[14-19] 15 Hz,[20,21] and 20 Hz[22-26]), in comparison with "slow" stimuli,[27,28] and with sham.[29,30] Stimulus timing has also been investigated by taking into account individual physiologic (alpha) characteristics in clinical[31] and behavioral[32] investigations, variability in those characteristics,[33] and the putative physiologic basis (theta burst stimulation) of the clinical effect.[34]

However, there is evidence from several fields of TMS research that specific stimulus timing effects are also dependent on the physiologic context of each stimulus, in particular on cellular, local field, and background electroencephalogram (EEG) activity.[35] Most fundamentally long-term potentiation, hypothesized to be a mechanism for the antidepressant effects of rTMS[36] was affected by background neuronal activity.[37] Confirmation of cellular activity directly affecting rTMS effect was found in a subsequent animal study[38] in which rTMS induced plasticity, as measured by variation in cell firing rates with time and by local field potentials, that showed a significant interaction with activity state (spontaneous versus evoked). These findings were later extended from behavioral activity state, to directly show an interaction of TMS response with prestimulus physiologic state.[39] Higher pre-TMS activity appeared to predict larger post-TMS responses in spontaneous activity. Moreover, as a corollary to this work, Crochet et al.[37] investigated specifically the effect of EEG on neuroplasticity. Using trains of stimuli at frequencies that mimic endogenous brain rhythms, they found that high levels of neuronal activity in the cortical network facilitated potentiation.

More generally, several studies have investigated how neuronal excitability is associated with physiologic activity. Most obviously, the well-accepted effects of (ipsilateral and contralateral) short-term inhibition and facilitation of the motor cortex,[40,41] using paired-pulse TMS, are assumed to involve some mechanism of cortical activity (albeit intraneuronal). Paired associative stimulation[42] shows a similar effect of stimulus timing in which the mechanism is more clearly via cortical activity.[43] That these neuronal excitability findings may link to background EEG has been shown in sleep cycle studies in which facilitation occurs in normal sleep but not REM sleep.[44] In addition, there are several lines of behavioral research, in which TMS is applied concurrently with a behavioral task, showing that cortical excitability is also affected by activity in the target area. Voluntary contraction has been shown to reduce excitability[45] and shorten peripheral conduction time[46] in the target muscle. This excitability may be affected by cognitive effort,[47] as motor potentials were affected by mental preparation to resist an involuntary movement evoked by a suprathreshold TMS without overt activation. Recent work by this author also proposed an EEG correlate of such preparation.[48] Analogous research has also been conducted with the visual cortex.[49] Phosphene color, for example, was affected by adaptation,[50] a process whereby excitability changes are induced by prolonged exposure to sensory stimulation.[51] Similarly, phosphene threshold may depend simply on the visual input.[52] Although not identical,