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Commentary

The Effects of Low-Intensity Repetitive Transcranial Magnetic Stimulation on White Matter Plasticity and Depression

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Myelination of axons enables the rapid transfer of information in neurons over large distances within an organism (1), and it is found both in the peripheral nervous system and in the central nervous system. Throughout the lifespan, the degree of myelination is dynamically changing; small perturbations in myelin dynamics of these highly complex networks can accumulate and may contribute to severe neurological and neuropsychiatric disorders such as major depressive disorder (MDD) and schizophrenia.

Changing the pathological myelination state to its native state is the goal of many neuromodulation techniques, like repetitive transcriptional magnetic stimulation (rTMS).

In rTMS, transient brain activation from repetitive bursts of short magnetic pulses, applied noninvasively over the human head, is used to accomplish lasting changes of pathological brain states and alleviate MDD symptoms (2–4). A multitude of structural modifications that occur in the brain as a consequence of rTMS might lead to the effects observed in various studies, ranging from modifications occurring in axon and synapse morphology at the microscale, to large-scale remodeling of neural networks involving multiple distal brain regions (2,5). Of particular interest, when considering the application of rTMS for the treatment of MDD, is the long-term rewiring of intra- and interhemispheric connections, affecting the communications of prefrontal–cingulate brain areas that are responsible for cognitive and emotional functions. In the current issue of *Biological Psychiatry: Global Open Science*, Seewoo *et al.* (6) present a variety of approaches that combine brain imaging techniques and behavioral manipulations to investigate low-intensity rTMS (LI-rTMS)–induced brain white matter (WM) repair in a rodent model of depression.

Rodents provide a feasible model for studying the influences of rTMS on depression. Specifically, their well-characterized brains, excellent genetic description, and well-studied behavior enables experimenting that may be difficult in other animal models or in humans. The small heads of rodents in relation to commercially available coils might be seen as a limiting factor. However, physiological studies show that the neural activity evoked by TMS in the rodent brain is largely comparable to that in the human brain (7). This may suggest similar mechanisms for the rTMS-induced neural reorganization and mitigation of depression in rodents and humans. Therefore, rodents have a high potential for being an optimal animal model for the development of a physiological understanding and finding a TMS-based treatment for MDD in humans.

When subjected to chronic restraint stress (CRS) by constraint inside a narrow tube, rodents show a behavioral phenotype of depressive-like condition and express accompanying changes in neurophysiology. This form of depression can be considered analogous to human depression caused by everyday stress. In their previous work, Seewoo *et al.* (8) show that many of the biological markers that show indicative changes in human patients also undergo concordant changes in the rodent model of depression and that those changes are correlated with the behavioral measures of disease. However, this mild form of inducing depression may drive subtle changes of brain organization different from that in other more debilitating forms of depression induced via drug injection, physical exhaustion, or mutagenesis. Moreover, some animals exhibit conditioned inhibition of fear, raising doubts about the robustness of CRS in inducing depression. Nevertheless, on a brighter note, this mild form has the advantage that its effects are reversible, making it suitable for multiple testing with different forms of therapy and comparing them in the same animal and to control treatments.

Seewoo *et al.* (6) exposed juvenile rodents to 13 daily CRS sessions, each 2.5 hours in duration, to induce a depression syndrome. They then carried out diffusion-weighted magnetic resonance imaging (dMRI) of these animals over a span of 4 weeks to assess ensuing WM changes resulting from the CRS procedure and compared them with WM changes in healthy unrestrained animals. Both diffusion tensor (DT) metrics and diffusion kurtosis (DK) metrics were used to measure myelination-related changes occurring in WM tracts. The authors observed divergent changes in DT metrics between the restrained and unrestrained groups in the internal capsule (IC) and fimbria (Fm) that were independent of brain-maturation changes. They interpret these changes as evidence of a delayed WM maturation in restrained animals for these regions. While both groups showed changes in DT metrics with maturation in external capsule (EC), the change was larger for the restrained animal group. Moreover, the DK metrics, which account for deviation of diffusion displacement from a gaussian profile, and which are highly sensitive to microstructural changes in tissue architecture, largely support the above observation with changes occurring in IC, Fm, and EC. However, caution is needed when interpreting the results of DT and DK metric changes with regard to WM myelination–associated changes. Previous results show that both

SEE CORRESPONDING ARTICLE ON PAGE 153

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measures can exhibit opposite changes, or even fail to show changes, depending on the progress and severity of demyelination of WM tracts (9). Subsequently, the authors extracted additional fiber bundle parameters (fixel) from dMRI, showing impaired corpus callosum (CC) development in restrained animals and complying with the results from DT- and DK-derived changes in Fm, IC, and EC.

The authors then used two low-intensity rTMS paradigms—2 weeks of daily 10-minute stimulation at 10 Hz (6000 pulses total) or 1 Hz (600 pulses total)—to probe LI-rTMS–related changes in WM tracts of healthy unrestrained animals. Stimulation was provided by a custom-made coil with 13 mT that induces subthreshold currents in the rodent brain. Both DT and DK metrics showed changes after 10-Hz and 1-Hz LI-rTMS treatment with differences apparent in WM tracts (IC, Fm, EC, and CC), and at different time points from the onset of LI-rTMS treatment. In general, however, the changes in DT and DK metrics were visible earlier for 10-Hz LI-rTMS–treated animals compared with 1-Hz LI-rTMS–treated animals. It is also noteworthy that many of the changes in DT and DK metrics persisted and continued to change well after cessation of daily LI-rTMS sessions. Seewoo *et al.* (6) then chose to use only the 10-Hz subthreshold LI-rTMS treatment for exploring the LI-rTMS–driven effect on CRS-related WM changes.

Animals exposed to CRS then received 10-Hz LI-rTMS (6000 pulses) delivered 3 times daily, 1 hour apart, 5 days a week, for 2 weeks. dMRI was next acquired during and after the cessation of LI-rTMS treatment to ascertain WM changes. Both DT and DK metrics show changes in fimbria specific to LI-rTMS treatment not seen in the sham/control group, which is taken as an indication of rescue of abnormal myelination associated with CRS. However, while the DT and DK metrics decreased in fimbria after LI-rTMS treatment, in the same region those measures showed an increase with time in healthy unrestrained animals. This does not naturally mean that the underlying myelination changes in the above two cases are antagonistic, but because of the complex relationship of DT and DK metrics to demyelination severity, the inferred recovery of abnormal myelination as a result of LI-rTMS treatment has to be verified using other experimental techniques. Fixel-based metrics show a greater increase in IC for LI-rTMS–treated animals compared with the sham/control group, whereas the difference of the same metrics in EC was insignificant between the treatment groups. In CC, both DT and DK metrics and fixel-based metrics show changes that are representative of recovery of myelination after LI-rTMS treatment in restrained animals.

Finally, Seewoo *et al.* (6) verify whether the recovery of myelination inferred from dMRI is reflected in immunohistology. Brain tissue was stained for myelin basic protein (MBP) for evaluating the differences in myelin content across treatment groups. Unsurprisingly, the MBP stain of CC showed greater intensity in restrained animals treated with LI-rTMS compared with sham/control groups, confirming the findings of dMRI. The possibility of a histological validation of dMRI results is a major advantage over human studies. This demonstrates that basic mechanisms can be better studied using rodent models, which offer much more sophisticated methods for quantitative physiological characterization of the underlying mechanisms. The result obtained using MBP staining here, however, must be confirmed in the future with other histology measures that quantify detailed morphological and chemical changes associated with delayed myelination.

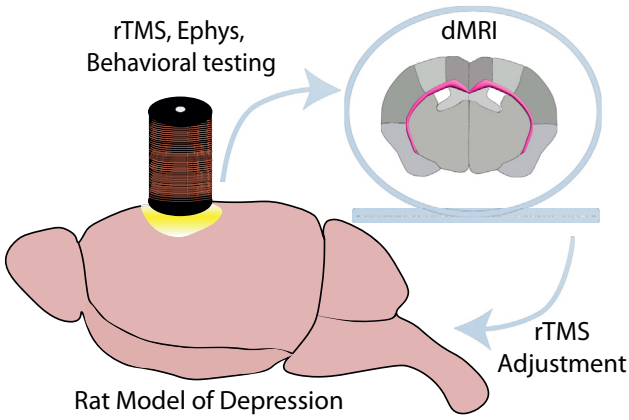

Figure 1. Future studies should exploit the advantage of the rodent model to show a detailed relationship between the physiological changes and the stimulation parameter in the same animal. dMRI, diffusion-weighted magnetic resonance imaging; Ephys, electrophysiology; rTMS, repetitive transcriptional magnetic stimulation.

The study represents outstanding work, applying repeated dMRI to infer effects on the myelination state of LI-rTMS–treated animals, with direct implications for human depression studies using similar dMRI measures. Apart from the complex relationship between dMRI measures and myelination state mentioned above, this study needs to be complemented by further experiments. First, human experiments clearly show a relationship between treatment efficacy and stimulation intensity, with the efficacy falling off as the intensity is lowered (10). It is unclear whether the results from low-intensity rTMS intervention in rodents can be translated to rTMS treatment of human patients that requires higher intensities.

Future studies that use rTMS in a rodent model of depression should exploit the advantage of the rodent model to provide a detailed relationship between WM changes and activity/behavior on an animal-by-animal basis (Figure 1). In addition, experiments must address the influence of stimulation intensity on myelination recovery and assess measurements of axonal conduction, network synchrony, and behavioral consequences. Gaining a clear picture of rTMS treatment–induced neurophysiological changes using rodent models means that we can accelerate the search for a treatment for depressive disorder that affects 1 in 5 people across the lifespan and hugely impairs quality of life.

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Article Information

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