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Effectiveness of rTMS in depression in young adults

Dear editor

With interest we took notice of the article by Goldman and colleagues, describing age as a (non)determinant of effectiveness in treating major depressive disorder (MDD) with repetitive transcranial magnetic stimulation (rTMS). We therefore wondered if the same held for young adults (YA) in European clinics, that combined rTMS with psychotherapy and used protocols with fewer pulses (1200–1500 pulses) and sessions. In Dutch YA between 15 and 20 years of age, suicide is the number one cause of death and the prevalence of depression has increased over the last years [1]. Unfortunately, antidepressants are often less effective in this vulnerable group relative to older adults and more side effects and adverse events (e.g. suicidal behaviour) are reported [2]. Early intervention is crucial, with a demand for new and safe treatment modalities in this age group. rTMS is a non-invasive method of neuromodulation utilizing electromagnetic fields to alter neural activity in relatively focal areas of the brain, generally the dorsolateral prefrontal cortex (DLPFC). rTMS is considered a safe, tolerable and effective treatment, with few side effects and response rates varying between 29 and 66.3% [3]. Some studies suggest that age is not a predicting factor for response, however limited research has been conducted on rTMS in primarily YA [4]. Therefore, this letter describes a post-hoc analysis, assessing the effectiveness of rTMS in depressed YA (aged 18–25 years) compared to older adults.

Retrospective data from patients receiving rTMS treatment was collected from multiple outpatient rTMS clinics in the Netherlands, including Neurocare clinics, Neurowave and the Mood disorder clinic of the Amsterdam UMC, location AMC. Part of the data was previously used in a naturalistic open-label study [5]. Inclusion criteria were 1) patients older than 18 years; 2) a primary diagnosis of MDD; and 3) treated with rTMS aimed at the DLPFC. A depression rating scale, either the Beck Depression Inventory-II (BDI-II) or the 17-item Hamilton Depression Rating Scale (HDRS-17), had to be used to assess the severity of the depression at least before and after the treatment. Exclusion criteria were 1) patients with a primary diagnosis other than MDD and 2) patients younger than 18 years of age. Primary outcome measures were response and remission rates in both age groups. Response was defined as $\geq$50% reduction in BDI or HDRS score and remission as a BDI score below 12 or a HDRS score below 8. HDRS scores were converted to BDI scores to calculate the means of the whole group.

Patients were treated with either low frequency rTMS over the right dorsolateral prefrontal cortex (DLPFC) or high frequency rTMS over the left DLPFC. When the initial protocol did not render substantial effect, therapists switched to the other protocol and, when needed, sequential bilateral rTMS was given. Prior work already demonstrated that there are no differences in effectiveness between these protocols [5]. Furthermore, during the treatment patients received simultaneous or concurrent cognitive behavioural therapy (CBT).

The total sample consisted of 308 patients, from which 34 patients were between the age of 18 and 25 and were therefore included in the YA group and the remaining 274 patients were included in the older adult group above 25 years. Demographics for both groups were comparable, as can be seen in Supplementary Table 1. The YA group had a significant higher percentage of females (70.6% in the YA group compared to 50.4% in the adult group, X^2 (1) = 4.962; p = 0.026). There were no significant differences between the two age groups in total sessions rTMS received, the rTMS-protocol used or in the use of psychotropic medication. There was no significant difference in overall comorbidity, although comorbidity tended to be more prevalent in the YA group (47.1% vs. 34.3%. X^2 (1) = 4.142, p = 0.143). Moreover, the prevalence of comorbid autism spectrum disorder (8.8% vs 1.9%, p = 0.047) was significantly higher in the YA group; also the prevalence of eating disorders (8.8% vs 2.6%, p = 0.086) was relatively high in this group.

The Dutch Measure of Therapy Resistant Depression (DM-TRD) score was determined for a part of the cohort (n = 107: 8 YA, 99 adult), as the necessary information to calculate this score was not available for all patients. In this subgroup, therapy resistance tended to be higher in the YA group compared to the adult group, albeit not significant (13.0625 vs 11.3889, p = 0.230).

As shown in Fig. 1, baseline BDI score was significantly higher (F = 9.403; p = 0.002) in the YA group (mean of 37.9 vs. 32.1) compared to the adult group. This significance disappeared mid and post treatment. Concerning the primary outcome, there were no significant differences in response (64.7% vs 63.1%; X^2 (1) = 0.032, p = 0.858) and remission rates (47.1% vs 50.0%; X^2 (1) = 0.105, p = 0.746). This is remarkable, because a higher baseline score is associated with a lower response to rTMS treatment [6].

When response and comorbidity were analysed in the separate age groups, comorbidity seems to be of more influence on response in the older adults. In YA, the response rate was 66.7% when no comorbidity was present and 62.5% when comorbidity was present (X^2 (1) = 0.064, p = 0.800). In the older adults, the response rate was 67.2% when no comorbidity was present and 55.3% when comorbidity was present (X^2 (1) = 3.759, p = 0.053). This is in line with studies on other antidepressant treatments, showing a lower response rate in patients with comorbidity and a high DM-TRD [7].

In conclusion, this study suggests that, despite YA having higher baseline BDI scores and a tendency towards more comorbidity and a higher degree of refractoriness, rTMS was not less effective compared to older adults. rTMS is a reasonable, effective treatment

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A

Psychometrics	Young adults (n=34)	Older adults (n=274)
Baseline, m (sd)	37.8 (11.9)**	32.1 (10.1)**
Mid-treatment	22.9 (13.6)	19.3 (10.8)
Post-treatment	17.6 (15.9)	15.5 (12.5)
Response, n (%)	22 (64.7)	173 (63.1)
Remission	16 (47.1)	137 (50.0)

B

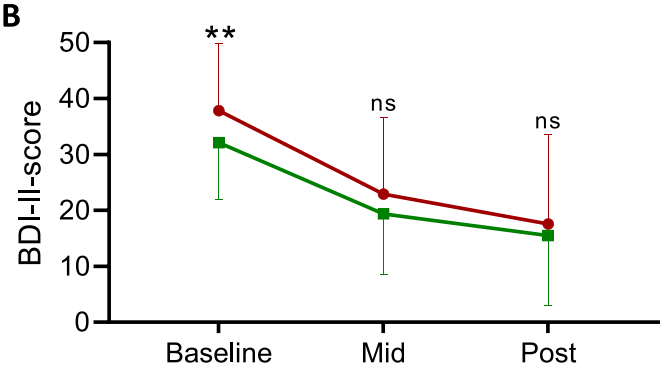

Fig. 1. Summarizing figure showing (A) rates of response and remission, and mean (sd) BDI–II–scores at baseline,mid-treatment and post-treatment.Changes in mean (sd) scores of both age groups are plotted(B),depicting the course of treatment.BDI-II; Beck Depression Inventory-II.** = $p < 0.01$. ns; not significant.m (sd); mean (standard deviation).

option for depressed YA. Even though YA and their parents may worry about long term effects on the developing brain, research shows a similar discontinuation rate and safety. The findings of this study can be used to inform YA considering rTMS.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E.D. is director and owner of Neurowave. S.V., A.L., I·O, M.A. and K.S. report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.03.008.

References

[1] CBS. Zelfdoding in Nederland: een overzicht vanaf 1950, 18-8-2021 [Suicide in the Netherlands: an overview since 1950. Available from: https://www.cbs.nl/nl-nl/longread/statistische-trends/2021/zelfdoding-in-nederland-een-overzicht-vanaf-1950/2-resultaten].
[2] Wagner S, Wollschlager D, Dreimuller N, Engelmann J, Herzog DP, Roll SC, et al. Effects of age on depressive symptomatology and response to antidepressant treatment in patients with major depressive disorder aged 18 to 65 years. Compr Psychiatr 2020;99:152170.
[3] Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 2014;75(5):477–89. quiz 89.
[4] Goldman P, Pedersen E, Bailey M, Hasse M, Koo M. Age as a determinant of transcranial magnetic stimulation efficacy for major depressive disorder in a naturalistic clinic setting. Brain Stimul 2022;15(3):695–6.
[5] Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: clinical outcomes and predictors from a large naturalistic study. Brain Stimul 2018;11(2):337–45.
[6] Kaster TS, Downar J, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, et al. Trajectories of response to dorsolateral prefrontal rTMS in major depression: a THREE-D study. Am J Psychiatr 2019;176(5):367–75.
[7] van Dijk DA, van den Boogaard TM, Deen ML, Spijker J, Ruhé HG, Peeters F. Predicting clinical course in major depressive disorder: the association between DM-TRD score and symptom severity over time in 1115 outpatients. Depress Anxiety 2019;36(4):345–52.

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