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Using neuroimaging to individualize TMS treatment for depression: Toward a new paradigm for imaging-guided intervention

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ABSTRACT

The standard clinical technique for using repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) is associated with limited efficacy to date. Such limited efficacy may be due to reliance on scalp-based targeting rather than state-of-the-science methods which incorporate fMRI-guided neuronavigation based on a specific model of neurocircuit dysfunction. In this review, we examine such a specific model drawn from regulatory focus theory, which postulates two brain/behavior systems, the promotion and prevention systems, underlying goal pursuit. Individual differences in these systems have been shown to predict vulnerability to MDD as well as to comorbid generalized anxiety disorder (GAD). Activation of an individual's promotion or prevention goals via priming leads to motivational and affective responses modulated by the individual's appraisal of their progress in attaining the goal. In addition, priming promotion vs. prevention goals induces discriminable patterns of brain activation that are sensitive to the effects of depression and anxiety: MDD is associated with promotion system failure, anhedonic/dysphoric symptoms, and hypoactivation in specific regions in left prefrontal cortex, whereas GAD is associated with prevention system failure, hypervigilant/agitated symptoms, and hyperactivation in right prefrontal cortex (PFC). These left and right PFC locations can be directly targeted in an individualized manner for TMS. Additionally, this individually targeted rTMS can be integrated with cognitive interventions designed to activate the neural circuitry associated with promotion vs. prevention, thus allowing the neuroplasticity induced by the rTMS to benefit the systems likely to be involved in remediating depression. Targeted engagement of cortical systems involved in emotion regulation using individualized fMRI guidance may help increase the efficacy of rTMS in depression.

1. Current status of rTMS treatment for unipolar depression

Repetitive transcranial magnetic stimulation (rTMS) was approved by the FDA in 2008 for treatment-resistant unipolar major depression. However, despite its increasing use, typical effect sizes of rTMS treatment have been modest (Berlim et al., 2014; Lefaucheur et al., 2014), and both methodological and conceptual challenges remain regarding how to optimize its efficacy (Downar and Daskalakis, 2013; Daskalakis et al., 2008). This review considers two such challenges: specifically, targeting and context of stimulation. Rather than being targeted on specific brain regions functionally linked to depression on an individualized basis, rTMS is presently targeted by finding scalp locations which in general overlie brain regions which have been linked anatomically to depression in group-based analyses. We propose that refining rTMS via a systematic model of the functional neurocircuitry underlying depression, applying such a model to personalize the site of stimulation, and combining that stimulation with focused cognitive techniques targeting the brain circuits of interest is likely to improve its efficacy.

rTMS was first shown to be efficacious for the treatment of depression in the mid-1990s (George et al., 1995; and replicated: Pascual-Leone et al., 1996a, 1996b). Stimulation was applied at 20 Hz to left dorsolateral prefrontal cortex (DLPFC). This anatomical location was targeted because left prefrontal regions had shown decreased activation with depression in imaging studies, because patients with left prefrontal strokes were at increased risk for developing depression, and because left unilateral electroconvulsive therapy (ECT) was more effective than right (George et al., 1995). High frequency rTMS was chosen because it has the general property, at least when given at or above motor threshold, of increasing cortical excitability. In addition, it

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was postulated that repeated administration of high frequency stimulation would counteract the left prefrontal hypoactivation found with depressed patients (Kimbrell et al., 1999).

Given the initial success of the George et al. (1995) study, a number of similarly designed clinical trials followed in which their treatment paradigm was generally followed (George et al., 2010), with some exceptions, for example, using low frequency stimulation over right prefrontal cortex (e.g., Klein et al., 1999). This process of treatment development culminated in a successful industry-sponsored trial (O'Reardon et al., 2007), leading to FDA approval at the following parameters: 4 s trains of 10 Hz rTMS (26 s inter-train interval) to left PFC at 120% motor threshold intensity for 3000 pulses daily for 6 weeks. While a number of meta-analytic studies have concluded that rTMS has a significant anti-depressant effect in comparison to sham stimulation (e.g., Schutter, 2009; Slotema et al., 2010), the typical effect sizes have been modest. For example, the response and remission rates in the O'Reardon et al. (2007) trial were 25% and 16%. These rates are relatively disappointing, given typical remission rates of 65–75% using ECT (Sackeim et al., 2008). More recent studies have generally found modest response and remission rates as well: a recent meta-analysis of 29 studies (1371 patients) reported similar average rates (e.g., 29% average response rate) across studies (Berlim et al., 2014). Thus, while rTMS is clearly a promising treatment for unipolar depression, there remains significant work to be done in order to maximize its clinical utility.

2. Challenges in targeting of TMS for treating depression

One possible reason for the limited clinical response rates associated with TMS to date is non-optimized targeting (Downar and Daskalakis, 2013). The original method for determining the coil position used by George et al. (1995) was to find the site over motor cortex that evoked a maximal finger twitch, and then moving the coil to a point 5 cm anterior, with the 5 cm based on an estimation from the Talairach Atlas. This targeting system was built into the device used in the clinical trials leading up to FDA approval, and became part of the standard TMS treatment protocol for depression. In retrospect, the choice of this targeting method may not have been optimal, as it ignored variability due to head size, which is taken into account in neuroimaging methods such as the International 10/20 System for EEG. Indeed, it has been demonstrated using structural MRI that the original 5 cm rule in general often resulted in coil positions well short of DLPFC (Fitzgerald et al., 2009a), and that using structural MRIs to position the TMS coil over DLPFC resulted in response and remission rates of 42% and 30% respectively, compared with 18% and 11% using the 5 cm rule (Fitzgerald et al., 2009b).

Through the use of brain imaging, TMS targeting has begun to be refined from scalp-based methods to the use of neuronavigational systems which permit the targeting of individual cortical locations with potentially millimeter accuracy (Sparing et al., 2010). The combined use of MRI and neuronavigation allows a further step in efficacy of targeting TMS coils: moving from anatomical positioning to positioning based on functional imaging. In this case, sites of activation found in a single individual's fMRI can be overlaid on his or her structural MRI, and targeted directly. Such neuronavigational approaches are, in some cases, translated from basic neuroscience research and represent an important frontier in the application of TMS to treatment of psychiatric disorders.

Sack et al. (2009) provided a demonstration of the dramatic increase in the efficacy of TMS in modulating cortical function as one proceeds from scalp-based systems through neuronavigation using structural MRIs, group fMRI, and individual fMRI. Previously, TMS applied to parietal cortex during a Stroop-like task caused changes in task performance (Kadosh et al., 2007). In Sack et al. (2009), TMS was targeted to parietal cortex by the different methods in four different groups of subjects, using a scalp-based system (10/20 coordinate P4), anatomical imagery (individual structural MRI), group-based functional imagery (a group-averaged site based on Talaraich coordinates), and individual functional imagery (peak parietal activation in individual fMRI images recorded during task performance). Based on the task performance of each group, a power analysis was used to estimate the number of subjects needed to achieve a TMS effect on task performance at a $p < 0.05$ significance level. It was found that only five subjects were needed to observe a statistically significant behavioral effect of TMS on the task when individual fMRIs were used for targeting, while double that number were required to see the same effect using structural MRIs or group fMRIs, and a total of 47 subjects were needed when the 10/20 system was used. The dramatic differences in the effects on statistical power in this experiment were solely due to differences in targeting strategy, specifically the availability of individual-level fMRI data from a relevant task.

As has now been demonstrated repeatedly in a variety of experimental contexts, imaging-guided TMS can target and engage specific functional brain networks with high resolution and with the highly desirable ability to take into account individual differences in location. We propose that a further refinement in targeting can be included to generate long-lasting changes in these specifically-engaged networks by adding a dynamic element: that is, by *activating* the network of interest (e.g., by having the subject perform a task requiring neural processing within the network) *simultaneously* with TMS stimulation.

The well-developed paradigm of paired-associate stimulation (PAS) provides an example of this principle in its simplest form. In standard PAS, co-activation of sensori-motor cortex with afferent stimulation of the median nerve in the wrist precisely timed to arrive as a TMS pulse is delivered to motor cortex has been shown to significantly enhance cortical response in subsequent testing (Ziemann et al., 2008). Similarly, it has been suggested that increasing cortical plasticity in targeted networks with TMS while simultaneously activating them with tasks involving processing specific to those networks could induce enhanced effects. Such a synergistic impact of TMS plus a behavioral task could increase network-specific plasticity via a Hebbian-like synaptic mechanism that follows the functional principle "fire together, wire together" (Ragert et al., 2003; Thickbroom, 2007).

Such an enhancement effect has been demonstrated, for example, in the use of multiple sessions of simultaneous rTMS and working memory task performance to remediate working memory deficits in sleep-deprived individuals, where memory performance showed continued enhancement a full day after the last rTMS session (Luber et al., 2013). In this study, 5 Hz rTMS was applied while subjects performed a working memory task during four sessions over the course of 48 hours of sleep deprivation. Twenty-seven subjects (13 active TMS, 14 sham) completed the protocol. Another 21 (10 active TMS, 11 sham) non-sleep deprived subjects participated as controls. At the end of the sleep deprivation period, the sleep-deprived subjects receiving sham rTMS exhibited degraded performance in the working memory task, with slowed RT and lapsing (i.e., non-responses in task trials) at a rate of 6.4 per block of trials. In contrast, those receiving active rTMS performed similarly to the non-sleep deprived controls, exhibiting a similar speeding of RT attributed to practice, and a reduced lapsing rate of 1.7. Importantly, the sleep deprived group receiving active TMS showed rTMS-induced facilitation of DMS performance a full 18 hours after the last rTMS session, long after the acute action of rTMS at the local site of stimulation wore off. In the pre- and post-sleep deprivation contrasts of fMRI recorded during working memory performance, multivariate covariance modeling revealed that the Active TMS sleep deprived group (but not the Sham group) had a significant increase in fMRI-derived activity in a cortical area directly beneath where the TMS coil had been positioned. In affecting neural circuitry involved in WM to ameliorate the impact of SD, this study thus united the ideas of using multiple sessions to create a cumulative effect with the method of simultaneous task and TMS activation of cortical neurons to generate Hebbian-like effects. Although it should be noted that the Luber et al.