

# Theta-burst transcranial magnetic stimulation in depression: when less may be more

**This scientific commentary refers to 'Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study', by Li *et al.*, (doi:10.1093/brain/awu109).**

Major depressive disorder is associated with increased mortality, significant morbidity, and substantial impairments in functioning. It is estimated that by the year 2020, depression will be second only to heart disease in terms of disease burden as measured by disability-adjusted life years (Murray and Lopez, 1996). Treatment-resistant depression is conventionally defined as a failure to respond to at least two adequate medication trials or as a relapse during treatment; it represents a common dimension of this illness that translates into significant public healthcare costs. Only one-third of patients with major depressive disorder achieve full remission of their symptoms after a single trial of antidepressant medication and even with multiple medication trials, 30–40% of patients fail to respond fully (Keller *et al.*, 1992). Treatment-resistant depression is associated with significantly greater medical costs and productivity loss than treatment-responsive forms, highlighting the need for more effective non-pharmacological strategies. In this issue of *Brain*, Li *et al.* (2014) report data from a randomized sham-controlled study to show that a modified form of repetitive transcranial magnetic stimulation (TMS) produces therapeutic benefits in patients with treatment-resistant depression.

High frequency (e.g. 10 Hz) repetitive TMS applied to the left dorsolateral prefrontal cortex is an FDA approved treatment for adults with resistant depression. A number of large multicentre studies and recent meta-analyses have indicated that high frequency repetitive TMS has reasonable therapeutic efficacy compared to sham stimulation. For example, O'Reardon *et al.* (2007) reported response rates of 24.5% with high frequency repetitive TMS compared to 13.7% with sham repetitive TMS following 6 weeks of treatment. In a recent meta-analysis, Berlim *et al.* (2014) reported response rates of 29.3% with high frequency repetitive TMS compared to 10.4% with sham repetitive TMS. Collectively, these results indicate that high frequency repetitive TMS can be effective in treatment-resistant depression, but there is clearly scope for improvement.

Modification of repetitive TMS parameters such as stimulus frequency and duration may be one means of enhancing repetitive TMS efficacy. Conventional high frequency repetitive TMS paradigms, such as those used in the abovementioned trial (O'Reardon *et al.*, 2007), deliver 3000 pulses of 10 Hz stimulation over the course of 37.5 min. An alternative approach is theta-burst stimulation (TBS), in which a three-pulse 50-Hz burst is applied at 5 Hz. In intermittent TBS, a 2-s train of TBS is delivered every 10 s for ~190 s (600 pulses in total). Intermittent TBS induces a form of

plasticity that resembles long-term potentiation (Huang *et al.*, 2005), changes to which are increasingly implicated in the pathophysiology of major depressive disorder (Player *et al.*, 2013). Huang *et al.* (2005) demonstrated that application of intermittent TBS to motor cortex produced a consistent increase in the TMS-induced motor evoked potential (MEP) compared to baseline: an increase that could be considered a marker of cortical plasticity. By contrast, continuous TBS, which involves a continuous 40 s train of TBS to give a total of 600 pulses, produced a decrease in the TMS-induced MEP compared to baseline; a change that may be a marker of long-term depression (Huang *et al.*, 2005).

In this issue of *Brain*, Li *et al.* (2014) provide the first direct evidence that intermittent TBS applied to the left dorsolateral prefrontal cortex or a combination of intermittent plus continuous TBS applied to the left and right dorsolateral prefrontal cortex, respectively, are significantly more effective than continuous TBS or sham TBS in treatment-resistant depression. Response rates after 10 treatment sessions were 40% for intermittent TBS and 66.7% for the combination of intermittent plus continuous TBS—considerably higher than those reported in the high frequency repetitive TMS studies. This greater efficacy is reason enough to be encouraged by these findings. However, there are several other reasons. First, this study demonstrates that intermittent TBS can be applied safely and effectively over a much shorter time period (10 min versus 40 min using traditional high frequency approaches) (O'Reardon *et al.*, 2007) and may permit about four times more treatments per day than standard approaches. Given that large numbers of individuals are affected by treatment-resistant depression and that repetitive TMS is one of very few clinically proven treatments for this disorder, such modifications may lead to more widespread use of repetitive TMS through reduced costs and the ability to manage greater patient volumes.

Equally important, however, is the glimpse this study provides *vis à vis* the neural mechanisms involved in resistant depression. As mentioned above, intermittent TBS was initially shown to consistently induce plasticity in motor cortex (Huang *et al.*, 2005). Other plasticity-inducing neurostimulation methods include transcranial direct current stimulation (DCS) and paired associative stimulation (PAS). Unlike intermittent TBS, transcranial DCS and PAS take upwards of 30 min to produce plasticity enhancing effects and only transcranial DCS has shown evidence of treatment efficacy in depression. There are many reasons why future intermittent TBS treatment studies in resistant depression should evaluate plasticity as a biomarker of treatment response. First, it is conceivable that intermittent TBS-induced changes in neural plasticity may predict treatment response and/or help to optimize the treatment course. That is, greater plasticity in response to intermittent TBS at baseline may predict greater intermittent TBS

symptom response, and vice versa for poor response. Second, the evidence that intermittent TBS can enhance plasticity in the cortex was obtained in healthy subjects; the parameters needed to induce plasticity in depression remain undetermined. Li *et al.* applied intermittent TBS for three times as long as in the initial intermittent TBS study (Huang *et al.*, 2005), suggesting that more prolonged intermittent TBS may be necessary to induce plasticity in patients. Third, the parameters required to consistently induce plasticity over a 2–4 week treatment course may also vary and require weekly titration. Finally, just as mood fluctuates throughout the day, there may be intrinsic diurnal variation in the intermittent TBS plasticity response that may also require daily parameter titration. All of these considerations highlight the need for a treatment biomarker that could help to optimize this promising treatment. Such personalization efforts should lead to substantially greater efficacy and tolerability.

We have previously proposed that an individualized approach may be used to guide high frequency repetitive TMS treatments in resistant depression. For example, high frequency repetitive TMS produced changes in neurophysiological indices of GABAergic inhibitory neurotransmission in motor cortex (de Jesus *et al.*, 2014), including the cortical silent period, which is altered in patients with resistant depression (Levinson *et al.*, 2010). In healthy subjects, increasing the number of stimuli (i.e., 6000) produced greater lengthening of the cortical silent period, but there was variability between individuals in the number of stimuli needed to produce this effect (de Jesus *et al.*, 2014). It follows that changes in these biomarkers (i.e., plasticity-induced changes to the MEP or the cortical silent period) may ultimately reveal key neurophysiological mechanisms that can be used to titrate repetitive TMS parameters to more effectively tailor treatment to the individual.

Established methods designed to evaluate plasticity have until recently been limited to motor cortex. However, single pulse TMS combined with electroencephalography is an innovative approach that has been developed to reliably measure cortical-evoked responses from motor and non-motor regions, and this approach has been used recently to demonstrate plasticity in the left dorso-lateral prefrontal cortex (Rajji *et al.*, 2013). Combining TMS with functional MRI also holds promise, with changes in blood oxygen level-dependent response being the dependent variable of interest in this latter case.

Although the findings of Li *et al.* are very encouraging, several additional studies are needed before intermittent TBS is adopted into routine clinical practice. First, it is self-evident that the efficacy of intermittent TBS in resistant depression should be replicated in larger scale clinical trials. Second, as high frequency repetitive TMS is the gold standard treatment approach, a direct comparison of intermittent TBS and standard high frequency repetitive TMS is required to establish non-inferiority of intermittent TBS in a large randomized clinical trial. Such trials are currently underway. Third, these clinical trials should evaluate an array of treatment biomarkers that either directly or indirectly relate to neural plasticity or inhibition—neural mechanisms that are associated with treatment response to intermittent TBS or other forms of repetitive

TMS (Huang *et al.*, 2005; de Jesus *et al.*, 2014), as well as with depression (Levinson *et al.*, 2010). Nevertheless, the innovative trial by Li *et al.* should provide investigators with the impetus to further develop this potentially effective and efficient form of repetitive TMS as a treatment for resistant depression.

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