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HOT TOPICS

Using metabolic imaging to investigate neuromodulatory mechanisms of rTMS

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Repetitive transcranial magnetic stimulation (rTMS) induces varieties of behavioral effects ranging from cognitive domains to FDA-approved treatments for migraine and depression. Despite these exciting applications, open questions remain about rTMS mechanisms. Through studies that combine TMS with other measures (neuroimaging, electroencephalogram, etc.), we have gained a better understanding of how rTMS influences brain activity; however, these findings leave gaps in our knowledge of the neurochemical underpinnings of how rTMS affects behavior. Neurochemical and related metabolic fluctuations covary with cognitive and disease states and may inform variations in treatment outcome. Investigating the influence of rTMS on metabolism provides the potential to use metabolite concentrations as predictors of TMS response given that rTMS is designed to change behavior via neural effects.

Magnetic resonance spectroscopy (MRS) is one non-invasive tool that can further add to the mechanistic understanding of rTMS. MRS identifies molecular concentrations of metabolites in vivo. In conjunction with TMS, the functional changes associated with perturbation of neurotransmitter receptors can be validated with measurement of the metabolites themselves [1]. A recent study in depressed adolescents found that the glutamate/glutamine ratio, representing the brain's primary excitatory neurotransmitter, was increased in the anterior cingulate cortex and DLPFC after rTMS treatment and was associated with clinical improvement up to 6 months post treatment [2]. Nevertheless, MRS has several limitations: MRS acquisition is lengthy, collected one voxel at a time, and has low signal-to-noise ratios for glutamate at lower magnetic field strengths [1].

One new approach adding specificity in resolving the glutamate signal is glutamate-weighted chemical exchange saturation transfer or "gluCEST". GluCEST measures the exchange of glutamate amine with water rather than directly measuring the metabolite as in MRS. This change in measurement gives gluCEST greater spatial resolution and sensitivity than MRS and other amine imaging paradigms such as positron emission topography with a glutamate tracer [3, 4]. In a new study by Cember et al. gluCEST was used in conjunction with continuous theta burst stimulation (cTBS, a putative inhibitory form of rTMS) to visualize local and off-target glutamatergic changes after stimulation to the primary motor cortex (M1). As hypothesized, glutamate was found to be less concentrated in ipsilateral M1 after active cTBS in comparison to sham [5]. This result represents a validation of previously observed cTBS effects on other imaging and physiological signals. gluCEST, albeit promising, is not without shortcomings. gluCEST is not specific to glutamate, with only ~70% of the signal representing glutamate concentration [4]. Additionally, gluCEST cannot differentiate between extracellular and intracellular glutamate, and due to pH differences between environments it may overweight extracellular pH in comparison to their actual concentrations [5].

Nevertheless, both MRS and gluCEST provide valuable new evidence for how neuromodulatory rTMS induces biochemical changes. Future work could benefit from collecting additional data within studies such as electrophysical and functional imaging data to increase our understanding of how rTMS generates behavioral changes via the brain. By continuing to investigate TMS with these methods, we will learn more about rTMS mechanisms of action towards increasing the scope of its use and the precision of its application.

REFERENCES

1. Cuypers K, Marsman A. Transcranial magnetic stimulation and magnetic resonance spectroscopy: Opportunities for a bimodal approach in human neuroscience. NeuroImage. 2021;224:117394.
2. Croarkin PE, Nakonezny PA, Wall CA, Murphy LL, Sampson SM, Frye MA, et al. Transcranial magnetic stimulation potentiates glutamatergic neurotransmission in depressed adolescents. Psychiatry Res Neuroimaging. 2016;247:25–33.
3. Bagga P, Pickup S, Crescenzi R, Martinez D, Borthakur A, D'Aquilla K, et al. In vivo GluCEST MRI: Reproducibility, background contribution and source of glutamate changes in the MPTP model of Parkinson's disease. Sci Rep. 2018;8:2883.
4. Cai K, Haris M, Singh A, Kogan F, Greenberg JH, Hariharan H, et al. Magnetic resonance imaging of glutamate. Nat Med. 2012;18:302–6.
5. Cember A, Deck BL, Kelkar A, Faseyitan O, Zimmerman JP, Erickson B. et al. Glutamate-Weighted Magnetic Resonance Imaging (GluCEST) detects effects of transcranial magnetic stimulation to the motor cortex. NeuroImage. 2022;256:119191. https://doi.org/10.1016/j.neuroimage.2022.119191.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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