

## Neuroscience and Psychiatry

# Multimodal Applications of Transcranial Magnetic Stimulation for Circuit-Based Psychiatry

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**A growing body of research** is advancing our understanding of the anatomy and physiology of brain networks and the mechanisms by which they process cognition, behavior, and emotion.<sup>1</sup> This "circuit revolution" is changing our conceptualization of psychiatric pathophysiology and calls for technologies to reliably and safely assess the structure and function of brain circuits in humans.

Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulation technique that applies powerful and rapidly changing magnetic fields over the surface of the skull and generates targeted electrical currents in the brain, leading to neuronal action potentials. Transcranial magnetic stimulation has a well-established safety profile and is able to modulate brain activity without surgery, anesthesia, or the induction of seizures.<sup>2</sup> Transcranial magnetic stimulation is a widely used technique in cognitive and systems neuroscience, and a number of clinical applications, both diagnostic and therapeutic, exist. Diagnostically, it is used by clinical neurophysiologists in conjunction with electromyography to assess pathologies that compromise the motor system.<sup>3,4</sup> In addition, the use of neuronavigated TMS for presurgical cortical mapping was recently cleared by the US Food and Drug Administration. Therapeutically, high-frequency TMS to the left dorsolateral prefrontal cortex was cleared by the US Food and Drug Administration in 2008 for the treatment of major depressive disorder, and a total of 4 different TMS systems have been cleared since.

After 1985, protocols were quickly developed to assess the physiology of the human motor system, including cortical excitability, inhibitory and excitatory mechanisms, conduction time, connectivity, and plasticity. These are the exact same properties that we now need to understand across affective, behavioral, and cognitive circuits, to establish solid circuit-based models of neuropsychiatric disease with the potential to affect clinical practice. Therefore, TMS can be a critical tool in psychiatry, with scientific and clinical relevance beyond its current therapeutic applications. To achieve its full potential, though, multimodal combined technologies are needed to measure the neurobiological effects of TMS beyond the motor cortex. Solutions for the reliable real-time integration of TMS with electroencephalography (EEG), positron emission tomography, magnetic resonance imaging, and other neuroimaging methods have been developed and are increasingly available.<sup>5</sup> Transcranial magnetic stimulation protocols, while diverse, fall under 3 main categories: single-pulse, paired-pulse, and repetitive TMS.

Single-pulse TMS is used in motor conduction studies to assess the integrity of the corticospinal motor pathway, a measure of connectivity.<sup>3,4</sup> One pulse of appropriate intensity is applied over the motor cortex, and the response in the muscle (ie, the motor-evoked potential [MEP]) is measured by use of electromyography. By assess-

ing the time between the TMS pulse and the beginning of the MEP, one can identify pathological changes in neurons and synapses.

Single pulses are also used for motor threshold (MT) determination, a measure of cortical excitability that reflects the state of neuronal membranes, synapses, and their glutamate receptors.<sup>6</sup> The MT is defined as the minimum TMS intensity needed to induce a muscle contraction or MEP larger than 50  $\mu$ V in at least 50% of the trials.<sup>3,4</sup> The resting MT is measured with the muscle at rest, and the active MT is measured during isometric contraction (the active MT is typically lower). These measures are stable and reproducible, but can change with factors that modulate cortical excitability, including medications or pathological states.

A related protocol is the cortical silent period, a period of electromyographic suppression following a TMS pulse to the motor cortex during active isometric contraction of the contralateral muscle (not during rest). The cortical silent period measures cortical inhibition mediated by  $\gamma$ -aminobutyric acid receptor class B (GABA<sub>B</sub>).<sup>6</sup>

These simple protocols illustrate 2 fundamental properties of TMS. First, the physiological effects are circuit-wide and not limited to the target brain region; if a single TMS pulse over the motor cortex induces a contralateral muscle contraction, it must change the properties of the primary and secondary motor neurons all the way to the motor unit. The cortical target therefore provides access to an entire functional circuit. Second, the effects of stimulation are state-dependent; the fact that the active MT is lower than the resting MT and the fact that the silent period is only observed when the targeted muscle is active demonstrate that the effects of TMS depend on the physiological state of the brain regions and networks that it is trying to change. These 2 principles apply to motor and nonmotor neurostimulation; complex networks that support affect, behavior, and cognition dynamically fluctuate across different states (in health and in disease), and these physiological oscillations condition the biological and clinical effects of TMS.

Paired-pulse protocols have been established to study intracortical inhibition and facilitation. They require the application of 2 TMS pulses of different intensities (typically between 80% and 120% of the MT) and interstimulus intervals (usually in the order of a few milliseconds). Combined studies using TMS and pharmacology have identified the neurotransmitters involved in these physiological dynamics.<sup>6</sup> The 2 most studied protocols are short-interval cortical inhibition and intracortical facilitation.<sup>3,4</sup>

Short-interval cortical inhibition consists in the application of a first (conditioning) subthreshold stimulus (eg, 80% of the MT, but unable to elicit MEPs) followed by a second (test) suprathreshold stimulus (eg, 120%), with a short interstimulus interval of 1 to 5 milliseconds. The MEP from the test stimulus is compared with an identical TMS test stimulus that was not preceded by a conditioning pulse. This intervention results in an inhibitory response, characterized by a reduction of the MEP amplitude thought to be mediated by GABA<sub>A</sub> receptors.<sup>6</sup>



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Intracortical facilitation uses the same paired-pulse configuration (subthreshold conditioning pulse followed by a suprathreshold test pulse) but with a longer interstimulus interval of 10 to 17 milliseconds, resulting in an excitatory response mediated primarily by glutamate.<sup>6</sup>

Repetitive TMS can modulate cortical excitability and connectivity by inducing long-term depression-like and long-term potentiation-like plastic changes that outlast the period of stimulation. The effects are parameter-dependent: while low-frequency trains (typically 1 Hz) lead to suppression of activity in the targeted brain region, high-frequency stimulation ( $\geq 5$  Hz, although typically 10–20 Hz) results in excitatory effects in most people. Newer protocols, such as theta burst stimulation, have recently been developed that also induce differential effects on cortical excitability (eg, inhibition or facilitation) with greater efficiency.<sup>7</sup> Repetitive TMS is used therapeutically, given its capacity to modulate neurophysiology beyond the time of stimulation, but also, in cognitive neuroscience, it is used to assess the causal role of brain regions or networks.<sup>8</sup>

A number of studies have used motor neurophysiology single- or paired-pulse TMS protocols to identify general mechanisms of disease, biomarkers, and predictors of treatment response in psychiatric populations.<sup>9</sup> Although these results reveal global cross-circuit pathological changes in excitability, inhibition, facilitation, or cortical plasticity, they are generally nonspecific. This is primarily because these measures typically focus on the motor system, which may be affected in psychiatric disorders but is generally not the critically altered circuit. To fully understand the neurophysiological mechanisms of neuropsychiatric syndromes, we need tools that transcend the motor system and allow us to interrogate relevant affective and cognitive networks.

Neuroimaging and neurophysiological methods are used to explore the pathophysiology of neuropsychiatric conditions, and they have been critical to the circuit revolution. These methods are strictly observational and therefore limited to establishing correlations between neurobiology and behavior or symptom severity. Brain stimulation, in general, and TMS, in particular, are interventions, and therefore they permit concluding causality. Nevertheless, TMS had

been limited by the methods available to measure its effects: either motor neurophysiology or behavioral/clinical measures. In recent years, however, multimodal approaches have been developed that combine TMS with neuroimaging and central neurophysiology (EEG) to overcome these problems.<sup>5</sup>

These advances have recently allowed for the use of traditional single- and paired-pulse TMS protocols combined with EEG in non-motor systems. In this issue of *JAMA Psychiatry*, Sun and colleagues<sup>10</sup> used a paired-pulse TMS protocol (long-interval cortical inhibition) combined with simultaneous EEG to assess GABA-mediated cortical inhibition in patients with major depressive disorder before starting a course of magnetic seizure therapy. They hypothesized that the antisuicidal therapeutic efficacy of magnetic seizure therapy is mediated by GABAergic systems, and, therefore, stronger TMS-evoked inhibitory responses reflecting well-functioning GABAergic circuits would predict a positive therapeutic response. Indeed, Sun and colleagues<sup>10</sup> report that 2 different EEG measures of cortical inhibition (a negative evoked potential in the EEG that happens approximately 100 milliseconds after a stimulus or event of interest and long-interval cortical inhibition) evoked by TMS to the left dorsolateral prefrontal cortex, but not to the left motor cortex, predicted remission of suicidal ideation with great sensitivity and specificity. This study<sup>10</sup> illustrates the potential of multimodal TMS to study physiological properties of relevant circuits in neuropsychiatric populations. Significantly, it also highlights the anatomical specificity of these measures because the predictive value was exclusive to the inhibitory properties of prefrontal circuits but not motor systems.

Multimodal TMS applications allow us to study the physiology of human brain circuitry noninvasively and with causal resolution, expanding previous motor applications to cognitive, behavioral, and affective systems. These innovations can significantly affect psychiatry at multiple levels, by studying disease-relevant circuits to further develop systems for neuroscience models of disease and by developing tools that could be integrated into clinical practice, as they are in clinical neurophysiology clinics, to inform decision making, the differential diagnosis, or treatment planning.

#### ARTICLE INFORMATION

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Nexstim, Neuronix, Starlab Neuroscience, Neuroelectronics, Axilum Robotics, Magstim Inc, and Neosync and is listed as an inventor on several issued and pending patents on the real-time integration of TMS with electroencephalography and magnetic resonance imaging. No other disclosures are reported.

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