

# Is there evidence for the use of noninvasive brain stimulation techniques for children and adolescents with mental illness?

To the Editors,

Repetitive transcranial magnetic stimulation (rTMS) holds promise as an alternative treatment for adults with treatment-resistant depression. Recent meta-analyses have revealed the efficacy of rTMS on treatment-resistant depression symptoms<sup>1</sup> and cross-diagnostic symptom domains of neuropsychiatric disorders.<sup>2</sup> The Japanese Ministry of Health, Labour and Welfare has approved rTMS since 2017 as a treatment option for adult patients who do not respond to medication treatment. The Japanese Society of Psychiatry and Neurology (JSPN) revised a practical guide for the appropriate use of rTMS for treatment-resistant depression (in Japanese) in 2023. This guide does not recommend rTMS for depression in children and adolescents, that is, those under 18 years old.

A great number of clinics in Japan have recently offered “off-label” treatment for children and adolescents with depression as well as any mental illness (according to a cursory Google search conducted on December 1, 2023). However, the effectiveness of rTMS for children and adolescents with depression or other mental illnesses remains unclear.

We searched PubMed for papers published in English from database inception to October 17, 2023, using the following title or abstract search terms: (1) participant terms, for example, children or adolescents (age range: under 18 years old); (2) intervention terms, for example, rTMS; and (3) study design terms, for example, randomized controlled trial (RCT). We identified RCTs that were published in English and investigated the relative efficacy of rTMS compared with sham conditions as well as any other treatments in children and adolescents with mental illness because of our interest in the effects of rTMS on children and adolescents with mental illness. We identified 419 papers and eight randomized clinical trials that met our predefined inclusion criteria after screening the abstracts. Of the eight trials, five met our predefined inclusion criteria, including one focusing on attention-deficit/hyperactivity disorder (ADHD), three investigating autism spectrum disorder (ASD), and one evaluating obsessive-compulsive disorder (OCD). One 6-week RCT revealed a significant improvement in ADHD symptoms on rTMS but not on sham stimulation. Furthermore, two 9-week RCTs demonstrated a significant improvement in the social domain of

ASD symptoms on rTMS, but not on sham stimulation, whereas one 4-week RCT revealed no treatment effects of rTMS. Furthermore, a single-session RCT revealed no significant changes in OCD symptoms in the active versus sham group. Our mini-review revealed that most articles were pilot studies and/or relatively small-scale studies with various rTMS protocols and/or outcomes. Furthermore, four of five studies investigated changes in clinical symptoms as secondary outcomes. Details are shown in Supplementary Tables 1–3 and Figure S1. Furthermore, we identified one meta-analysis of rTMS in children and adults with ADHD; however, only one open trial on children and adolescents with ADHD was excluded to avoid undue inflation of bias across domains.<sup>3</sup>

Little rigorous evidence is currently available regarding other approaches for treating patients with treatment-resistant depression,<sup>4</sup> especially children and adolescents. Many factors, such as inadequate dose or treatment duration, misdiagnosis, treatment nonadherence, psychiatric and medical comorbidities, and psychosocial stressors, cause treatment resistance in children and adolescents with depression.<sup>5</sup> First, clinicians should thoroughly explore and remedy those factors in children and adolescents with various mental illnesses and treatment-resistant depression. The possibility of short- and long-term side-effects when using rTMS in children and adolescents with mental illness requires more empirical studies, although rTMS is relatively safe.<sup>3,6,7</sup>

Evidence regarding the efficacy of rTMS for children and adolescents with mental illness is currently lacking, although rTMS does show promise. The neurodevelopmental processes ongoing in children and adolescents, compounded by the pathophysiological processes affecting those with neuropsychiatric and neurodevelopmental disorders, warrant careful consideration.<sup>7</sup> Currently available evidence does not support the broad off-label use of rTMS in children and adolescents; thus, the broad expedited translation of rTMS to clinics requires caution.<sup>7</sup> Recent systematic reviews supported the efficacy of rTMS treatment for adolescents with major depressive disorder<sup>8</sup> or the safety of rTMS treatment in children and adolescents within the currently applied protocols.<sup>9</sup> Herein, our mini-review endorses the validity of the revised practical guide for the appropriate use of rTMS for treatment-resistant depression by the

---

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Psychiatry and Clinical Neurosciences Reports* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Society of Psychiatry and Neurology.

JSPN. Currently, we cannot recommend the use of rTMS for treating mental illness in children and adolescents.

#### AUTHOR CONTRIBUTIONS

Takashi Okada and Hideki Negoro conceptualized the study. Noa Tsujii wrote the original study protocol and did all initial database searching. Noa Tsujii, Kosuke Okazaki, and Hiroaki Kihara did the article screening and data extraction. Masahide Usami, Junichi Fujita, Fumie Horiuchi, and Hideki Negoro supervised screening and full-text appraisal. Noa Tsujii wrote the first version of the manuscript. All authors contributed to and approved the final version of the manuscript.

#### CONFLICT OF INTEREST STATEMENT

For the past 3 years, Professor Tsujii has held the position of endowed chair founded by Toyama prefecture. He reports procuring personal fees from Mitsubishi-Tanabe, Mochida, Otsuka, Shionogi, Takeda, Yoshitomi, and Nobelpharma. Dr Okazaki reports procuring personal fees from Takeda Pharmaceutical Company Ltd and Viatrix Inc. Dr Kihara reports procuring personal fees from Shionogi & Co., Ltd and Takeda Pharmaceutical Company Ltd. Dr Usami reports procuring personal fees from Janssen Pharmaceuticals, Inc.; Takeda Pharmaceutical Company Ltd; Shionogi & Co., Ltd; Otsuka Pharmaceutical Co., Ltd; TAKATA Pharmaceutical Co., Ltd.; and Nobelpharma Co., Ltd, not pertaining to the present study. Dr Fujita reports procuring personal fees from Takeda and Nobelpharma. And he holds stock/stock options in Shionogi. Professor Horiuchi is an Editorial Board member of *PCN Reports* and a co-author of this article. To minimize bias, she was excluded from all editorial decision-making related to the acceptance of this article for publication. She reports procuring personal fees from Otsuka, Shionogi, Takeda, Nobelpharma, MSD and Janssen. Her department is Ehime prefectural endowed chairs. Professor Okada reports procuring personal fees from Janssen Pharmaceutical, Inc.; Takeda Pharmaceutical Company Ltd; Yoshitomi-yakuhin Corporation; and Nobel Pharma. Professor Okada has also received research grants from the Japan Society for the Promotion of Science; Ministry of Education, Culture, Sports, Science and Technology; and Otsuka Pharmaceutical Company. Dr Negoro reports procuring personal fees from Janssen Pharmaceutical, Inc.; Shionogi & Co., Ltd; Eisai Co., Ltd.; Nobelpharma Co., Ltd.; Otsuka Pharmaceutical Company; and Takeda Pharmaceutical Company Ltd.

#### DATA AVAILABILITY STATEMENT

All relevant data are within the paper.

#### ETHICS APPROVAL STATEMENT

N/A

#### PATIENT CONSENT STATEMENT

N/A

#### CLINICAL TRIAL REGISTRATION

N/A

Noa Tsujii MD, PhD<sup>1</sup>   
 Kosuke Okazaki MD, PhD<sup>2,3</sup>  
 Hiroaki Kihara MD, PhD<sup>4</sup>  
 Masahide Usami MD, PhD<sup>5</sup>   
 Junichi Fujita MD, PhD<sup>6</sup>  
 Fumie Horiuchi MD, PhD<sup>7</sup>   
 Takashi Okada MD, PhD<sup>3,8</sup>   
 Hideki Negoro MD, PhD<sup>2</sup>

<sup>1</sup>Department of Child Mental Health and Development,  
Toyama University Hospital, Toyama, Toyama, Japan

<sup>2</sup>Shigisan Hospital,  
Herarland Shigisan, Ikoma, Nara, Japan

<sup>3</sup>Department of Psychiatry,  
Nara Medical University, Kashihara, Nara, Japan

<sup>4</sup>Department of Neuropsychiatry,  
Kanazawa Medical University, Uchinada, Ishikawa, Japan

<sup>5</sup>Department of Child and Adolescent Psychiatry, Kohnodai Hospital,  
National Center for Global Health and Medicine, Chiba, Japan

<sup>6</sup>Department of Child Psychiatry,  
Yokohama City University Hospital, Yokohama, Kanagawa, Japan

<sup>7</sup>Department of Child Psychiatry,  
Ehime University Graduate School of Medicine, Toon City, Japan

<sup>8</sup>Department of Developmental Disorders,  
National Institute of Mental Health,  
National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

#### Correspondence

Noa Tsujii, MD, PhD, Department of Child Mental Health and Development, Toyama University Hospital, 2630 Sugitani, Toyama-shi, Toyama, 930-0194, Japan.  
Email: [tujiiinoa@med.u-toyama.ac.jp](mailto:tujiiinoa@med.u-toyama.ac.jp)

#### ORCID

Noa Tsujii  <http://orcid.org/0000-0003-3434-6280>

Masahide Usami  <http://orcid.org/0000-0002-1145-9971>

Fumie Horiuchi  <http://orcid.org/0000-0002-0833-0173>

Takashi Okada  <http://orcid.org/0000-0001-5580-9913>

#### REFERENCES

- Vida RG, Sághy E, Bella R, Kovács S, Erdősi D, Józwiak-Hagymásy J, et al. Efficacy of repetitive transcranial magnetic stimulation (rTMS) adjunctive therapy for major depressive disorder (MDD) after two antidepressant treatment failures: meta-analysis of randomized sham-controlled trials. *BMC Psychiatry*. 2023;23:545.
- Kan RLD, Padberg F, Giron CG, Lin TTZ, Zhang BBB, Brunoni AR, et al. Effects of repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex on symptom domains in neuropsychiatric disorders: a systematic review and cross-diagnostic meta-analysis. *Lancet Psychiatry*. 2023;10:252–9.
- Westwood SJ, Radua J, Rubia K. Noninvasive brain stimulation in children and adults with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *J Psychiatry Neurosci*. 2021;46:E14–33.

4. Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, Ripperger-Suhler J, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2023;62:479–502.
5. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. *Depress Anxiety*. 2011;28:946–54.
6. Nakamura M. Neuroscience and levels of evidence from clinical rTMS trials for neurodevelopmental disorders. *Jpn J Clin Psychiatry*. 2020;49:723–33 (in Japanese).
7. Oberman LM, Francis SM, Lisanby SH. The use of noninvasive brain stimulation techniques in autism spectrum disorder. *Autism Res*. 2023;17:17–26. <https://pubmed.ncbi.nlm.nih.gov/37873560/>
8. Sigrist C, Vöckel J, MacMaster FP, Farzan F, Croarkin PE, Galletly C, et al. Transcranial magnetic stimulation in the treatment of adolescent depression: a systematic review and meta-analysis of aggregated and individual-patient data from uncontrolled studies. *Eur Child Adolesc Psychiatry*. 2022;31:1501–25.
9. Salehinejad MA, Siniatchkin M. Safety of noninvasive brain stimulation in children. *Curr Opin Psychiatry*. 2024;37:78–86.

#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.