Non-invasive Neurostimulation Therapies Laboratory, Department of Psychiatry

Antidepressant use & treatment resistance affect brain age in patients with major depression receiving repetitive transcranial magnetic stimulation

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Background

Repetitive transcranial magnetic stimulation (rTMS) is a first-line treatment option for major depressive disorder (MDD) patients who are resistant to traditional pharmacotherapy. While rTMS shows promise, clinical outcomes vary [1]. Understanding how the brain responds to rTMS and the clinical variables associated with brain health may identify those most likely to respond. A novel way of measuring brain health is brain age and its deviation from chronological age, known as the brain-predicted age difference (brain-PAD). This study assessed whether **1) baseline brain-PAD predicts rTMS response, and 2) rTMS treatment reduces brain-PAD.**

Methods

655 MDD patients underwent rTMS [2-4]. Depression severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD-17) [5], and treatment resistance was measured using the antidepressant treatment history form (ATHF) [6]. ATHF scores ≥ 2 defined treatment resistance. Percent improvement was calculated as:

$$\text{Percent Improvement} = \left(\frac{\text{HRSD}_{\text{baseline}} - \text{HRSD}_{\text{post-treatment}}}{\text{HRSD}_{\text{baseline}}} \right)$$

T1w MRI scans were assessed for quality and brain age was estimated using BrainageR [7]. Brain-PAD was calculated as:

$$\textit{Brain-PAD} = \textit{Predicted Brain Age} - \textit{Chronological Age}$$

Two ANCOVA's were run with brain-PAD as the dependent variable, and percent improvement and timepoint (before vs. after rTMS) as the independent variables. Sex, age, single antidepressant use, combination antidepressant use, benzodiazepine use, and treatment resistance were included as co-variates.

Results

Table 1. Demographic and medication breakdown. *Abbreviations:* ATHF, antidepressant treatment history form; HRSD-17, 17-item Hamilton Rating Scale for Depression; SD, standard deviation.

PARAMETER	MEAN (SD) OR N (%)
MALE FEMALE	258 (39.4%) 397 (60.6%)
AGE	47.48 (14.36)
BRAIN AGE	44.42 (14.30)
BRAIN PAD	-2.83 (6.99)
AGE OF ONSET	22.78 (13.43)
EPISODE LENGTH IN MONTHS	33.62 (54.42)
HRSD-17 BASELINE	22.31 (4.70)
HRSD-17 FINAL	13.04 (7.39)
PHARMACOTHERAPY: ATHF TRIALS 0 TRIALS FAILED 1 TRIAL FAILED ≥ 2 TRIALS FAILED ANTIDEPRESSANT ALONE ANTIDEPRESSANT COMBINATION BENZODIAZEPINE LITHIUM AUGMENTATION	 40 (6.1%) 269 (41.1%) 346 (52.8%) 321 (49.0%) 135 (20.6%) 225 (34.4%) 25 (3.8%)

Table 2. Results of the first ANCOVA (n = 563) revealed age and antidepressant use to be significant predictors of brain age.

VARIABLE	DF	SUM SQ	F-VALUE	P-VALUE
% IMPROVEMENT (HRSD-17)	1	10	0.219	0.640
SEX	1	4	0.083	0.773
AGE	1	1135	24.335	**< 0.001*** **
ANTIDEPRESSANT USE	1	181	3.879	**0.049***
ANTIDEPRESSANT COMBINATION	1	46	0.977	0.323
BENZODIAZEPINE USE	1	101	2.173	0.141
DRUG RESISTANCE (ATHF ≥ 2)	1	81	1.727	0.189

Table 3. Results of the second rmANCOVA (n = 466) revealed age and treatment resistance to be significant predictors of brain age. Follow-up analysis on the interaction of timepoint (pre- vs. post-rTMS) with age and treatment resistance did not reveal any significant findings (p > 0.05).

VARIABLE	DF	SUM SQ	F-VALUE	P-VALUE
TIMEPOINT	1	0	0.005	0.974
SEX	1	60	1.362	0.332
AGE	1	263	5.945	**0.007****
ANTIDEPRESSANT USE	1	276	6.237	0.060
ANTIDEPRESSANT COMBINATION	1	71	1.599	0.194
BENZODIAZEPINE USE	1	57	1.299	0.361
DRUG RESISTANCE	1	414	9.358	**0.003****

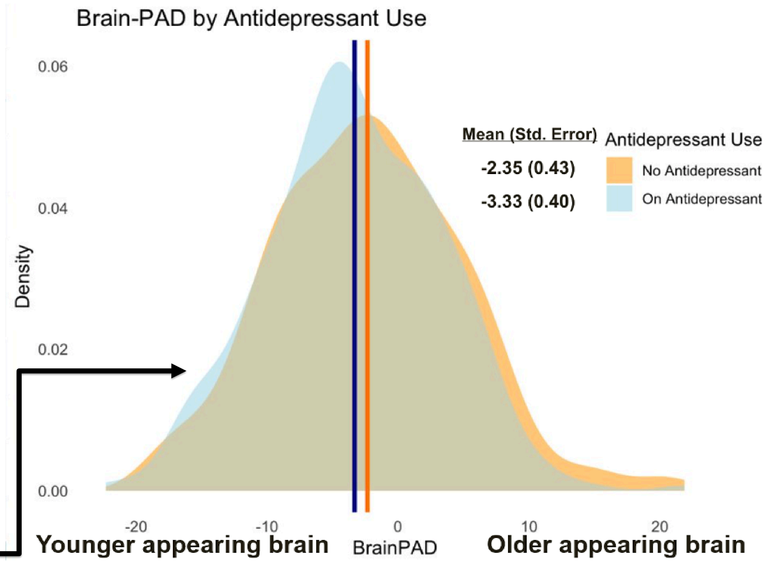

Figure 1. Those on antidepressants had a significantly (p = 0.049) lower brain-PAD (signifying a younger appearing brain) relative to those not on antidepressants.

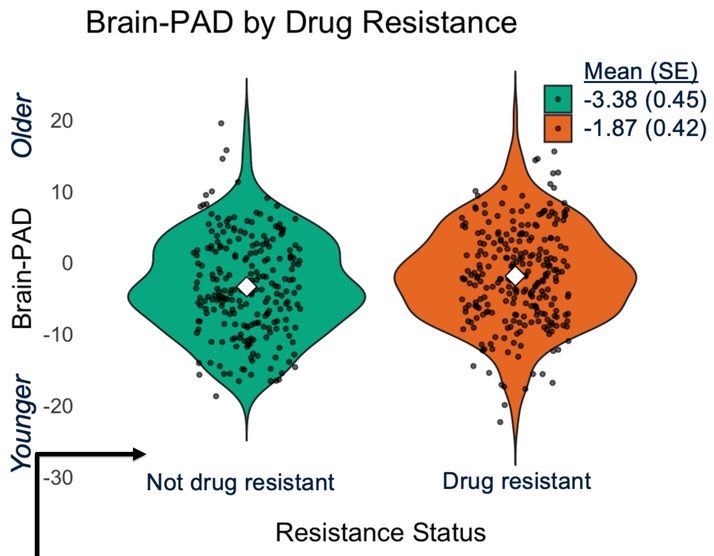

Figure 2. Those who were not treatment resistant (less than two failed treatments) had a younger appearing brain (p = 0.003) relative to those who had two or more failed treatments.

Discussion

In our large sample, brain-PAD was negative at baseline (-2.8 years), which deviates from the literature (+1 years). MDD patients taking antidepressants had a younger appearing brain, and those who had at least two previously failed treatments had an older appearing brain. The potential neuroprotective effects of antidepressants and neural correlates associated with treatment resistance warrant further investigation. This may help identify treatment-resistance factors and optimize medications to enhance rTMS outcomes.

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