Commentary

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Modulating Anterior Midcingulate Cortex Using Theta Burst Stimulation

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Leveraging the significant translational potential of noninvasive brain stimulation requires clear exposition of its effects on neuronal activity across the brain. Within the widely studied domain of transcranial magnetic stimulation, previous research has successfully identified stimulation protocols capable of producing rapid and sustainable neuroplastic changes with brief administration periods (1). These protocols, grouped under the umbrella of theta burst stimulation (TBS), involve the delivery of high-frequency "bursts" of magnetic pulses repeated at a theta (~5 Hz) frequency. Two of these protocols, continuous TBS (cTBS) and intermittent TBS (iTBS), have been shown to produce directionally opposite effects on the motor cortex (2). Specifically, investigations into the change in the motor-evoked potential amplitudes after TBS of the motor cortex have suggested robust suppression of cortical excitability after cTBS and an enhancement after iTBS (2). Bidirectional control over cortical excitability is valuable for examining causal relationships between neuronal activity and behavior and for manipulating atypical activity underlying disease. While the directional effects of cTBS and iTBS on motor cortex excitability have been well documented, confirming these effects in regions other than the motor cortex has proven difficult. Particularly in the prefrontal cortex, investigations into the patterns of excitability modulations produced by cTBS and iTBS have produced mixed results (3). Since regions within the prefrontal cortex are critically implicated in the dysfunction associated with psychiatric disorders (4), determining how these protocols influence cortical excitability is essential for designing effective interventions.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Baker *et al.* (5) document their observations of the directional effects of cTBS and iTBS over the prefrontal cortex, particularly the anterior midcingulate cortex (aMCC). Previous work has shown that rhythmic stimulation of the dorsolateral prefrontal cortex (DLPFC) modulates neural correlates of reward processing through downstream effects in the reward network (6). Specifically, modulating the excitability of the left DLPFC changes the magnitude of a differential event-related potential that reflects sensitivity to positive feedback relative to negative feedback. This measure, called the reward positivity effect, is hypothesized to be generated within the aMCC (7). This effect is computed as the difference between the trial-averaged potentials at a midfrontal channel (electrode site FCz in the International 10-20 system) after positive feedback and negative feedback. Given the sensitivity of this event-related potential measure to aMCC excitability after stimulation of the DLPFC (6), it is well suited to examine the directional effects of cTBS and iTBS. Accordingly, using a within-subjects design, the authors examined changes in the reward positivity effect in the aMCC after cTBS and iTBS over the left DLPFC. TBS was delivered using an automated mechanism adapting to head movements in real time, which ensured consistent targeted delivery of the magnetic pulses throughout the administration period. The reward positivity effect was determined using a simple decision-making task in which positive and negative feedback were probabilistically presented after choices. Baseline measurements of reward positivity effect and behavioral choice patterns were compared with successive measurements after stimulation. Directional effects of cTBS and iTBS were determined by examining whether stimulation increased or decreased the reward positivity effect and its association with behavior.

The reward positivity effect was differentially affected by iTBS relative to cTBS. After iTBS, a consistent reduction in the amplitude of the reward positivity effect was observed. The authors interpret this effect as a disruption in dopaminergic signaling leading to reduced reward sensitivity in the aMCC. Suppression of reward valuation was also evident in behavioral performance as iTBS was followed by a slowing of reaction times, potentially reflecting reduced motivation. Consequently, iTBS of the prefrontal cortex appeared to be associated with a suppression of reward-related cognitive processing. This finding is in contrast with the enhancement of function commonly observed during iTBS of the motor cortex (2). On the other hand, cTBS over the DLPFC did not modulate the reward positivity effect. This finding also stands in contrast to the suppression of function after cTBS over the motor cortex (2) and the prefrontal cortex (3). Together, these findings suggest that cTBS and iTBS may affect the prefrontal cortex in complex ways that may not align with expectations from previous work.

Significant variability in the effects of noninvasive brain stimulation is partially attributed to anatomical, functional, and clinical differences across individuals (8). Consequently, there is considerable interest in personalizing brain stimulation to the unique structural and functional attributes of an individual to maximize the efficacy of the stimulation. Given the considerable variability in findings across studies performing iTBS and cTBS over the prefrontal cortex (3), Baker *et al.* (5) propose another metric to facilitate personalization. While the DLPFC stimulation site was determined through conventional targeting methods based on the International 10-20 system in their first experiment, the authors used a cortical thickness approach in their second experiment. Specifically, TBS was delivered at the DLPFC site with the maximum cortical thickness. The authors reasoned that stimulating at a DLPFC site with greater

SEE CORRESPONDING ARTICLE ON PAGE 1052

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thickness would stimulate a greater density of neurons and synaptic connections of the DLPFC with the broader reward network. If so, the influence of TBS on reward positivity in the aMCC should be more robust. Indeed, the authors observed a stronger suppression of reward positivity effect toward the end of their measurement period, although the effects were less consistent across time. Even with this personalized form of stimulation, cTBS did not produce any significant effects on reward positivity performance. The authors were thus able to replicate the major findings from their first experiment with a stronger effect size for iTBS, motivating the potential feasibility of such an approach in basic and clinical neuroscience investigations.

Baker *et al.* (5) offer interesting insights into the effects of iTBS and cTBS over the prefrontal cortex and motivate questions for future research. Combined with previous research documenting considerable variability in the effects of TBS over the prefrontal cortex on executive functioning (3), the new findings further support the idea that TBS affects prefrontal functioning in complex ways. It is possible that the effects of TBS may be dependent on the particular state engaged by the ongoing task (1,9). Future studies should seek to specifically examine the effects of TBS according to the type of executive function under examination. Personalizing stimulation targets according to cortical thickness is another novel addition to the battery of factors motivated to improve the consistency and effectiveness of TBS across individuals. However, further work is needed to validate this approach. For example, future studies could use neuroimaging to examine the differential effects of cortical thickness–guided stimulation and conventional stimulation of the DLPFC on reward-related activation patterns in the aMCC. In addition, following the authors' reasoning to target the site of cortical thickness to maximally stimulate the neuronal and synaptic connections in the target area, future studies could potentially identify targets using a combination of gray matter thickness and interareal white matter connectivity determined using diffusion imaging. Such developments in anatomical personalization may improve the efficacy of TBS, enhancing its potential for translational applications. Finally, various psychiatric conditions are characterized by impairments in reward processing and motivation (10). The observations by Baker *et al.* (5) motivate the use of TBS and other transcranial magnetic stimulation protocols for the specific purpose of improving such deficits in psychiatric populations.

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References

1. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG (2013): Noninvasive brain stimulation: From physiology to network dynamics and back. Nat Neurosci 16:838–844.
2. Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005): Theta burst stimulation of the human motor cortex. Neuron 45:201–206.
3. Lowe CJ, Manocchio F, Safati AB, Hall PA (2018): The effects of theta burst stimulation (TBS) targeting the prefrontal cortex on executive functioning: A systematic review and meta-analysis. Neuropsychologia 111:344–359.
4. Hare BD, Duman RS (2020): Prefrontal cortex circuits in depression and anxiety: Contribution of discrete neuronal populations and target regions [published online ahead of print Feb 21]. Mol Psychiatry.
5. Baker TE, Lin M-H, Gueth M, Biernacki K, Parikh S (2020): Beyond the motor cortex: Theta burst stimulation of the anterior midcingulate cortex. Biol Psychiatry Cogn Neurosci Neuroimaging 5:1052–1060.
6. Baker TE, Lesperance P, Tucholka A, Potvin S, Larcher K, Zhang Y, *et al.* (2017): Reversing the atypical valuation of drug and nondrug rewards in smokers using multimodal neuroimaging. Biol Psychiatry 82:819–827.
7. Holroyd CB, Yeung N (2012): Motivation of extended behaviors by anterior cingulate cortex. Trends Cogn Sci 16:122–128.
8. Cocchi L, Zalesky A (2018): Personalized transcranial magnetic stimulation in psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 3:731–741.
9. Polanía R, Nitsche MA, Ruff CC (2018): Studying and modifying brain function with non-invasive brain stimulation. Nat Neurosci 21:174–187.
10. Sharma A, Wolf DH, Ciric R, Kable JW, Moore TM, Vandekar SN, *et al.* (2017): Common dimensional reward deficits across mood and psychotic disorders: A connectome-wide association study. Am J Psychiatry 174:657–666.