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Accelerated 1 Hz dorsomedial prefrontal transcranial magnetic stimulation for generalized anxiety disorder in adolescents and young adults: A case series

Dear Editor

Generalized anxiety disorder (GAD) is one of the most common conditions affecting adolescents and young adults, with prevalence increasing markedly over the past decade [1,2]. Although psychotherapy and pharmacotherapy are often effective, >30% of patients do not respond to such interventions [3,4]. Moreover, patients and caregivers are often reluctant to pursue pharmacotherapy due to concerns over tolerability [4,5] or the potential for worsening suicidality [4].

Transcranial magnetic stimulation (TMS) shows increasing evidence of potent anxiolytic efficacy, alongside its longer-established role in treatment-resistant depression [6,7]. Regarding optimal target, recent work suggests distinctive target networks for dysphoric versus anxiosomatic symptom clusters [8], with the latter network showing a major focus in the dorsomedial prefrontal cortex (DMPFC) region. Regarding optimal sequence in this population, low-frequency (1 Hz) TMS offers advantages for safety and tolerability, while achieving similar therapeutic effects to other protocols against depression and anxiety [9] and potentially superior effects against suicidality [10]. It is thus of interest to determine whether a 1 Hz protocol targeting DMPFC could prove safe and effective in young adults/adolescents with GAD as the primary presenting concern.

Here we report observations on the safety, tolerability, and anxiolytic effectiveness of a 30-session course of open-label 1 Hz DMPFC-TMS, from a retrospective chart review in 26 male and female patients, ages 13–22, meeting DSM-5 criteria for GAD as the primary diagnosis, between January 1 and December 31, 2023. Patients were referred by their prescribing psychiatrist following a standard clinical diagnostic interview and informed consent discussion regarding off-label TMS treatment in this population and indication. Patients with acute suicidality, TMS contraindications, neurological illness, or psychotic illness were not offered treatment. All patients as well as their parent/legal guardian gave written informed consent to treatment, and to the use of their anonymized data for retrospective review purposes. Treatment was provided free of charge to all patients on a compassionate basis.

To maximize scheduling convenience for patients and families, treatment was accelerated to a 10-day course (5 days/week), with 3 sessions/day at ≥60-min intervals, to allow for appointments of ~2h, enabling treatment each day before/after school or work. Each session delivered 600 pulses at 1 Hz, single-train, at 120% of lower-extremity resting motor threshold, to right DMPFC (coil vertex 2 cm lateral to Fz, current flow posterior-anterior), via a Cool-DB80 coil and MagPro R30 stimulator.

The primary outcome measure was the clinician-rated Hamilton Rating Scale for Anxiety (HAM-A), with the 10-item Severity Measure for Generalized Anxiety Disorder-Child (GAD-10) as a secondary self-rated outcome measure, and 9-item Patient Health Questionnaire-Child (PHQ-9-A) as a self-rated supplementary outcome measure for depression. Questionnaires were administered at baseline (0–5 days before treatment), after each 5 days of treatment, and at 2 and 4 weeks post-treatment.

Clinical and demographic characteristics of the sample are detailed in Supplementary Table 1. Sixteen patients were adolescents ages 13–17; ten were young adults ages 18–22. 20/26 had previous pharmacotherapy (detailed in Supplementary Table 2), 5 had a previous hospitalization, 0 had previous ECT, and 3 had ≥1 previous suicide attempt. Regarding safety, there were no serious adverse events reported. 26/26 of patients completed the full 10-day course; no patients discontinued treatment due to poor tolerability or logistical challenges. 25/26 attended the immediate post-treatment assessment, with 21/26 at 2 weeks and 12/26 at 4 weeks post-treatment.

Remission (HAM-A≤7) ensued in 13/26 (50.0%) after day 10 of treatment and 13/26 (50.0%) at 2 weeks post-treatment. 6/12 (50.0%) attending week 4 followup met remission criteria. Response (≥50% HAM-A reduction from baseline) ensued in 18/26 (69.2%) after day 10 of treatment and 14/26 (53.9%) at 2 weeks post-treatment. 9/12 (75.0%) attending week 4 followup met response criteria. Overall, HAM-A scores improved from 19.5 ± SD7.0 at baseline to 7.9 ± SD4.4 (paired $t_{24} = 8.18$; $p = 1.0 \times 10^{-8}$) at day 10 and to 8.3 ± SD5.6 (paired $t_{20} = 6.83$; $p = 1.2 \times 10^{-6}$) at week 2 post-treatment. On GAD10, 13/26 (50.0%) achieved remission (GAD10 < 10) and 16/26 (61.5%) achieved response after day 10 of treatment; overall GAD10 scores improved from 18.7 ± SD7.6 at baseline to 9.7 ± SD5.7 (paired $t_{24} = 8.04$; $p = 2.1 \times 10^{-8}$) at day 10 and to 9.8 ± SD6.5 (paired $t_{20} = 6.04$; $p = 6.6 \times 10^{-6}$) at week 2 post-treatment. Comparing adolescents (13–17) versus young adults (18–22), there were no significant differences in percent improvement from baseline to day 10 on either the HAM-A (54.2% ± SD25.1% vs. 60.3% ± 24.7%, $t_{24} = 0.61$; $p = 0.55$) or GAD-10 (41.7% ± SD27.1% vs. 50.8% ± SD26.4%, $t_{24} = 0.85$; $p = 0.41$). Trajectories of response and kernel density estimates of the distribution of percent improvement are presented in Fig. 1 for HAM-A, and in Supplementary Material for secondary and supplementary outcome measures.

In summary, 1 Hz DMPFC-TMS appears safe and well-tolerated in the adolescent/young adult GAD population, with 0/26 dropouts for logistical or tolerability issues; 3x daily treatment for 10 visits appears to have good compatibility with work/school schedules. Anxiolytic effects appear robust, with 50% of patients achieving remission after 10 days and 69% of patients achieving response criteria on HAM-A. Secondary effects on depression and suicidality also appear robust.

Acknowledged limitations of this preliminary report include the lack of a sham control group, the heterogeneity of the patient sample in terms of comorbidities and previous treatments, a tightly-focused set of

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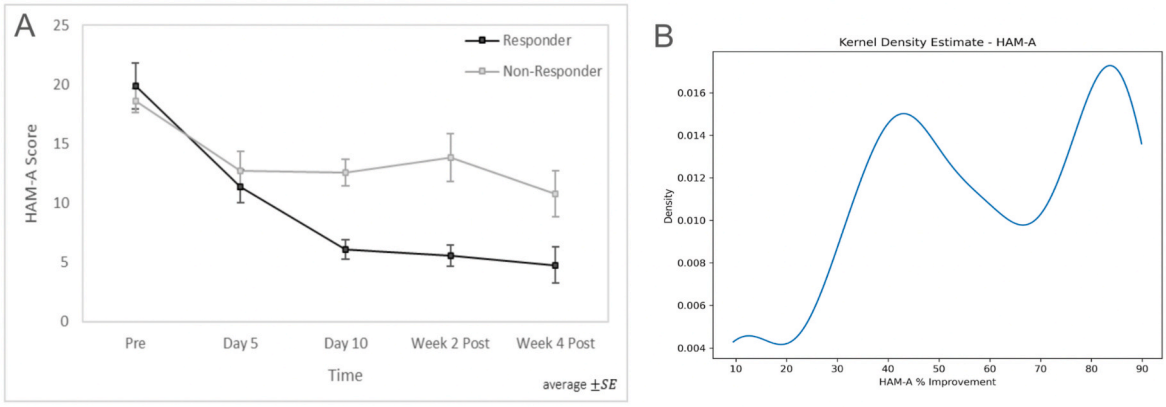

Fig. 1. Clinical response to 3x daily 1 Hz DMPFC-TMS in adolescents and young adults with GAD. A. Trajectories of improvement on HAM-A for treatment responders (18/26) and nonresponders (8/26). B. Kernel density estimate of the distribution of response to treatment, HAM-A response/nonresponse and improvement percentage is calculated from comparisons of scores at baseline versus the end of treatment (Day 10). Kernel bandwidth = 0.30.

outcome measures that may have failed to capture important effects on comorbidities or functional outcomes, and a lack of collateral outcome measures from caregivers, teachers, work supervisors. These deficiencies should be addressed in a follow-up trial incorporating a blinded, randomized, sham-controlled design, in a larger patient sample adequately powered to detect clinically meaningful effects. If successful, such a trial could lead to a novel, potent, and rapidly effective treatment for one of the most prevalent mental health disorders in younger individuals.

CRediT authorship contribution statement

Paul E. Croarkin: Conceptualization, Writing – original draft, Writing – review & editing. **Aleksandra Dojnov:** Formal analysis, Writing – original draft, Writing – review & editing. **Victoria J. Middleton:** Data curation, Investigation, Project administration, Writing – review & editing. **Jennifer Bowman:** Data curation, Investigation, Project administration, Writing – review & editing. **Joseph Kriske:** Conceptualization, Investigation, Project administration, Resources, Writing – review & editing. **Nancy Donachie:** Conceptualization, Investigation, Resources, Writing – review & editing. **Shan H. Siddiqi:** Conceptualization, Methodology, Writing – review & editing. **Jonathan Downar:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Dr. Croarkin has received research grants from the Brain and Behavior Research Foundation, National Institute of Mental Health, National Science Foundation, Neuronetics Inc, NeoSync Inc, and Pfizer Inc. He has received in-kind support (equipment, supplies, and genotyping) for research studies from Assurex Health Inc, Neuronetics Inc, and MagVenture Inc. He has consulted for Engrail Therapeutics Inc, Myriad Neuroscience, Procter & Gamble, and Sunovion. Dr. Downar has received research grants from the National Institute of Mental Health, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Klarman Family Foundation, the Arrell Family Foundation and the Buchan Family Foundation, travel stipends from Lundbeck and ANT Neuro, in-kind equipment support for investigator-initiated trials from MagVenture, and is an advisor for Arc Health, TMS Neuro Solutions and Restorative Brain Clinics, and is a co-founder of Ampa Health. Dr. Siddiqi is an owner of intellectual property involving the use of brain connectivity to target transcranial magnetic stimulation, a scientific consultant for Magnus Medical, performs investigator-initiated research funding from Neuronetics and Brainsway, receives speaking fees from Brainsway and Otsuka, and is a shareholder in Brainsway and Magnus Medical. None of these entities were involved in the work presented here. Ms. Middleton, Mr. Kriske, Ms. Bowman, and Dr. Donachie are employed by Salience Health. Aleksandra Dojnov is employed by Ampa Health. The other authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.02.018.

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