Review

Biological Psychiatry: CNNI

Personalized Transcranial Magnetic Stimulation in Psychiatry

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that allows for modulating the activity of local neural populations and related neural networks. TMS is touted as a viable intervention to normalize brain activity and alleviate some psychiatric symptoms. However, TMS interventions are known to be only moderately reliable, and the efficacy of such therapies remains to be proven for psychiatric disorders other than depression. We review new opportunities to personalize TMS interventions using neuroimaging and computational modeling, aiming to optimize treatment to suit particular individuals and clinical subgroups. Specifically, we consider the prospect of improving the efficacy of existing TMS interventions by parsing broad diagnostic categories into biologically and clinically homogeneous biotypes. Biotypes can provide distinct treatment targets for optimized TMS interventions. We further discuss the utility of computational models in refining TMS personalization and efficiently establishing optimal cortical targets for distinct biotypes. Personalizing cortical stimulation targets, treatment frequencies, and intensities can improve the therapeutic efficacy of TMS and potentially establish noninvasive brain stimulation as a viable treatment for psychiatric symptoms.

Keywords: Biotypes, Brain networks, Brain stimulation, Connectivity, Personalized medicine, TMS

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Psychiatric disorders are characterized by distinct behavioral symptoms and abnormalities in brain function and structure. These symptoms can be mitigated with a number of behavioral and pharmacological interventions (1,2). However, existing interventions only partially offset the burden of disease, and a number of individuals remain clinically symptomatic after treatment (3,4). New therapeutic avenues that may complement existing pharmacological and psychological therapies are therefore required.

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that offers the potential to successfully complement existing behavioral and pharmacological treatments for some psychiatric disorders (5). TMS is a widely used technique for noninvasively modulating neural activity via the application of a rapidly changing magnetic field over the scalp. Depending on the stimulation protocol, TMS can either increase or inhibit local neural activity, consistent with the processes of long-term potentiation and long-term depression, respectively (6). In principle, TMS can therefore be used to balance altered local neural activity and restore related complex changes in activity of brain networks underpinning psychiatric symptoms (7). Unfortunately, the impact of existing TMS interventions on both brain activity and symptoms is highly variable [for a review see (7)]. Whereas some individuals respond positively to treatment, with a commensurate normalization of brain activity, other individuals with similar clinical profiles often show no response to TMS interventions (8).

Can this heterogeneity in treatment efficacy be improved through personalizing interventions to suit an individual's sex, age, clinical profile, brain anatomy, connectivity of the simulated region, or other physiological indicators? Currently, cortical stimulation targets, stimulation intensities, burst intervals, and intervention frequencies have been established largely based on trial and error as well as anecdotal evidence supporting choices and parameters that have been effective in a majority of individuals. Personalizing interventions according to neural mechanisms of action can potentially benefit the many individuals for whom current TMS interventions have proven to be ineffective.

In this review, we consider new opportunities to improve the reliability of TMS interventions in psychiatry by taking advantage of emerging knowledge about the impact of TMS on brain regions that are distant from the local stimulation site. To understand the neural mechanisms of action underlying TMS, in addition to the local effects of TMS evident in cortical neuropil within the stimulation vicinity (9–11), it is crucial to account for downstream effects that may be distant to the stimulation site (12–14). Advances in the field of neural connectomics (15) herald new opportunities to take into account heterogeneity in brain connectivity when planning TMS interventions.

We consider two distinct opportunities to personalize TMS interventions that have been enabled through developments in the field of connectomics and computational neuroscience. First, we consider the prospect of biotyping individuals according to brain connectivity and behavioral symptoms, with

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the goal of delineating unique interventions for each specific biotype. Second, we consider recently developed computational models of brain networks that aim to predict downstream effects of local cortical stimulation. These models can be used to evaluate the efficacy of an exhaustive number of stimulation targets in silico.

TRANSCRANIAL MAGNETIC STIMULATION

TMS is a validated noninvasive brain stimulation technique for modulating the activity of neurons within a region of the cortex (16–18). TMS is based on the principle of electromagnetic induction and delivers a strong, but short-lived, magnetic field that induces a perpendicular electrical field (19). The resulting electrical currents can subsequently depolarize neuronal axons (Figure 1A). The local effects of TMS are typically studied in the motor system because motor evoked potentials (MEPs) provide a direct behavioral correlate that can be easily measured (20–24). An increased motor response (MEP) in the targeted muscle following TMS is generally considered a proxy of local neural excitation, whereas a reduction of the MEP is thought to indicate inhibition (17,21). However, the effect of TMS on the targeted neuropil is not necessarily a categorical effect and may be better quantified along a response spectrum. Furthermore, MEPs represent a relatively coarse measure of complex neural changes. These considerations are critical but are often overlooked when using MEPs as a proxy of TMS-induced changes in neural activity. More generally, given that gyral geometry and tissue conductivity can differ between the motor cortices and other regions, using MEPs to guide selection of TMS parameters in regions distant from the motor cortices is challenging. Neuroimaging indices such as electroencephalography signal power may provide more principled alternatives. A typical TMS system is shown in Figure 1B, including a figure-of-eight stimulation coil (Figure 1C).

In addition to acute effects, repetitive TMS (rTMS) can change local neural activity for a period that outlasts the duration of the stimulation (25). Owing to its lasting effects and low risk of adverse side effects, rTMS has become the protocol of choice for clinical trials assessing the potential use of TMS as a therapeutic tool to alleviate symptoms of psychiatric disorders [for a review see (25)]. A popular protocol to chronically inhibit or excite neural activity is high-frequency (5–20 Hz) and low-frequency (1 Hz) rTMS (26,27). High-frequency TMS is used to excite neural activity in the targeted area, whereas low-frequency TMS is used to inhibit neural activity. The use of these protocols has been approved by the U.S. Food and Drug Administration as a therapy for treatment-resistant depression and has since proven to be an efficacious and safe adjunctive intervention for the disorder (28). Theta burst stimulation (TBS) is a newer protocol that allows for the modulation of neural activity in a shorter time compared with high-frequency and low-frequency rTMS (approximately 1–3 minutes vs. 15–20 minutes). The development of TBS was borne from animal studies showing that continuous or intermittent patterns of stimulation in the theta frequency range induce long-term potentiation and long-term depression (29–32). The neurobiological foundations, short duration, and relatively low intensity of stimulation (70% resting motor threshold) represent major advantages of TBS protocols and make them readily translatable to clinical settings. More recent stimulation protocols, such as quadripulse magnetic stimulation, have been developed (33,34), but their clinical safety and efficacy in psychiatry remain to be established.

TMS IN PSYCHIATRY: CHALLENGES AND OPPORTUNITIES

The use of TMS as a potential tool to evaluate neural function and improve symptoms of psychiatric disorders can be traced

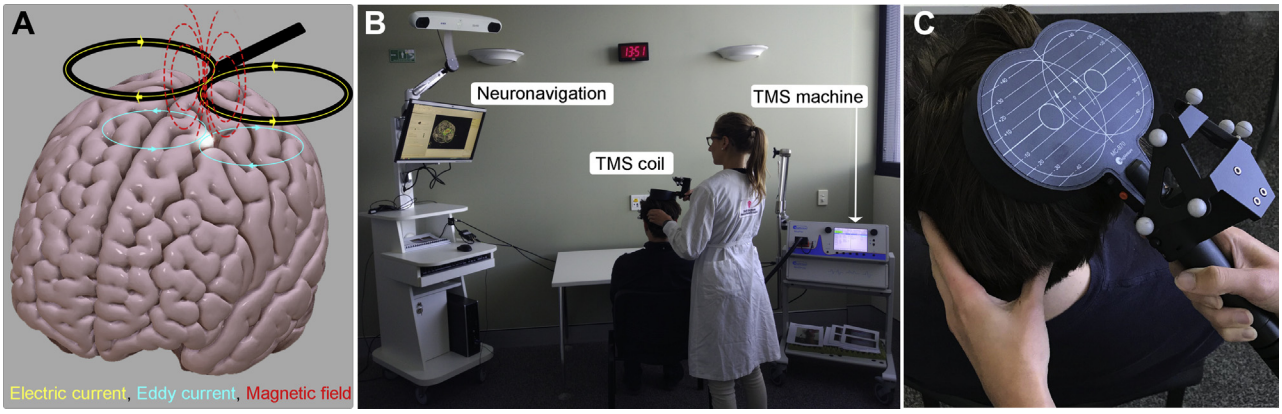

Figure 1. **(A)** Representation of current flow in a standard figure-of-eight transcranial magnetic stimulation (TMS) coil. Electrical current in the stimulation coil is used to generate a magnetic field. The magnetic field induces secondary currents (eddy currents) within cortical neuropil. Eddy currents can modify neural activity (101), resulting in effects that are consistent with long-term potentiation and long-term depression. **(B)** Illustration of a typical TMS system, including coil (positioned on scalp), pulse generator, and neuronavigation system. **(C)** TMS is delivered via a stimulation coil that is positioned close to the scalp of the individual receiving treatment. Typically, the individual remains in a seated position throughout the stimulation. The operator navigates the TMS coil to the desired cortical target using scalp landmarks or with guidance from a neuronavigation system, as depicted in panel **(B)**. The intensity of the stimulation is increased until a motor cortex threshold is reached. This threshold is determined by stimulating (single-pulse) the primary motor cortex and measuring the resulting motor evoked potential in the contralateral hand muscle of the individual using electromyography. Although the individual may sense a tapping on the head and other muscle-related sensations that may cause mild discomfort, the treatment is painless and considered safe as long as appropriate safety guidelines are followed (102). TMS interventions for psychiatric disorders such as depression and obsessive-compulsive disorder are typically repeated daily for a period of 3–4 weeks.