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Research paper

Older age associated with better antidepressant response to H1-coil transcranial magnetic stimulation in female patients

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ABSTRACT

Background: TMS is increasingly used to treat depression, but predictors of treatment outcomes remain unclear. We assessed the association between age and TMS response given inconsistent prior reports limited by small sample size, heterogeneity, outdated TMS parameters, lack of assessment of H1-coil TMS, and lack of an a priori hypothesis. We hypothesized that older age would be associated with better treatment response based on trends in recent large exploratory analyses.

Methods: We conducted a naturalistic retrospective analysis of patients (n = 378) ages 18–80 with depression (baseline Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) > 5) who received 29–35 sessions of TMS between 2014 and 2021. Response was assessed using percent reduction of QIDS-SR. The relationship between percent response or remission and age group was assessed using the chi-square test.

Results: 85 % of patients received the standard protocol of H1-coil TMS to the left DLPFC. Percent response and remission rates for the entire study sample increased with age (response: p = .026; remission: p = .0023). This finding was stronger in female patients (response: p = .0033; remission: p = .00098) and was not observed in male patients (response: p = .73; remission: p = .26). This was confirmed in a sub-analysis of patients who only received the standard protocol with the H1-coil for the entire treatment course.

Limitations: Naturalistic retrospective analysis from one academic center.

Conclusions: Older age is associated with a better antidepressant response to H1-coil TMS in female patients. This was demonstrated in a hypothesis-driven confirmation of prior exploratory findings in a large sample size with a homogeneous data collection protocol across all participants.

1. Introduction

Treatment resistant depression (TRD) is a common and costly condition, with an annual prevalence of nearly 3 million people in the Unites States and an annual economic cost of over $40 billion US (Zhdanava et al., 2021). Repetitive transcranial magnetic stimulation (TMS) was cleared by the US Food and Drug Administration in 2008 for adults with depression who had failed at least one antidepressant; it has consistently been shown to be safe and effective, and is increasingly being used (Cohen et al., 2022; Perera et al., 2016). However, factors associated with better response to TMS remain to be clearly delineated (Brini et al., 2023). Given the disease burden of TRD and growing use of TMS, it has become increasingly important to identify clinical and demographic factors that can predict treatment response.

Age is one demographic predictor that was found in early studies to be negatively correlated with TMS clinical outcomes, with poorer outcomes observed in older patients (Figiel et al., 1998; Fregni et al., 2006; Kozel et al., 2000). Based on this, there has been a bias against referring older patients for TMS treatment, and some insurance providers in the United States have actively chosen to limit accessibility to TMS for older patients (Cotovio et al., 2022). More recent studies have found mixed results regarding association between age and efficacy of TMS, with some supporting the early observation (Abo Aoun et al., 2023; Carpenter et al., 2012; Pallanti et al., 2012; Rostami et al., 2017) and others finding no association (Ciobanu et al., 2013; Janicak et al., 2013; Lisanby et al., 2009). In contrast, other studies (Fitzgerald et al., 2016; Sackeim et al.,

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2020; Trevizol et al., 2020), including two recent large exploratory analyses (Sackeim et al., 2020; Trevizol et al., 2020) have found a better TMS response in older patients, with the Sackeim et al., study observing a better response in older women in particular. A subsequent meta-analysis of the TMS outcome literature reported that higher mean age was associated with greater antidepressant benefit (Valiengo et al., 2022).

Mechanistic hypotheses have been offered to account for putative aging effects on efficacy. With the early findings of reduced efficacy in older patients, it has been hypothesized that (1) age-related cortical atrophy leads to increased coil-to-cortex distance, producing a weaker electric field in target cortex in older patients (Kozel et al., 2000; Mosimann et al., 2002; Nahas et al., 2004) and/or (2) age-related decreased neuroplasticity compromises response to TMS (Pallanti et al., 2012). Alternatively, to account for the findings of increased benefit with aging, it has been hypothesized that increased excitability of the atrophic brain (Wagner et al., 2008) may allow for sufficient stimulation with lower intensity (Sabesan et al., 2015), which may theoretically lead to better response to TMS.

Limitations of most early studies include small sample size and outdated TMS parameters, while the largest recent studies (Sackeim et al., 2020; Trevizol et al., 2020) did not offer a priori hypotheses regarding demographic factors and treatment outcomes. Rather, their aim was to screen a wide range of potential predictors of response to TMS. Thus, these hypothesis-generating findings require independent confirmation. Additionally, literature on aging effects with TMS is mainly based on studies using a relatively focal figure-of-eight coil for magnetic stimulation. To our knowledge, no prior study using TMS treatment delivery with the H1-coil has reported on the relationship between age and treatment outcomes. The H1-coil is believed to induce more diffuse stimulation (Roth et al., 2007) and thus may potentially mitigate concerns about coil-to-cortex distance in older patients. To address this knowledge gap, we performed a naturalistic retrospective chart review of a large patient population receiving predominantly H1-coil TMS for depression at a single academic center to investigate the association between patient age and treatment response to H1-coil TMS. This partly addresses the heterogeneity in prior studies, as we had a large sample of patients receiving only high-frequency left-sided H1 coil TMS at a single site with a consistent data collection protocol. We hypothesized that increasing age would be associated with better response to H1-coil TMS.

2. Methods

2.1. Study population

We conducted a naturalistic retrospective chart review of patients 18 years of age and older who received TMS for depression at McLean Hospital in Belmont, MA between 2014 and 2021. McLean Hospital is an academic psychiatric hospital affiliated with Harvard Medical School. The TMS service is a tertiary referral center and receives referrals both from within McLean at the inpatient and outpatient levels, as well as from the community, both from the local community and internationally. Individuals receiving TMS in both the inpatient and outpatient settings were included. Approval was obtained from the Mass General Brigham Institutional Review Board to conduct a retrospective chart review with waiver of consent (Protocol # 2022P002273).

2.2. Assessment

Depressive symptoms were assessed using the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al., 2003), which was administered at baseline (prior to beginning treatment) and after every 10 TMS sessions for most patients, with some variability in time points due to clinical or logistical factors. Response to treatment was assessed using percent reduction of QIDS-SR from baseline to treatment 29–35 (assessment performed closest to treatment 29 was used, as it is typical in this clinic to start tapering after treatment 30). For patients who received multiple courses of TMS, only the first course was considered for this analysis. We included patients who (1) received at least 29 TMS treatments in their first course, (2) completed their baseline QIDS-SR assessment no later than at their third TMS treatment, (3) completed a QIDS-SR assessment between TMS treatments 29 and 35, (4) had age entered in the database, and (5) had a baseline QIDS-SR assessment of >5, thus meeting criteria for depression per QIDS-SR. Additional information about the number of patients meeting the inclusion and exclusion criteria is detailed in Supplemental Fig. 1. Response was defined as ≥50 % reduction in the QIDS-SR score from baseline and remission was defined as a QIDS-SR score ≤ 5, as per consensus criteria (Rush et al., 2006).

2.3. Transcranial magnetic stimulation

TMS was administered using an H1 coil (Brainsway Ltd., Burlington, MA) (Levkovitz et al., 2015) using the standard clinical protocol that is currently recommended and most commonly used in clinical practice with the H1 coil (McClintock et al., 2018). Resting motor threshold was measured by identifying the minimum intensity needed to induce a contraction in the right abductor pollicis brevis or first digital interosseous muscles. Treatments were administered to the left dorsolateral prefrontal cortex (DLPFC), located 6 cm anterior to the resting motor threshold site. Intensity was titrated to 120 % of the individual resting motor threshold, as tolerated. A total of 1980 pulses were delivered per session at a frequency of 18-Hz.

Variability in treatment parameters within the TMS treatment course occurred for a minority of patients (Supplemental Table 1), with respect to (1) type of TMS coil (figure-of-eight rather than H1-coil), (2) number of pulses delivered per treatment, or (3) target location (right or bilateral DLFPC rather than left DLPFC).

2.4. Statistical analysis

The relationship between percent response or remission and age group was assessed using the chi-square test. Age groups were defined to span 15 years, aside from the first group, which only spanned 12 years (age 18–34). Age was categorized into discrete groups to replicate Sackeim et al.'s methods (Sackeim et al., 2020), with larger bins chosen for our analysis given our smaller sample size. To further probe the relationship between percent response or remission and age group, we also conducted an ordinal regression using age group, sex, (age group)* (sex) interaction, and baseline QIDS as predictors. To further assess the relationship between age and TMS response, association between age as a continuous variable and percent reduction in QIDS-SR was analyzed with Spearman's correlation. This relationship was further assessed using a linear regression controlling for baseline QIDS. Data were tested for normality using the Shapiro-Wilk test. Group differences between male and female patients were assessed using the *t*-test or Mann Whitney *U* test as appropriate. The F test of equality of variances was used to compare distribution of ages of male and female patients in the sample. All statistical tests were two-sided and a significance level of $p < .05$ was used.

3. Results

378 patients (62 % female) met inclusion criteria. There was no significant difference between male and female patients in terms of mean age, variance in age, or baseline depression severity. Baseline demographics are detailed in Table 1, while age distributions are depicted in Supplemental Fig. 2. The majority (96 %) of baseline QIDS-SR assessments were performed prior to or at the first TMS treatment and the majority (92 %) of final QIDS-SR assessments used in this analysis were performed at treatment 29 or 30, as further detailed in

Table 1
Characteristics of study population (n = 378). There were no statistically significant differences between QIDS-SR scores of female and male patients at baseline or at assessment at treatment 29–35.

	Female patients (n = 236, 62.43 %)[a]	Male patients (n = 136, 35.98 %)[a]	Total	p-Value
Age				
Mean	47.43	44.78	46.40	0.145
Standard deviation	16.71	17.55	17.05	0.513
Minimum	18	19	18	
Maximum	79	80	80	
QIDS-SR				
Baseline, mean ± standard deviation	16.81 ± 4.05	15.91 ± 4.05	16.48 ± 4.07	0.0705
Tx 29–35, mean ± standard deviation	9.96 ± 5.16	9.61 ± 4.86	9.79 ± 5.04	0.721
Percent reduction, mean ± standard deviation	40.60 ± 26.70	38.10 ± 29.91	39.90 ± 27.90	0.420

[1] Of the 378 total individuals in the sample, four (1.06 %) reported sex as "Other" and two (0.53 %) had missing data with respect to sex.

Supplemental Table 2.

Of the entire study sample, 85 % (n = 321) received the standard H1-coil TMS protocol for the entire treatment course. Of the other 15 % (n = 56), 43 patients received the standard protocol of H1-coil TMS for over 50 % of their treatment course. Among the remaining 13 patients there was variability within the treatment course with respect to type of TMS coil (figure-of-eight versus H1-coil), the number of pulses delivered per treatment, and the target location (left vs right vs bilateral DLFPC) (Supplemental Table 1). One patient had missing data with respect to TMS treatment parameters.

The response and remission rates for the entire study sample (n = 378) were 40.5 % and 22.8 %, respectively. The response and remission rates for female patients (n = 236) were 42.0 % and 20.3 %, respectively and for male patients (n = 136) were 37.5 % and 26.5 %, respectively. The percent response and remission rates for the entire study sample increased with age (response: $\chi^2 = 9.29$, df = 3, $p = .026$); remission: $\chi^2 = 14.54$, df = 3, $p = .0023$) (Fig. 1A), with a similar finding seen in female patients (response: $\chi^2 = 13.72$, df = 3, $p = .0033$; remission: $\chi^2 = 16.32$, df = 3, $p = .00098$) (Fig. 1B). In male patients, there was no significant variability in response and remission rates with respect to age and no clear trend (response: $\chi^2 = 1.30$, df = 3, $p = .73$; remission: $\chi^2 = 4.03$, df = 3, $p = .26$) (Fig. 1C). This effect was unchanged when setting a cut-off of 20 treatments (data not shown). Similar results were obtained in a sub-analysis that included only patients who received the standard protocol with the H1-coil for the entire treatment course for the full sample (n = 321, response: $\chi^2 = 9.26$, df = 3, p = .026; remission: $\chi^2 = 13.42$, df = 3, $p = .0038$), female patients alone (n = 202, response: $\chi^2 = 15.29$, df = 3, $p = .0016$; remission: $\chi^2 = 17.32$, df = 3, $p = .0006$), and male patients alone (n = 115, response: $\chi^2 = 0.66$, df = 3, $p = .88$; remission: $\chi^2 = 2.24$, df = 3, $p = .52$) (Supplemental Fig. 3). Ordinal regression confirmed there was a significant effect of age group in female patients (response, $p = .0040$; remission, $p = .011$) but not in male patients (response, $p = .68$; remission, $p = .42$) but the (age group)*(sex) interaction did not reach significance in the entire study sample (response, $p = .054$; remission, $p = .076$). Similar results were obtained in a sub-analysis that included only patients who received the standard protocol with the H1-coil for the entire treatment course (female patients: response, $p = .0028$ and remission, $p = .0084$; male patients: response, $p = .86$ and remission, $p = .70$; full sample: response, $p = .060$ and remission, $p = .14$).

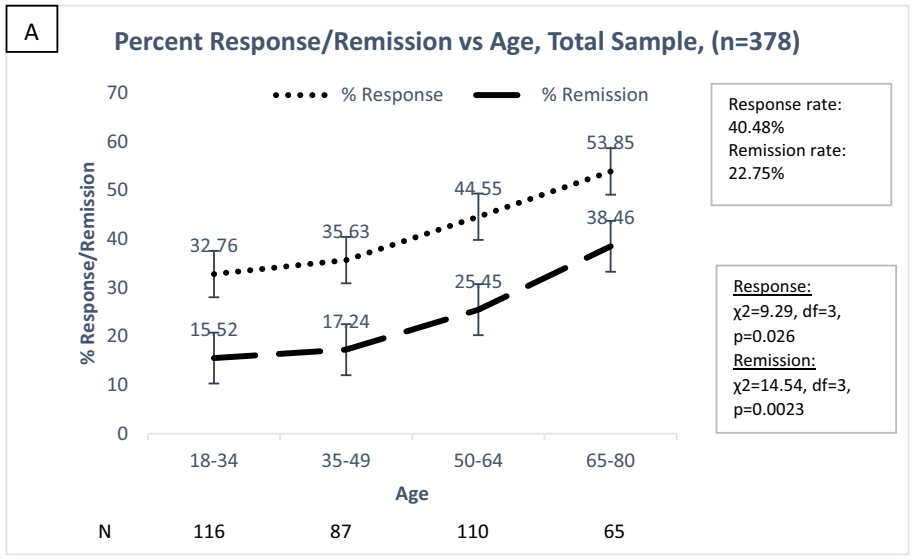
Pooling all participants across age groups to consider age as a continuous variable, age was significantly correlated with percent reduction in QIDS-SR (Spearman's $r = 0.14$, $p = .0081$) (Fig. 2A). Post-hoc analysis showed that this correlation was stronger in female patients (Spearman's $r = 0.25$, $p = .00014$) and was not found in male patients (Spearman's $r = -0.031$, $p = .72$) (Fig. 2B–C). This effect was unchanged when setting a cut-off of 20 treatments (data not shown). Similar results were obtained in a sub-analysis that included only patients who received the standard protocol with the H1-coil for the entire treatment course for the full sample (n = 321, Spearman's $r = 0.16$, $p = .0039$), female patients alone (n = 202, Spearman's $r = 0.30$, $p = .000020$), and male patients alone (n = 115, Spearman's r = −0.031, $p = .74$) (Supplemental Fig. 4). This effect was unchanged when controlling for baseline QIDS using a linear regression model (entire study sample, $p = .0056$; female patients, $p = .00060$; male patients, $p = .52$). Similar results were obtained in a sub-analysis that included only patients who received the standard protocol with the H1-coil for the entire treatment course (full sample, $p = .0061$; female patients, $p = .00043$; male patients, $p = .59$).

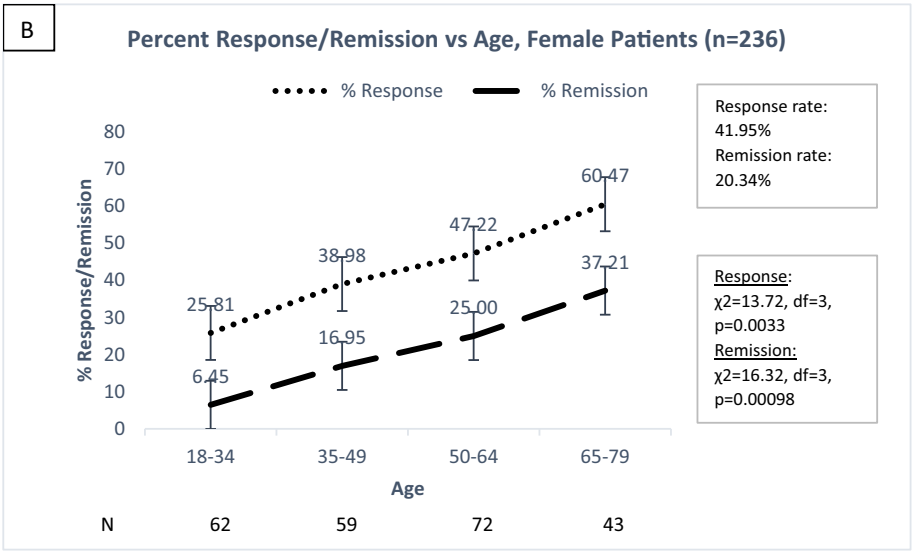
4. Discussion

In this naturalistic retrospective chart review of 378 patients receiving TMS for depression at a single academic center, we found that antidepressant response to TMS increased with age. There was a significant positive correlation between age and improvement in depressive symptoms in the entire study sample. Post-hoc analyses showed that this effect was driven by female patients. These results were confirmed in a sub-analysis that included only patients who received the standard protocol with the H1-coil for the entire treatment course (n = 321).

Many early studies (Figiel et al., 1998; Fregni et al., 2006; Manes et al., 2001; Mosimann et al., 2004; Nahas et al., 2004) that either found no association between age and treatment response, or found a negative association, used outdated TMS parameters per modern standards (lower intensity and fewer treatments). It has been proposed that older patients were thus being "underdosed" in these early studies (Fitzgerald et al., 2016) and that they may be slower to respond, resulting in worse outcomes (Lisanby et al., 2009). However, later studies that used updated TMS parameters nevertheless replicated a lack of positive association with age and treatment response (Abo Aoun et al., 2023; Carpenter et al., 2012; Lisanby et al., 2009), thus suggesting that additional factors are likely at play. However, these studies conflict with several large recent studies on this topic that have described a better TMS response in older patients (Sackeim et al., 2020; Trevizol et al., 2020), with the Sackeim et al., study observing a better response in older women in particular, although interpretations were limited by an exploratory post hoc analysis study design. Our study thus set out to address this limitation by testing the a priori hypothesis that older patients will have a better response to TMS. Sackeim et al. found that response rates improved with age up to age 80 in female patients (with no association between age and response found in male patients); female patients over age 80 had worse treatment outcomes in that analysis (Sackeim et al., 2020), but we were unable to probe this question because our sample included only one patient in this age group.

One hypothesis that has been offered to explain the previously reported negative correlation between age and treatment response is cortical atrophy; as the distance between the TMS coil and the cortex increases, a weaker magnetic field reaches the cortex (Kozel et al., 2000; Mosimann et al., 2002; Nahas et al., 2004). It may be overly simplistic to correct for this by increasing stimulation intensity, since there are other factors involved (e.g. atrophic brain may have altered excitability and may also alter TMS-induced currents with respect to magnitude, location, and orientation) (Wagner et al., 2008). The H1-coil stimulates deeper and larger brain volumes than a figure-of-eight coil (Roth et al., 2007) and may thus, in theory, be less susceptible to atrophy-related decrease in effectiveness in older patients. In a randomized controlled trial investigating the efficacy, tolerability, and cognitive effects of H1-coil TMS for late-life depression, the remission rate in the active arm (n = 27) was 40.0 % (Kaster et al., 2018), compared to a remission rate of 32.6 % in the active arm (n = 89) previously reported for a general adult





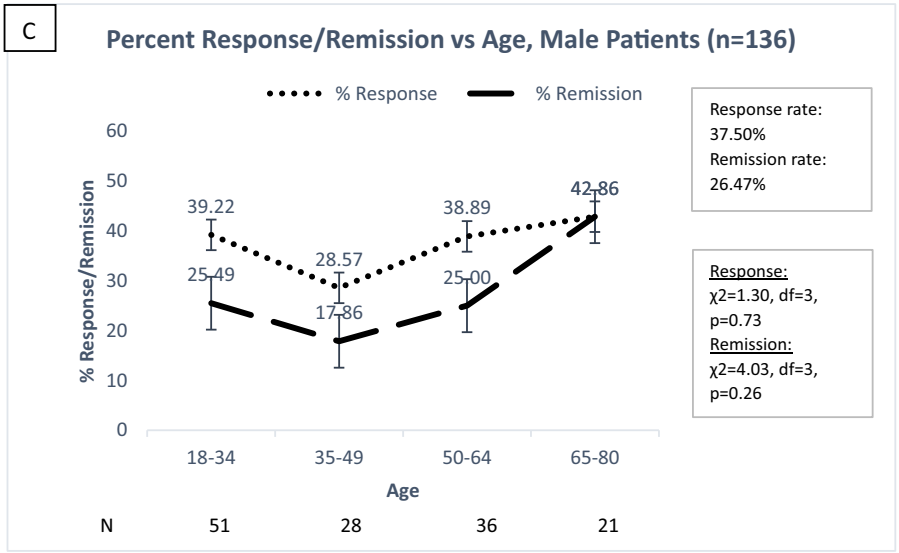


Fig. 1. Response and remission rates for (A) all patients and (B) female and (C) male patients as a function of age. Response was defined as ≥50 % reduction in the QIDS-SR score from baseline to assessment at TMS treatment 29–35 and remission was defined as a QIDS-SR score ≤ 5. The percent response and remission rates for the entire study sample increased with age, with a similar trend seen in female patients, while in male patients there was no significant variability in response and remission rates with respect to age and no clear trend.

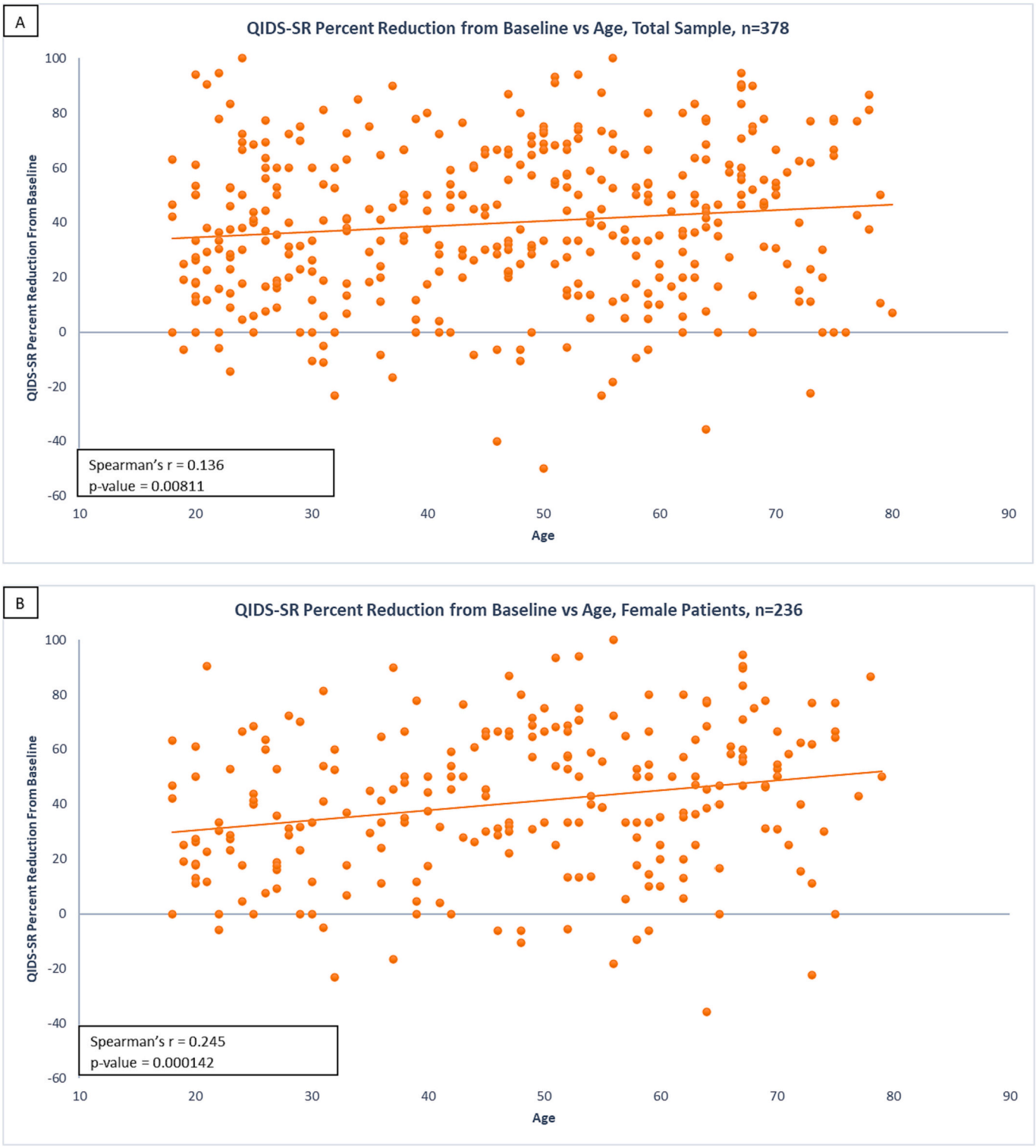


Fig. 2. Relationship between percent reduction of QIDS-SR score and age in (A) entire study sample (n = 378), (B) female patients (n = 236), and (C) male patients (n = 136). Percent reduction of QIDS-SR score was calculated from baseline to assessment at rTMS treatment 29–35 (assessment performed closest to treatment 29 was used). There was a statistically significant positive correlation between age and improvement in depressive symptoms in the entire sample (p = .0081). This correlation was stronger in female patients (p = .00014) and was not found in male patients (p = .72).

population for the same coil (Levkovitz et al., 2015). Additionally, results from a large post-marketing analysis of the H1 coil showed that older age was associated with superior continuous improvement but no significant association between sex and clinical outcomes was found; this may be because they did not consider the combined effects of age and sex in their analysis (Tendler et al., 2023). Since the majority of our sample received H1-coil TMS, this may partly account for our observed association with age.

The age dependence of response to H1 coil stimulation may be partly related to the bilaterality of the electric field induced by this coil

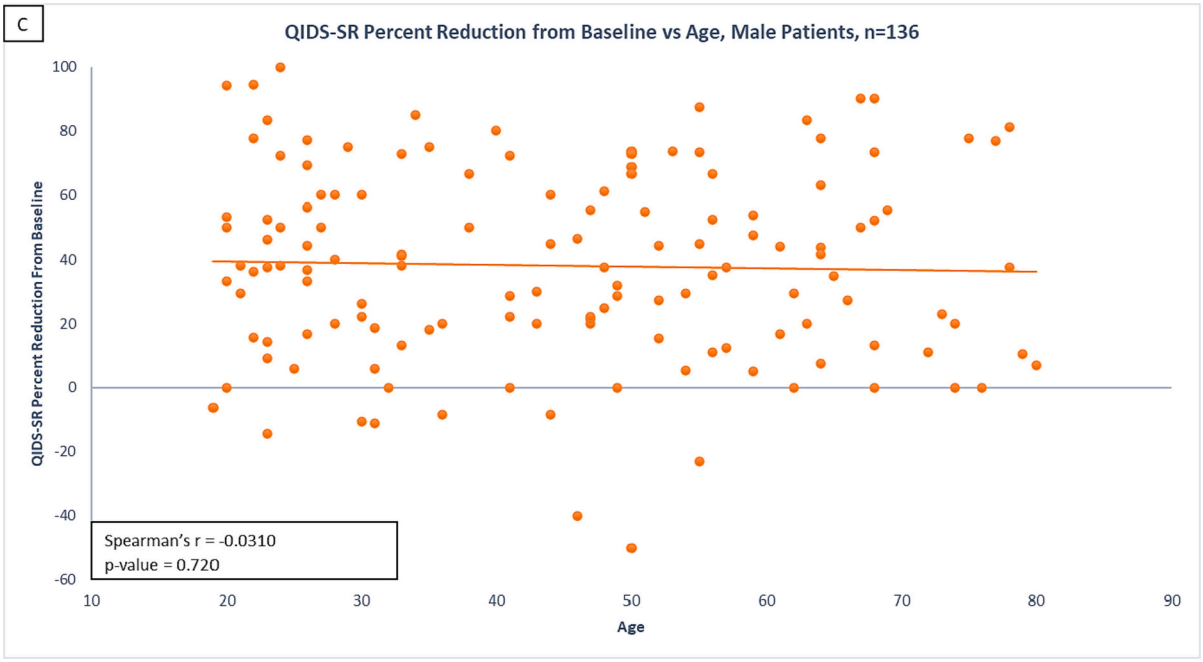


Fig. 2. (*continued*).

(Tendler et al., 2023). Prior studies have shown that older adults respond better to bilateral figure-of-eight coil TMS (Trevizol et al., 2019), but this has not been shown in other age groups (Aaronson et al., 2022). This may also in part explain the age-dependence in female patients reported by Sackeim et al., as approximately 43 % of participants in that study received sequential bilateral treatment with the figure-of-eight coil; however, the age and sex breakdown of patients receiving bilateral vs unilateral protocols in this study would need to be investigated more closely before drawing further conclusions, since the better TMS response was observed in older female patients in particular (Sackeim et al., 2020). Furthermore, it is difficult to make direct comparisons between treatment with the H1 coil and bilateral treatment with the figure-of-eight-coil given the different treatment parameters and the simultaneous versus sequential stimulation.

The positive correlation between age and improvement in depressive symptoms in our study sample was found only in female patients. Our results are contrary to several previous reports that showed a greater response in younger women (Huang et al., 2008; Malik et al., 2016; Su et al., 2005). It has been proposed that hormonal levels may drive better response in younger women, as estrogen can affect cortical excitability, modulate monoamine neurotransmitters, and enhance neuroplasticity, which are all factors that can affect TMS response (Malik et al., 2016; Su et al., 2005). While our results contradict these earlier findings, they are in line with results more recently reported by Sackeim et al., who similarly observed better TMS treatment response in older female patients, with no such trend seen in male patients in the largest data registry report to date (Sackeim et al., 2020). It has been proposed that the closer proximity of the brain to the scalp at the prefrontal cortex in women, due to sex specific differences in craniofacial anatomy, results in a stronger magnetic field reaching the cortex (Hanlon and McCalley, 2022). Future work may test this hypothesis by assessing sex, coil-to-cortex distance, and cortical excitability in a combined model to predict clinical outcomes. Additionally, in light of the estrogen-dependent fluctuations in synaptic plasticity associated with the menstrual cycle that have been described in the literature (Sumner et al., 2018), perhaps more consistent synaptic plasticity in the post-menopausal period may further account for the better TMS response in older women that we observed.

Strengths of our study include an a priori hypothesis, a relatively large sample size, and a consistent data collection protocol across all participants. There are also several limitations. It is a naturalistic retrospective analysis with no sham or control group. Since all data were collected at one tertiary academic center, this patient sample may not be representative of the general population with respect to disease severity and complexity, as in part evidenced by our lower observed response and remission rates compared to those previously reported for the H1-coil (Tendler et al., 2023). Including only patients who had at least 29 TMS treatments selected against patients who did not tolerate the treatment or had a rapid response, although these factors are less likely to bias our results since the significance of our findings was unchanged when repeating the analysis with a cut-off of 20 TMS treatments (data not shown). There was some variability in the timepoints of the baseline and final QIDS-SR assessments used in this analysis, but it was minimal. The data set we used in this analysis did not include information on the patients' history of depression (e.g., number of prior episodes, duration of current episode, age at first episode), psychiatric co-morbidities, psychiatric medications (current and prior trials), or TMS motor threshold and treatment intensity. Future studies may seek to assess whether these factors mediate the observed age-dependence of TMS response. Finally, there was some heterogeneity with respect to TMS parameters among the patients included in this study. While it would have been interesting to compare treatment response in our data set between patients who received H1-coil TMS for the entire duration of treatment to patients who did not, the latter group was too small and too heterogeneous with respect to TMS parameters. Future studies could compare treatment outcomes of figure-of-eight-coil and H1-coil TMS across the age spectrum. Another important area of future study is to assess the association between age and treatment response in a larger sample with a particular emphasis on patients age 80+ given the marked drop in treatment response previously observed in this population (Sackeim et al., 2020).

To our knowledge, this study is the first to show that older age is associated with better antidepressant response to H1-coil TMS in female patients. We have also confirmed prior exploratory findings with an a priori hypothesis in a large sample with a homogeneous data collection protocol across all participants. Our results suggest that age may be an important demographic factor to help identify patients who are more likely to benefit from this treatment modality. Older adults are known to

have a higher prevalence of treatment resistant depression with a decreased probability of treatment response (Cappon et al., 2022). Thus, our findings are particularly promising for this difficult to treat population, given the better tolerability of TMS in the geriatric population compared to pharmacotherapy and ECT (Cappon et al., 2022).

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None.

CRediT authorship contribution statement

Maria S. Kryatova: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Stephen J. Seiner:** Data curation, Writing – review & editing. **Joshua C. Brown:** Data curation, Writing – review & editing. **Shan H. Siddiqi:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Shan Siddiqi reports a relationship with Magnus Medical that includes: consulting or advisory and equity or stocks. Shan Siddiqi reports a relationship with Neuronetics that includes: funding grants. Shan Siddiqi reports a relationship with BrainsWay Ltd. that includes: equity or stocks and funding grants. Private practice consulting involving TMS targeting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.160.

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