Correspondence

Biological Psychiatry

The Potential of Repetitive Transcranial Magnetic Stimulation for Autism Spectrum Disorder: A Consensus Statement

To the Editor:

Autism spectrum disorder (ASD) affects approximately 1 in 59 children, but there are currently no biomedical treatments available that target the core symptoms (1). Preliminary evidence suggests that repetitive transcranial magnetic stimulation (rTMS) may have the potential to alleviate difficulties experienced by individuals with ASD (2). The evidence supporting the use of rTMS for ASD has led researchers in the field to form a consensus group that has met annually since 2014. Here we summarize discussions from the most recent meeting in May 2017, including recommendations for future research directions.

Presenters at the international consensus meeting described published clinical trials and protocols for social and executive deficits in ASD (3–6) and more recent unpublished trial data that raise questions about long-term efficacy. There are also efforts underway to examine conventional rTMS treatments for depression in an autistic population and mounting anecdotal reports in support of applying theta burst stimulation to prefrontal regions, including the right inferior frontal gyrus (7). Existing rTMS studies investigating therapeutic use in ASD have been reviewed in detail (8), and rTMS has significant promise for the alleviation of clinical symptoms in ASD.

Despite this promising evidence, studies continue to be hampered by small sample sizes, the inconsistent use of sham (placebo) protocols, and largely subjective clinical assessments. In addition, studies have not addressed the heterogeneous nature of ASD. It was agreed that future rTMS studies should recruit ASD participants based on the presentation of particular characteristics rather than simply having an ASD diagnosis. Blinded clinical ratings were also deemed critical. With respect to stimulation site, there needs to be a clear link between neurobiological targets and outcome measures. There was general agreement around the targeting of three cortical sites in particular: the right inferior frontal gyrus [targeting social impairments and communicative deficits (9)], the right temporoparietal junction/posterior superior temporal sulcus [targeting theory of mind, social comprehension, and attention (10)], and the left dorsolateral prefrontal cortex [targeting comorbid depressive disorder and executive dysfunction (11)].

To maximize treatment efficacy and safety of rTMS for ASD, optimal stimulation parameters must be determined. Variable stimulation parameters include pulse frequency, stimulation intensity, the number of magnetic pulses delivered, and intersession interval (12–14). Current rTMS protocols are based on the optimal stimulation parameters to induce neurophysiological changes in neurotypical individuals (15–18). However, individuals with ASD have been shown to exhibit atypical cortical plasticity (19–21) and reduced levels of cortical inhibition (22–25). Other individual factors, such as motor threshold and polymorphisms in *BDNF*, also contribute to interindividual variability in response to rTMS (26,27). Optimal stimulation parameters may therefore require a degree of individualization, but this requires valid and reliable neurobiological assessment.

To facilitate clinical translation, we also require further knowledge of the neurological basis of difficulties associated with ASD and reliable ways to measure these difficulties. Studies such as the Autism Biomarkers Consortium for Clinical Trials, a multisite trial investigating biomarkers for social-communicative functioning, may provide translatable knowledge. For instance, identifying reliable biomarkers could potentially identify individuals who are more likely to respond to particular treatments, including rTMS, or provide more sensitive metrics of engagement of targeted neural systems. There is also potential benefit in the use of interactive tasks and implicit measures to provide more naturalistic and sensitive measures of social functioning and underlying neurobiology (28,29).

To conclude, data from existing rTMS studies in ASD suggest that rTMS has therapeutic potential, but these studies have significant limitations that presently preclude translation. Definitive studies of the safety and efficacy of rTMS for ASD are needed. The variability in clinical presentation in ASD, coupled with the multitude of potential stimulation approaches, render this a complex and challenging endeavor. There is general agreement from this consensus group that progress will necessarily involve large, multisite, double-blind, sham-controlled trials with carefully selected neurobiological targets and outcome measures. It also remains that we require a greater understanding of neurophysiological heterogeneity in ASD, which may lead to opportunities for individualized assessments that can determine appropriate therapeutic protocols and maximize clinical outcomes.

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