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EXPLORING THE DICHOTOMY OF TRANSCRANIAL MAGNETIC STIMULATION'S FREQUENCIES ON BRAIN WAVE PATTERNS

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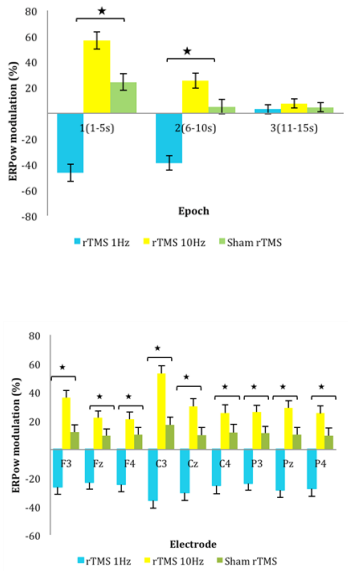
Graphical abstract



Abstract

Disturbance in brain oscillations is observed in many neuropsychiatric disorders. Any tool that has the potential to restore abnormal brain oscillations is therefore beneficial to patients with neuropsychiatric illnesses. Repetitive transcranial magnetic stimulation (rTMS) is one such tool. It is a non-invasive brain stimulation technique, which is able to alter brain oscillations depending on its parameters of stimulation and is used in clinical setting because of its potential therapeutic effects on the brain. However, the optimum stimulation parameters to induce the therapeutic effect of rTMS remains elusive. Therefore, it is important to investigate the differential effects between high versus low frequency of magnetic stimulation on the mechanism of brain oscillations in human subjects. Here we show, using combined rTMS and surface electroencephalography (EEG) that low and high frequencies of magnetic stimulation would induce dichotomy effects in EEG brain oscillatory activity. In particular, high-frequency rTMS 10Hz induces a synchronised oscillations for theta brain rhythm. In contrast, low-frequency rTMS 1Hz desynchronises neural oscillations on the same brain rhythm. Taken together, our results show that the desynchronisation effect of low-frequency rTMS 1Hz may potentially reverse the interference of altered neural oscillations. More extensive basic and clinical research using combined rTMS and EEG are needed to determine the optimum parameters of rTMS stimulation to restore adequate neural oscillations.

Keywords: Brain stimulation, cortical plasticity, electroencephalography (EEG), neuromodulation, neural oscillations

1.0 INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiologic method of delivering electrical stimuli by rapidly changing the magnetic field. It works by placing a magnetic coil near the subject's scalp. This coil will excite the cortical axon directly underneath it, trigger nerve depolarisation, propagate action potentials, and release neurotransmitters into the postsynaptic neurons [1]. TMS can be applied as single pulse or repetitive pulses. Using single pulse protocol, TMS can either excite or inhibit the brain depending on the parameters of stimulation, such as frequency, duration, intensity of stimulation, and the number of magnetic pulses. The effects of single-pulse or single-train can add up with repeated stimulation—the rTMS protocol—leading to the modulation of cortical activity beyond the stimulation period [2].

In humans, low and high stimulation frequencies of rTMS often result in opposite physiological effects. Studies on the human motor cortex using motor evoked potentials (MEP) as an index of cortical excitability, showed that high frequency rTMS at high intensities of stimulation leads to facilitatory aftereffects on corticospinal excitability, and low

frequency rTMS results in suppression of corticospinal excitability [3,4]. However, studies of combined rTMS and EEG over the human motor cortex using low frequency rTMS 1Hz and high frequency rTMS 5Hz showed a linear increase of EEG power modulation for the frequency bands of alpha (α) and beta (β) brain rhythms [5,6]. Another rTMS-EEG study by Veniero *et al.* (2011) attempted to emulate the classical dichotomy between low versus high frequency rTMS of MEP measurements [7]. They explored the modulations of the ongoing oscillatory activity of left primary motor cortex (M1) at rest after high frequency 20Hz rTMS and quantified the EEG oscillatory activity. Consistent with other rTMS-EEG co-registration studies, they observed increased EEG synchronisation in α (8-12Hz) more than β (13-30Hz) after high frequency 20Hz rTMS, and the α oscillations lasted for 5 minutes [7]. Consequently, the three previous rTMS-EEG studies on the motor cortex using different frequencies of magnetic stimulation [5,6,7] did not emulate the classical dichotomy between low versus high frequency rTMS as observed by behavioural measures of motor evoked potentials.

Previous combined rTMS/EEG studies that investigated brain rhythms, which can be modulated through direct brain stimulation, focused on alpha and beta brain rhythms but they could not differentiate the opposite effects of low and high frequency rTMS on cortical oscillations [5,6,7]. It is possible that a differential rTMS frequency-dependent effect on modulation of cortical oscillations could be better reflected by other brain rhythms such as the low-frequency theta. Therefore, the present study tests the hypothesis that the perturbations of low frequency oscillations of theta bands can be induced by rTMS delivered at different frequencies.

The contribution of the present study is two-fold. One is direct contribution to the neuropsychiatric patients, where the differentiation between the effects of low and high frequency of magnetic stimulation will help in their management, who was prescribed non-invasive brain stimulation as part of their treatment. Secondly, is the contribution in terms of neurophysiology mechanisms of different protocol of rTMS. At present, the mechanisms of cortical plasticity induced by differnt frequency rTMS is still vague and debatable. TMS-EEG co-registration study will help us to understand the underlying neurophysiological mechanisms of cortical plasticity in the macro-level rather than the micro-level of neuronal network.

2.0 TRANSCRANIAL MAGNETIC STIMULATION AND ELECTROENCEPHALOGRAM

Thirty healthy volunteers (19 males, 11 females; mean age 23.2 years ± 1.9) with no reported neurological history participated in the study. Participants were randomly divided into three experimental groups (rTMS 1Hz, rTMS 10Hz and sham rTMS 10Hz) of ten subjects each. All subjects gave written informed consent and the Local Ethics Committee approved the study.

TMS was carried out with a high-power Magstim-Rapid stimulator (Magstim, Whitland, Dyfed, UK). The magnetic stimulus had a biphasic waveform with a pulse width of about 300μs. TMS was delivered through a figure-of-eight shaped coil (70mm standard coil; Magstim), oriented so that the induced electric current flowed in a posterior-anterior direction over the left primary motor cortex (M1). The rTMS was applied over the left M1 (in the proximity of C3 electrode) simultaneously with EEG data collection. Four hundred stimuli (20 trains of 20 pulses each), were delivered for the frequencies of rTMS at 100% resting motor threshold (RMT). High-frequency rTMS 10Hz was delivered at the frequency of individual mu rhythm (mean 10.49Hz ± 0.45). The spectral distribution of the mu rhythm usually has an average peak of 10–11Hz in healthy adults which appear maximally over the central Rolandic or sensorimotor area during a relaxed state, but varies among individuals. In the present study, we decided to deliver the trains of rTMS at the frequency of individual mu rhythm to make sure that this parameter of rTMS was constant across all subjects taking into account the individual differences in the natural frequency of the resting motor cortex.

To demonstrate the EEG-induced oscillations, EEG data were analysed with commercial software (Vision Analyser, Brain Vision, Munich, Germany) followed by computation of event-related power (ERPow). ERPow represents the TMS effects on regional oscillatory activity during neural assemblies. A discrete Fast Fourier Transform of blocks of data points was computed for all electrodes and then averaged under the same conditions. Power spectra were estimated for all frequency bins between 0.5 and 40Hz (0.5Hz of maximum bin width). Recordings were Hamming-windowed to control spectral leakage. In order to reduce the effects of inter-subject and inter-electrode variation in absolute spectral power values and to quantify the event-related relative changes of EEG power at an electrode x ($ERPow_x$), an accepted event-related desynchronisation/ synchronisation (ERD/ERS) procedure was used according to equation (1). The ERPow (or ERD/ERS) transformation was defined as the percentage decrease/increase of instant power density at the 'event' compared to a 'pre-event' baseline. Therefore, ERPow decreases imply a decrease in synchrony of the underlying neuronal populations, which are expressed as negative values, while ERPow increases are expressed as positive values [8].

This protocol of ERPow (or ERD/ERS) transformation has been previously used in TMS-EEG studies to assess the modulation of interregional functional connectivity of neural assemblies (5,6,7,8,14,15,16).

$$ERPow_x = \frac{(Pow_{xevent} - Pow_{xreference})}{Pow_{x\,reference}} \times 100 \quad (1)$$

Spectral analysis of mean ERPow was submitted to repeated analysis of variance (ANOVA) measurements for theta (4-7Hz), alpha (8-12Hz) and beta (13-30Hz) frequency ranges. Three -way ANOVA was used with the factor: 'epoch' (first epoch 1-5 seconds post rTMS; second epoch 6-10 seconds post rTMS; third epoch 11-15 seconds post rTMS; fourth epoch 16-20 seconds post rTMS); 'frequency of rTMS (1, 10Hz and sham 10Hz); and 'electrode' (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4). For each ANOVA, the sphericity assumption was assessed with Mauchly's test. Greenhouse-Geisser epsilon adjustments for non-sphericity were applied where appropriate. For ERPow transformation, post-hoc paired t-tests (adjusted for multiple comparisons using the Bonferroni method) were used for significant main effects and interactions of ANOVAs. For all statistical tests, $p < 0.05$ was considered significant

3.0 RESULTS AND DISCUSSION

The main finding of this study was the acute short-lasting (10 seconds) rTMS frequency-dependent synchronisation effect on low-frequency EEG oscillations after short trains of magnetic stimulation. In particular, we found that rTMS 10Hz increased the EEG power (synchronisation) for theta bands; in contrast, rTMS 1Hz decreased the EEG power (de-synchronisation) on the same low-frequency rhythms. Figure 1 shows the grand average of ERPow the grand average of ERPow for theta band (4-7Hz) as a function of two factors: frequency of rTMS, and epoch. Specifically, the rTMS 10Hz group shows a significant difference from sham rTMS with an overall electrodes enhancement of EEG power modulation at epoch 1 (59%) and at epoch 2 (21%). The rTMS 1Hz group shows a de-synchronisation trend of theta at epoch 1 (-45%) and epoch 2 (-40%).

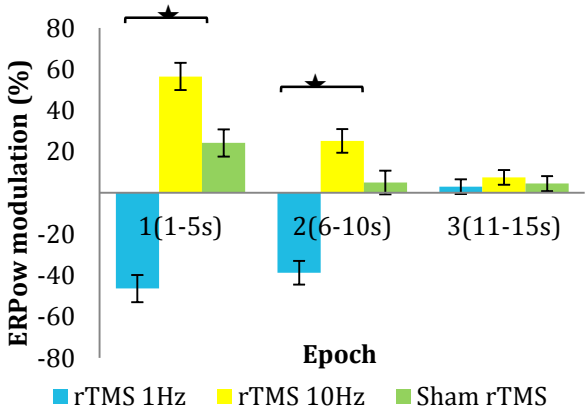


Figure 1 Grand average of event-related power (ERPow) transformation *(n = 30)* for theta (4-7 Hz) analysed as a function of the 'frequency of rTMS' (rTMS 1 Hz, rTMS 10Hz and sham rTMS 10Hz), and 'epoch of time' [first epoch (1-5 s), second epoch (6-10 s), third epoch (11-15 s)]

The ANOVA for the average of ERPow for θ band (4-7Hz) showed the following statistically significant main effects and interactions: "frequency of rTMS" ($F_{3,40}$ = 31.4, $p < 0.001$, $\eta_p^2 = 0.71$); "epoch" ($F_{2,80}$ = 21.6, $p < 0.001$, $\eta_p^2 = 0.35$); "epoch x frequency of rTMS" ($F_{6,80}$ = 49.3, $p < 0.001$, $\eta_p^2 = 0.79$); "electrode" ($F_{4.9,194.4}$ = 3.76, $p < 0.01$, $\eta_p^2 = 0.09$); "electrode x frequency of rTMS" ($F_{14.6,194.4}$ = 5.6, $p < 0.001$, $\eta_p^2 = 0.3$) and "epoch x electrode x frequency of rTMS" ($F_{21.7,289.6}$ = 4.7, $p < 0.001$, $\eta_p^2 = 0.26$). Post-hoc comparisons for "epoch x electrode x frequency of rTMS" showed a similar synchronisation effect for rTMS 10Hz and de-synchronisation for rTMS 1Hz compared with sham across all electrodes post magnetic stimulation. The most sensitive electrode was C3. The post-hoc comparisons of the three-way interactions for C3 electrode at epoch 1 revealed increase of EEG synchronisation for rTMS 10Hz versus sham (115.9 vs. 39.8%) and EEG de-synchronisation for rTMS 1Hz compared with sham rTMS (-55.3, -38.4 vs. 39.8%); a similar trend was seen in epoch 2 for rTMS 10Hz, 1Hz, and sham rTMS (32.9, -49.3, -33.7 vs. 5.2%) (Figure 2).

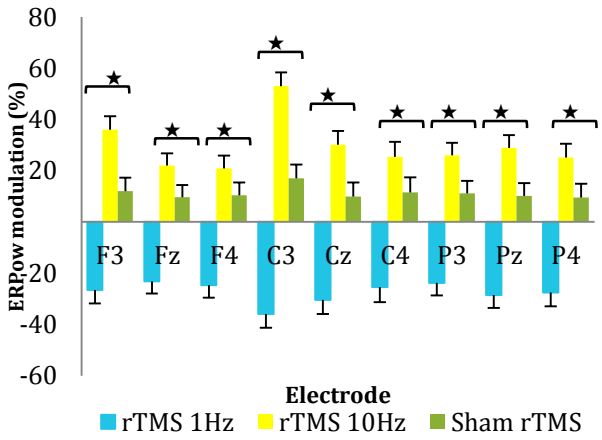


Figure 2 Frequency of rTMS x Electrode showed the same trend of increase EEG synchronisation of rTMS 10Hz but de-synchronisation for rTMS 1Hz for theta brain rhythms. C3 is the most sensitive electrode

Our results of rTMS 10Hz in normal subjects emulates the demonstration of abnormal, internally generated low-frequency oscillations of thalamocortical dysrhythmia observed in neuropsychiatric diseases [9]. The thalamocortical dysrhythmia theory is based on either diminish excitatory or increase inhibitory input at the thalamic level, which leads to a shift from tonic to burst firing of the thalamocortical neurons and subsequently with low-frequency pathologic oscillations [10]. The lengthy intervals of hyperpolarisation that intervene between bursts in the thalamo-cortico-thalamic network will disrupt the normal state-dependent flow of information between thalamus and cortex. The rTMS 10Hz in the present study appears able to modulate the rhythmic thalamocortical interplay by entraining the resonance between the thalamus and cortex at low

frequency thus generate a state that emulates the pathological thalamocortical dysrhythmia. This finding is supported by clinical studies using high-frequency rTMS 10Hz on neuropsychiatric patients, who demonstrated worsening of the disease symptoms [11,12].

The EEG de-synchronisation observed in rTMS 1Hz to the potential of rTMS to reverse the enhancement of low-frequency oscillations. These findings may provide an insight into the electrophysiological mechanisms underlying the successful improvement of many neuropsychiatric symptoms regardless of using different rTMS protocols of either low frequency or high frequency [13,14,15,16]. The low and high stimulation frequencies in human often result in opposite physiological effects measured by motor evoked potentials; low frequency (1Hz or lower) decreases cortical excitability whereas high frequency stimulation (more than 1Hz) increases cortical excitability. However, previous EEG and TMS investigations were unable to detect this differential effect of low and high frequency rTMS on modulation of cortical oscillations because they were focusing on alpha and beta bands. Moreover neuroimaging studies using fMRI reveals a roughly linear relationship of haemodynamic and oscillations of high and low frequency after short trains rTMS [17]. The increase in theta power is in complete accordance with the presence of low-threshold spike bursting activity, with theta rhythmicity in the medial thalamus of patients with thalamocortical dysrhythmia, as demonstrated by MEG and single-unit recordings during stereotactic surgery [18]. The results support the hypothesis that electrical brain stimulation like TMS can trigger an oscillation or reset the ongoing rhythmic activity of a local thalamic pacemaker [19].

4.0 CONCLUSION

Overall, the present study emphasised that the frequency of neural discharges is not epiphenomenal. Here for the first time, we show that not only rTMS can induce low-frequency oscillations but it may reverse the oscillatory phenomena depending on the frequency of stimulation used. Studies to date have not fully established the clinical indication for using rTMS as a diagnostic or therapeutic tool in any neuropsychiatric diseases. We show that not only rTMS can induce low-frequency oscillations but it may reverse the oscillatory phenomena depending on the frequency of stimulation used. Studies to date have not fully established the clinical indication for using rTMS as a diagnostic or therapeutic tool in any neuropsychiatric diseases [20,21]. Nevertheless, if our suggestion is true, then the ability of combined rTMS-EEG to modulate and measure the dysrhythmic thalamocortical oscillatory activity offers exciting possibilities of carefully designed clinical trials. Future work promises to provide advances in the therapeutic strategies of using non-invasive brain stimulation to reverse abnormal synchronisation in neuropsychiatric disorders. New rTMS-EEG study should also explore recent technology such as pattern recognition and computer-vision based technology on adaptive probalistic models for non-invasive brain stimulation techniques [22].

References

[1] Hallett, M. 2000. Transcranial Magnetic Stimulation and the Human Brain. *Nature*. 406: 147-150.

[2] Hoogendam, J. M. Ramakers, G. M. and Di Lazzaro, V. 2010. Physiology of Repetitive Transcranial Magnetic Stimulation of the Human Brain. *Brain Stimulation* 3: 95-118.

[3] Miniussi, C. and Thut, G. 2010. Combining TMS and EEG Offers New Prospects in Cognitive Neuroscience. *Brain Topography*. 22: 249-256.

[4] Frohlich, F. 2015. Experiments and Models of Cortical Oscillations as a Target for Noninvasive Brain Stimulation. *Progress in Brain Research*. doi:10.1016/bs.pbr.2015.07.025.

[5] Brignani, D. Manganotti, P. Rossini, P. M. and Miniussi, C. 2008. Modulation of Cortical Oscillatory Activity during Transcranial Magnetic Stimulation. *Hum Brain Mapp.* 29: 603-612.

[6] Fuggetta, G. Pavone, E. F. Fiaschi, A. and Manganotti, P. 2008. Acute Modulation of Cortical Oscillatory Activities during Short Trains of High-Frequency Repetitive Transcranial Magnetic Stimulation of the Human Motor Cortex: a Combined EEG and TMS study. *Hum Brain Mapp*. 29: 1-13.

[7] Veniero, D. Brignani, D. Thut, G. and Miniussi, C. 2011. Alpha-generation as Basic Response-Signature to Transcranial Magnetic Stimulation (TMS) Targeting the Human Resting Motor cortex: A TMS/EEG Co-Registration Study. *Psychophysiology*. 48: 1381-1389.

[8] Pfurtscheller, G. and Lopes da Silva, F. H. 1999. Event-Related EEG/MEG Synchronization and Desynchronization: Basic Principles. *Clin Neurophysiol.* 110: 1842-1857.

[9] Llinas, R. R. Ribary, U. Jeanmonod, D. Kronberg, E. and Mitra, P. P. 1999. Thalamocortical Dysrhythmia: A Neurological and Neuropsychiatric Syndrome Characterized by Magnetoencephalography. *Proceedings of the National Academy of Sciences of the United States of America*. 96: 15222-15227.

[10] Jeanmonod, D. 2003. Neuropsychiatric Thalamocortical Dysrhythmia: Surgical Implications. *Neurosurg Clin N Am*. 14: 251-265.

[11] Whitwell, J. L. 2011. Disrupted Thalamocortical Connectivity in PSP: A Resting-state fMRI, DTI, and VBM Study. P*arkinsonism & Related Disorders*. 17: 599-605.

[12] Llinas, R. R. and Steriade, M. 2006. Bursting of Thalamic Neurons and States of Vigilance. *Journal Of Neurophysiology*. 95: 3297-3308.

[13] Thut, G. and Pascual-Leone, A. 2010. A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience. *Brain Topography.* 22: 219-232.

[14] Noh, N.A. and Fuggetta, G. 2012. Human Cortical Theta Reactivity After Repetitive Transcranial Magnetic Stimulation. *Hum Brain Mapp*. 33: 2224-2237.

[15] Fuggetta, G. and Noh, N.A. 2013. A Neurophysiological Insights Into the Potential Link Between Transcranial Magnetic Stimulation, Thalamocortical Dysrhythmia and Neuropsychiatric Disorders. *Experimental Neurology*. 245: 87-95.

[16] Noh, N.A. Fuggetta, G. Manganotti, P. and Fiaschi, A. 2012. Long Lasting Modulation of Cortical Oscillations after Continuous Theta Burst Transcranial Magnetic Stimulation. *PloS One*. 7(4): e35080.

[17] Allen, E. A. Pasley, B. N. Duong, T. and Freeman, R. D. 2007. Transcranial Magnetic Stimulation Elicits Coupled Neural and Hemodynamic Consequences. *Science.* 317: 1918-1921.
[18] Buzsaki, G. and Draguhn, A. 2004. Neuronal Oscillations in Cortical Networks. *Science.* 304: 1926-1929.
[19] Ridder, D. Vanneste, S. Langguth, B. and Llinas, R. 2015. Thalamocortical Dysrhythmia: a Theoretical Update in Tinnitus. *Frontiers in Neurology.* doi: 10.3389/fneur.2015.00124.
[20] Chervyakov, A. V. Chernyavsky, A. Y. Sinitsyn, D. O. and Piradov, M. A. 2015. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. *Frontiers in Human Neurosc.* doi: 10.3389/fnhum.2015.00303.
[21] Gosseries, O. Thibaut, A. Boly, M. Rosanova, M. Massimini, M. Laureys, S. 2014. Assessing Consciousness in Coma and Related States Using Transcranial Magnetic Stimulation. *Ann Fr Anesth Reanim.* 33: 65-71
[22] Kerdvibulvech, C. 2014. A Methodology for Hand and Finger Motion Analysis Using Adaptive Probabilistic Models. *EURASIP Journal on Embedded Systems.* 18.