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BRIEF REPORT

The effect of older age on outcomes of rTMS treatment for treatment-resistant depression

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ABSTRACT

Clinical outcomes of repetitive transcranial magnetic stimulation (rTMS) for treatment of treatment-resistant depression (TRD) vary widely and there is no mood rating scale that is standard for assessing rTMS outcome. It remains unclear whether TMS is as efficacious in older adults with late-life depression (LLD) compared to younger adults with major depressive disorder (MDD). This study examined the effect of age on outcomes of rTMS treatment of adults with TRD. Self-report and observer mood ratings were measured weekly in 687 subjects ages 16–100 years undergoing rTMS treatment using the Inventory of Depressive Symptomatology 30-item Self-Report (IDS-SR), Patient Health Questionnaire 9-item (PHQ), Profile of Mood States 30-item, and Hamilton Depression Rating Scale 17-item (HDRS). All rating scales detected significant improvement with treatment; response and remission rates varied by scale but not by age (response/remission $\geq$ 60: 38%–57%/25%–33%; <60: 32%–49%/18%–25%). Proportional hazards models showed early improvement predicted later improvement across ages, though early improvements in PHQ and HDRS were more predictive of remission in those < 60 years (relative to those $\geq$ 60) and greater baseline IDS burden was more predictive of non-remission in those $\geq$ 60 years (relative to those < 60). These results indicate there is no significant effect of age on treatment outcomes in rTMS for TRD, though rating instruments may differ in assessment of symptom burden between younger and older adults during treatment.

Key words: repetitive transcranial magnetic stimulation (rTMS), measurement-based care, mood rating scales, late-life depression (LLD), late-life treatment-resistant depression (LLTRD), major depressive disorder (MDD)

Introduction

Late-life depression (LLD), defined as a major depressive episode (MDE) occurring after age 60, can be more challenging to treat than an MDE in younger adults. Response rates of LLD to first-line antidepressants range from 19% to 45% (Subramanian *et al.*, 2023), compared to around 50% in the general population (Otte *et al.*, 2016). Antidepressant medications also are highly associated with adverse events in older adults (Otte *et al.*, 2016; Subramanian *et al.*, 2023). For treatment-resistant depression (TRD), defined as failure to respond to two adequate antidepressant trials of adequate dose and duration, and especially late-life treatment-resistant depression (LLTRD), advanced treatment strategies include medication augmentation, ketamine, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or other

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neuromodulation treatments (Gebara *et al.*, 2023; Otte *et al.*, 2016; Subramanian *et al.*, 2023).

Among advanced strategies, ECT has been utilized for over 80 years. Although extremely effective, its high relapse rate, side effects, and logistical burden (particularly monitoring, time, and transportation requirements) have limited its use (Anand *et al.*, 2023; Subramanian *et al.*, 2023). Ketamine has more recently shown promise, though it is associated with significant side effects including dissociation, cravings, and cardiovascular effects such as hypertension in addition to its unclear durability of benefit (Anand *et al.*, 2023; Subramanian *et al.*, 2023; Yavi *et al.*, 2022). Some data indicate that rTMS is no less effective than ECT for non-psychotic TRD, with a more favorable side effect profile (Ren *et al.*, 2014; Subramanian *et al.*, 2023). However, it remains unclear whether rTMS is as efficacious in older adults compared with younger adults (Fregni *et al.*, 2006; Sackeim *et al.*, 2020; Valiengo *et al.*, 2022). This study examined the effect of age on naturalistic rTMS treatment outcomes in adults with TRD by analyzing categorical age-related differences and symptom-change trajectories with four self- and observer mood rating scales (Leuchter *et al.*, 2023).

Methods

Overview, patient population, clinical assessments, and rTMS protocols

This retrospective study examined 687 patients with TRD treated with a six to seven-week (at least 30 sessions) course of rTMS at the University of California, Los Angeles (UCLA) TMS Clinical and Research Service delivered using a measurement-based care paradigm as previously described (additional information in supplement) (Leuchter *et al.*, 2023). Symptom burden was assessed at pretreatment baseline and approximately every five sessions thereafter until the end of treatment using four assessment tools (9-item Patient Health Questionnaire [PHQ], the 30-item Inventory of Depressive Symptoms Self-Report [IDS-SR], the 30-item Profile of Mood States Brief [POMS], and observer-rated 17-item Hamilton Depression Rating Scale [HDRS]) with clinical response defined as improvement of at least 50% from pretreatment baseline score to final treatment score (i.e., score at session 30 or 35), and remission defined as PHQ $\leq$ 4, IDS $\leq$ 14, HDRS $\leq$ 7, POMS empirically $\geq$ 75% improved as previously described (Leuchter *et al.*, 2023).

Statistical methods

Analyses were completed with R version 4.1.1 and Stata version 18.0 (Stata Corp. LLC, College Station, Texas) as previously described with additional analyses to examine specific age-related effects (Leuchter *et al.*, 2023). Mean age for those who did and did not complete treatment was compared using a Mann-Whitney *U* test. Remission and response rates were calculated as above. Baseline scores and demographic differences between categorical age groups ($<$ 60 or $\geq$ 60 years old) were compared using a Mann-Whitney *U* test for each scale and Fisher's exact test for sex. Outcomes were examined separately for each rating scale as well as with a combined endpoint definition of clinical outcome on "at least one scale" (e.g., achieving remission or response on at least one scale). A mixed-effects linear regression model (MLM) was fit for each scale predicting the raw score using outcome group membership (non-responder vs. non-remitting responder vs. remitter) defined by the combined endpoint definition, session number, age group, and their corresponding interaction terms to determine whether there was evidence of time-by-outcome interactions by age group (Leuchter *et al.*, 2023). A series of logistic regressions was used to examine response and remission with age group and sex as categorical variables and their interaction to determine if response (or remission) differed by age or sex groups. Finally, baseline severity scores, age, and their interaction were examined as predictors of time-to-response and remission on each individual scale and combined endpoints using Cox proportional hazards modeling. To identify early signs of non-response, we applied two approaches: (1) examining percent change in the severity scores from baseline to session 5 (and separately session 10) as predictors of the time-to outcomes and (2) using a binary classification for percent improvement greater than or equal to 20% by session 10 and separately improvement of 10% by session 5. The positive and negative predictive values were also assessed.

Results

Demographics and baseline characteristics

In total, 897 patients (55% female, mean age 46) were included in the overall sample, 856 of whom had age data available, with 207 $\geq$ 60 years old and 649 $<$ 60 years old. Six hundred eighty-seven participants who completed a full course of treatment (at least 30 sessions) and had both baseline and end-of-treatment ratings scale over the course of treatment were included in these analyses, with completers being on average 3.5 years younger than non-completers (completer mean age = 45.1 $\pm$ 16.1, non-completer mean age = 48.6 $\pm$ 18.4; $p = 0.03$). The range of age was 16–100 years with 153 subjects $\geq$ 60 and 534 $<$ 60 years old. Subjects had on average

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Table 1. Response and remission rates by age group and scale: remission and response rates by scale and across scales using "at least one" criterion. Response rates for < 60 years range from 32% to 54%, and for ≥ 60 years range from 38% to 58%. Remission rates for < 60 years range from 18% to 31%, and for ≥ 60 years range from 25% to 36%. Number of individuals with age data who completed each scale and were able to be included in analysis shown, with smaller samples noted in the ≥ 60 years group. Response and remission rates are numerically greater in older adults

	Response		Remission		Total n	
	Age ≥ 60	Age < 60	Age ≥ 60	Age < 60	Age ≥ 60	Age < 60
IDS	39%	38%	25%	23%	153	529
POMS	51%	46%	26%	25%	102	391
PHQ9	57%	49%	33%	21%	129	470
HDRS	38%	32%	27%	18%	45	136
≥ 1 scale	58%	54%	36%	31%	153	534

moderately severe depressive symptoms on all rating scales prior to treatment (Supplemental Table 1). There were no between-age-group differences in sex, and younger adults had statistically greater baseline depression ratings across all scales (Supplemental Table 1).

Treatment outcomes and comparison across rating scales

Logistic regression models examining response and remission rates as functions of sex and categorical age group showed no statistically significant partial effects of sex or age group with one exception: remission on the PHQ was significantly greater for ≥ 60 than for < 60 years old controlling for sex (OR = 1.66, $z = 2.16$, $p = 0.03$). Rates of response and remission were numerically greater on tabulation but not statistically significantly greater for ≥ 60 compared to < 60 years old (controlling for sex) on other scales (Table 1). There was a significant age-by-sex interaction term for remission on the POMS showing higher rates of remission in women < 60 relative to men ≥ 60 (Odds Ratio = 0.30, $z = 2.07$, $p = 0.038$); all other main and interaction effects of age and sex were not significant. Fifty-five patients ≥ 60 years (36%) and 165 < 60 years (31%) were remitters on at least one scale; 89 patients ≥ 60 years (58%) and 286 patients < 60 years (54%) were responders on at least one scale; and 64 patients ≥ 60 years (42%) and 248 patients < 60 years (46%) were non-responders on all scales.

Treatment outcome trajectories

Although MLMs showed that trajectories significantly differed between non-responders, responders who did not remit, and remitters (Leuchter *et al.*, 2023), there were no significant differences in time-by-outcome group interaction between age groups for any of the scales (Fig. 1).

Early improvement and predictive value for outcome

Cox proportional-hazard modeling showed that there were interaction effects between age category and baseline severity affecting the likelihood of remission for the IDS (hazard ratio [HR] ≥ 60 = 0.90, HR < 60 = 0.94, $p = 0.016$), suggesting older patients were less likely to have remission than younger adults at the same level in baseline severity (Supplemental Table 2). This was not found for response on the IDS (Response HR ≥ 60 years = 0.98, HR < 60 years = 0.96, $p = 0.07$), nor was a similar interaction observed for response or remission on any other scale. Early improvements of both 10% at session 5 and 20% at 10 were not differentially predictive of response or remission for either age group on any scale (Response HR = 2.04–5.76; Remission HR = 1.16–3.77; all age interactions $p > 0.05$, Supplemental Table 2). However, a greater rate of early improvement was more predictive of remission in those under the age of 60 on both the PHQ (HR ≥ 60 = 1.22, HR < 60 = 2.60, $p = 0.003$) and HDRS (HR ≥ 60 = 0.65, HR < 60 = 22.8, $p = 0.026$; Supplemental Table 2).

Conclusions

We found no significant effect of age on efficacy of rTMS in the treatment of adults with TRD on three of four scales examined and potentially higher rates of remission with older age on the PHQ. Our findings were consistent with other recent work showing that response and remission rates are at least as high in older adults as in younger adults (Sackeim *et al.*, 2020; Valiengo *et al.*, 2022).

These findings also suggest that commonly used self and observer mood rating scales may perform differently in younger and older populations. While scales behave similarly across age

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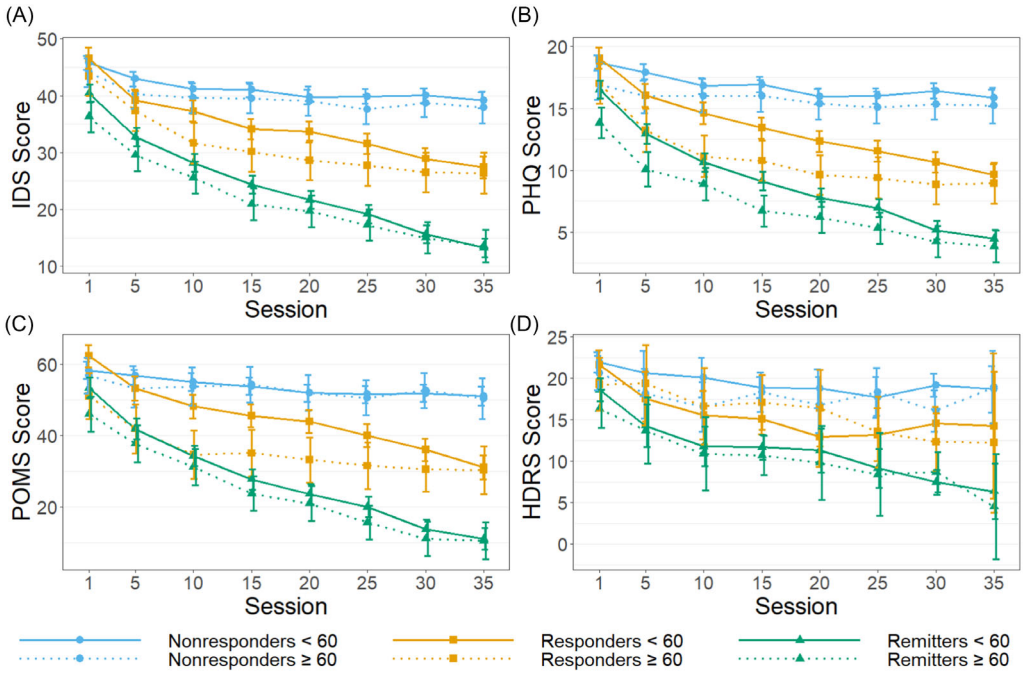

Figure 1. Symptom trajectories over treatment course by outcome and age groups: estimated scale scores over time by outcome group (as defined by the "at least one scale" criterion) and age group. IDS *a*, PHQ *b*, POMS *c*, HDRS *d*. Outcome group-by-time interactions do not significantly differ by age group. Ninety-five percent confidence intervals shown calculated from standard error.

categories in terms of the predictive value of early improvement, a greater rate of improvement on the PHQ9 and HDRS seems to be a more positive indicator in younger adults, and higher baseline severity on the IDS seems to be a more meaningful negative predictor of remission in older adults. These early changes are highly relevant to predicting treatment outcome (Leuchter *et al.*, 2023). Of course, with no clear "gold standard" for defining depression treatment outcomes, there are alternative explanations for these differences between scales. However, with the goal of maximizing clinical utility through enabling decision-making, expanding use of multi-scale measurement to characterize response is a logical and safe step to consider. That too will not always capture a complete picture and can increase the chance of a "false" response or mismatched results. Understanding that subtler differences in scale performance may be a factor at play can aid in reconciling discrepancies when discussing with patients in a clinical setting.

The results of this study should be interpreted in the context of several limitations, some of which have been previously discussed (Leuchter *et al.*, 2023). One particularly notable limitation in this case is the lack of accounting for some potential confounders including the natural course of an individual's depression and their treatment history. Subjects were categorized here based on the age at which they presented for TMS treatment rather than the age at which the current or index depressive episode began. It is possible that an effect of age might have emerged with one of these alternative approaches to examining disease onset. We found those who completed treatment were slightly younger (difference of 3.5 years between means) than those who did not, though it is not clear whether this statistical difference is clinically significant. This could still serve as a potential source of bias. This study also focused primarily on dichotomized age comparisons between under and over 60 (as is done for LLD) rather than age as a continuous variable or other age-related effects. Future studies should examine age in greater detail as a continuous measure as well as address the possibility of peri- or post-menopausal changes in females, including pediatric or adolescent populations, or examine the effect of age on the efficacy of different rTMS stimulation parameters.

These data are encouraging and indicate that rTMS is a highly efficacious treatment of LLTRD. It has been unclear what treatment should be offered first to patients who do not achieve remission using OPTIMUM's strategies (Gebara *et al.*, 2023; Subramanian *et al.*, 2023). These data along with those of other studies indicate that rTMS is an effective next step comparable to the positioning of rTMS for TRD in younger populations (Sackeim *et al.*, 2020; Valiengo *et al.*, 2022).

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Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S1041610224000462.

Data availability

The data that support the findings of this study are not available due to privacy or ethical restrictions.

Conflicts of interest

Within the past 36 months, MKL has served as a consultant to Neuroelectrics, Inc. AFL received research support from NeurOptics, and MagVenture. He has served as a consultant to NeoSync, Inc., eFovea, Options MD, Kernel, Inc., and ElMindA. He was Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA) and had equity interest in BBA.

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Description of author(s)' roles

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Acquisition, analysis, or interpretation of data: MK Leuchter, Citrenbaum, Wilson, Tibbe, and Jackson.

Drafting of the manuscript: MK Leuchter, Citrenbaum, Wilson, Tibbe, Jackson, and AF Leuchter.

Critical revision of the manuscript for important intellectual content: MK Leuchter, Citrenbaum, Wilson, Tibbe, Jackson, Krantz, Corlier, Wilke, Strouse, Hoftman, Tadayonnejad, Koek, Slan, Ginder, Distler, Artin, Lee, Adelekun, Einstein, Oughli, and AF Leuchter.

Statistical analysis: MK Leuchter, Citrenbaum, Tibbe, and Jackson.

Obtained funding: AF Leuchter, Tibbe, and Jackson.

Administrative, technical, or material support: Citrenbaum, Wilson, Tibbe, and Jackson.

Supervision: AF Leuchter, Krantz, and Jackson.

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