

Closing the Loop Faster: Closed-loop Accelerated rTMS-CBT Targeting EEG Alpha Phase for Depression and Suicide Risk

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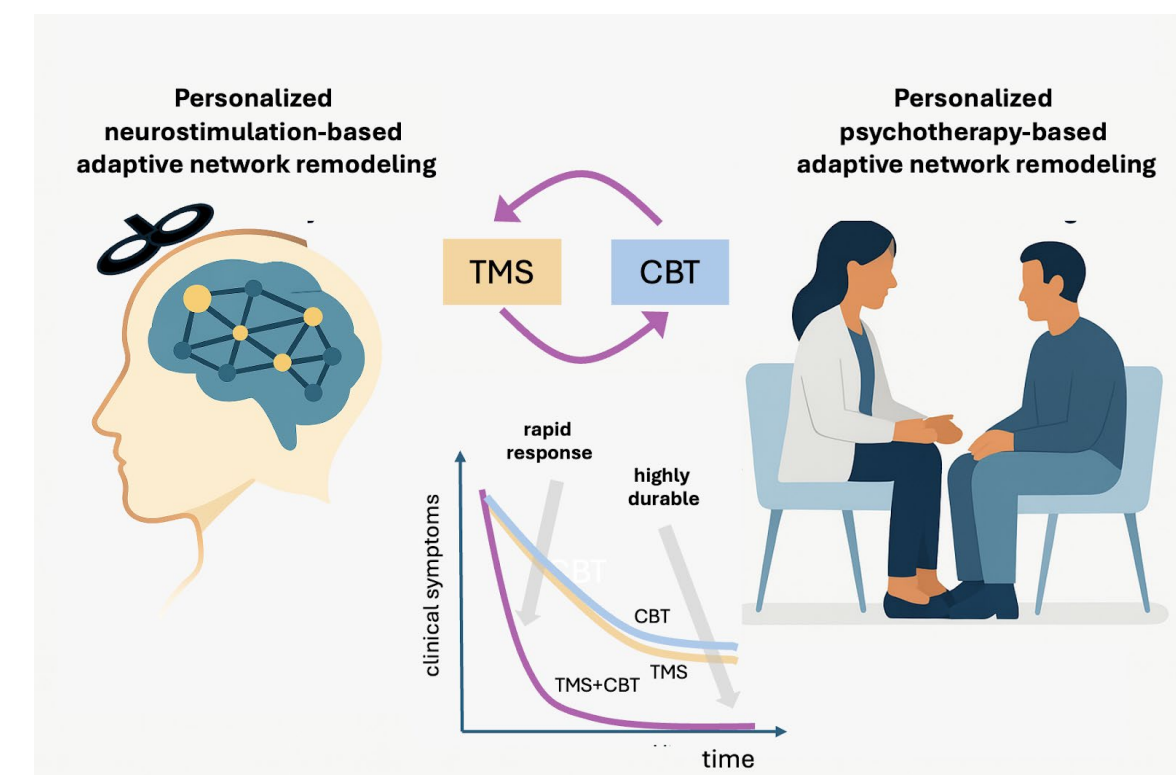
BACKGROUND

The current study performed accelerated closed-loop EEG-rTMS treatment on depressed participants, interleaved with Cognitive Behavioral Therapy (CBT), to assess clinical response and its correlation with potential EEG and MRI biomarkers.

Hypothesis: Accelerated real time closed-loop EEG-rTMS treatment sessions, interleaved with CBT, will result in improved clinical response, durable for over 3 months, decreased global mean field power, and increased entrainment

METHODS

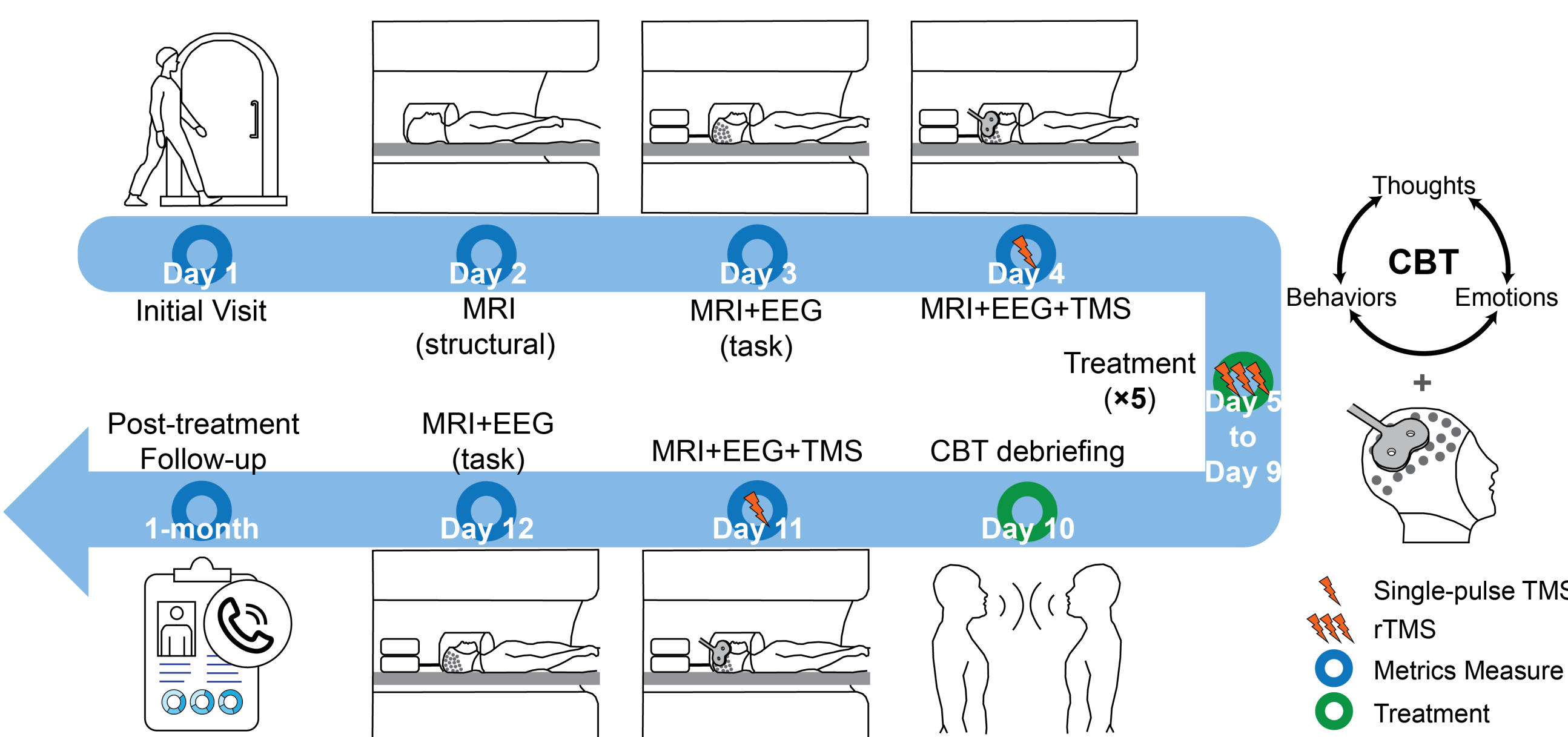
Participants: N = 20 (10 females); 41.25 ± 13.89 yrs



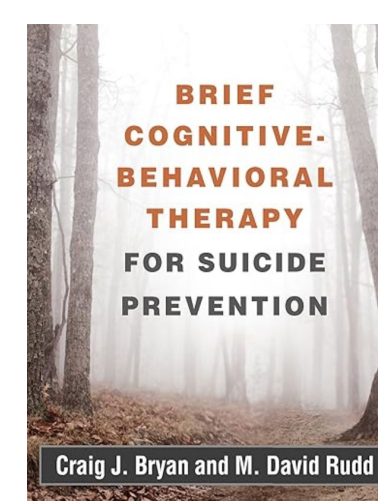
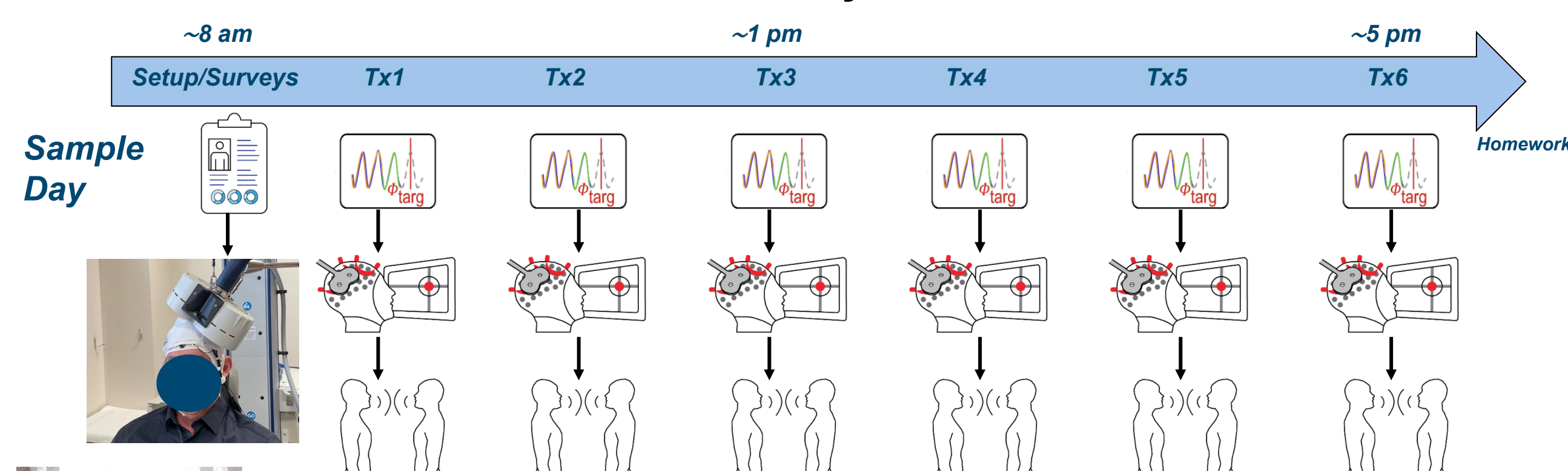
The hybrid close-loop rTMS-CBT treatment protocol applied:

- an accelerated rTMS protocol interleaved with CBT
- with individualized spatial optimization
- at the individual's alpha frequency (IAF)
- synchronized to optimal phase of brain oscillations

Study Visit Timeline



Treatment Day Timeline



1. **Accelerate CBT.** Weekly sessions of BCBT delivered in 6, 30-minute sessions/day x 5 days
2. **Accelerate rTMS.** Typical once daily rTMS delivered in 6 sessions/day x 5 days
3. **Interleave CBT/rTMS.** CBT follows rTMS to leverage acute post-rTMS neuroplasticity.

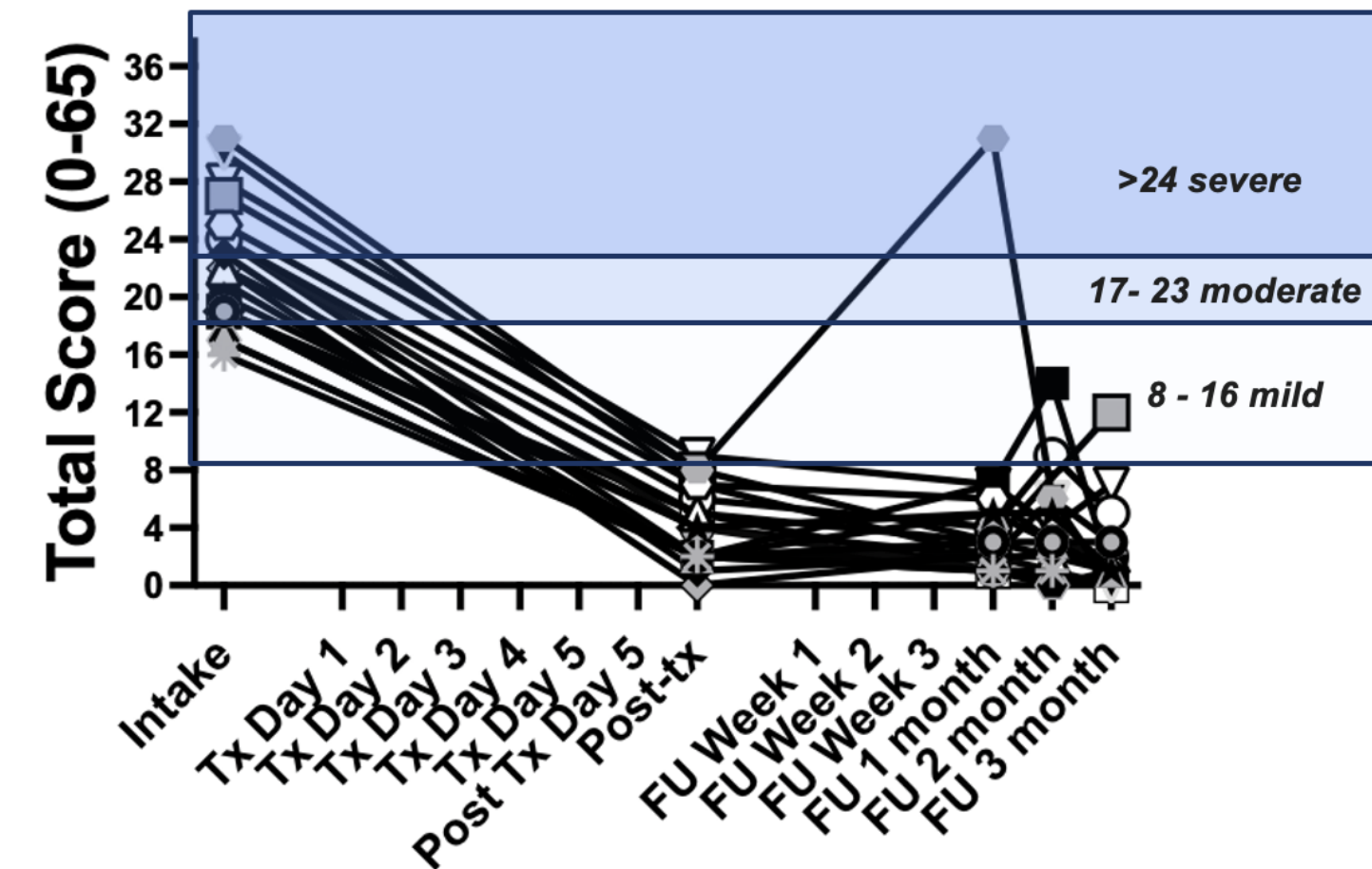
Tx Modality	DOSE: Total Pulses	Total Tx Duration	Tx Modality	DOSE: Total Minutes	Total Tx Duration
Conventional 10 Hz rTMS	60,000-90,000	20-30 days	Protocol BCBT	720	12 weeks
RECOVERS rTMS	90,000	5 days	RECOVERS BCBT	900	5 days

Clinical Symptomology: Depression and anxiety symptoms were assessed using the self-report Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7-item (GAD-7). The clinician-rated Hamilton Depression Rating Scale (HAM-D) was collected at multiple timepoints throughout the protocol from intake through the final follow-up visit.

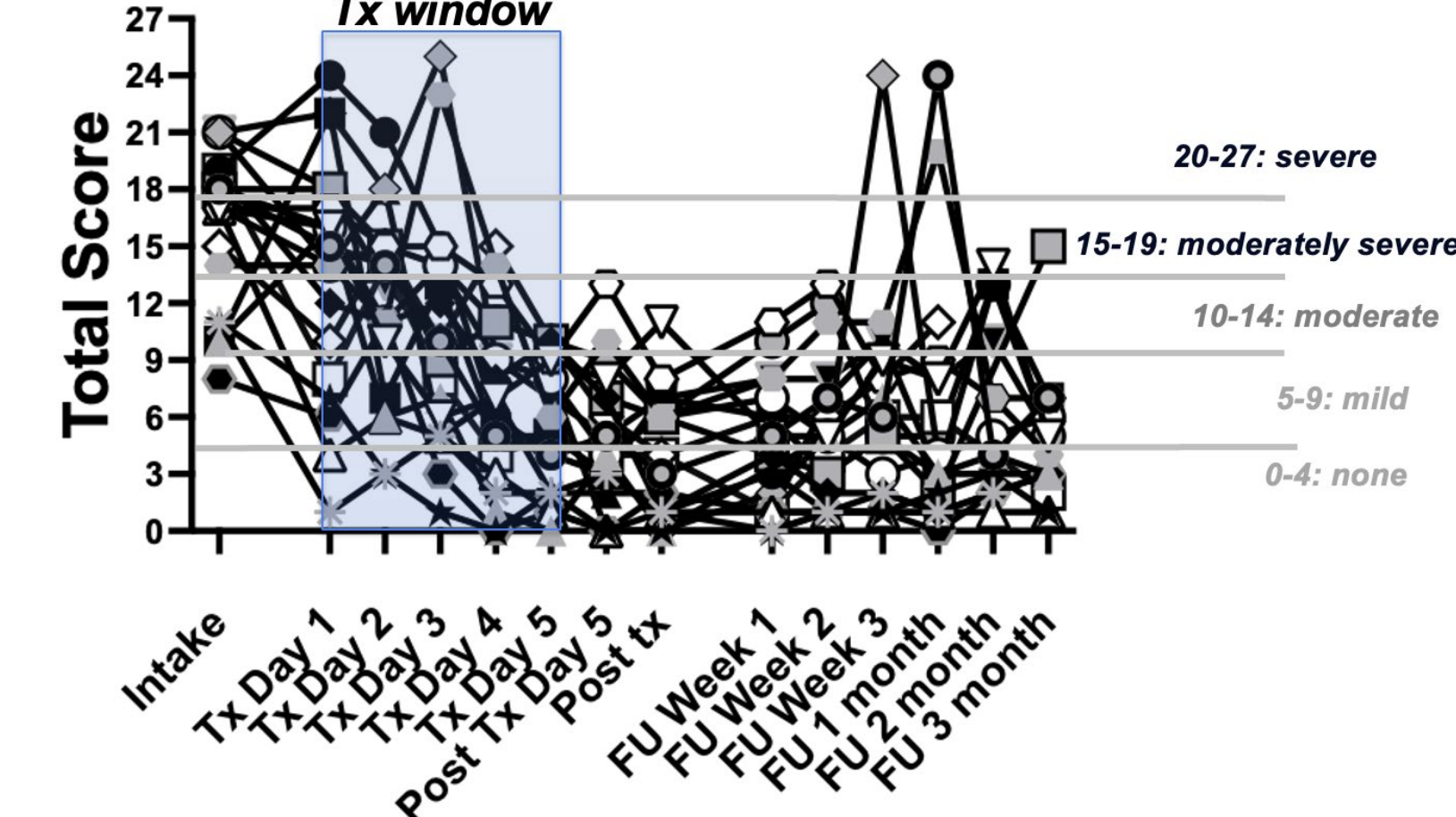
EEG Biomarkers: Global Mean Field Power (GMFP) was calculated from 5 min resting state EEG collected pre- and post- EEG-rTMS treatment sessions. Entrainment (ITPC phase alignment) was calculated using EEG data after between pulse trains during treatment.

RESULTS

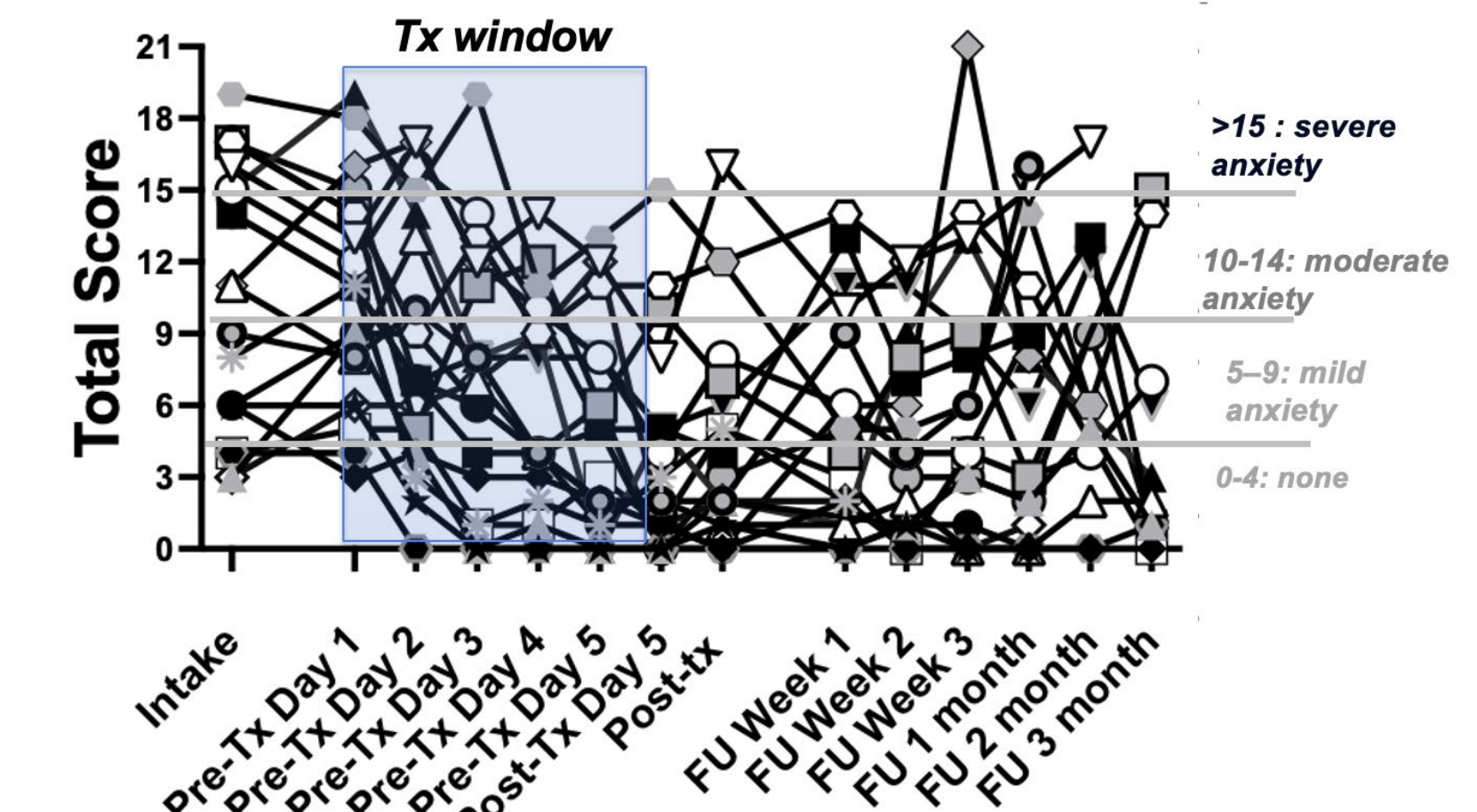
Hamilton Ratings Scale for Depression HAMD-17



Patient Health Questionnaire-9 PHQ-9



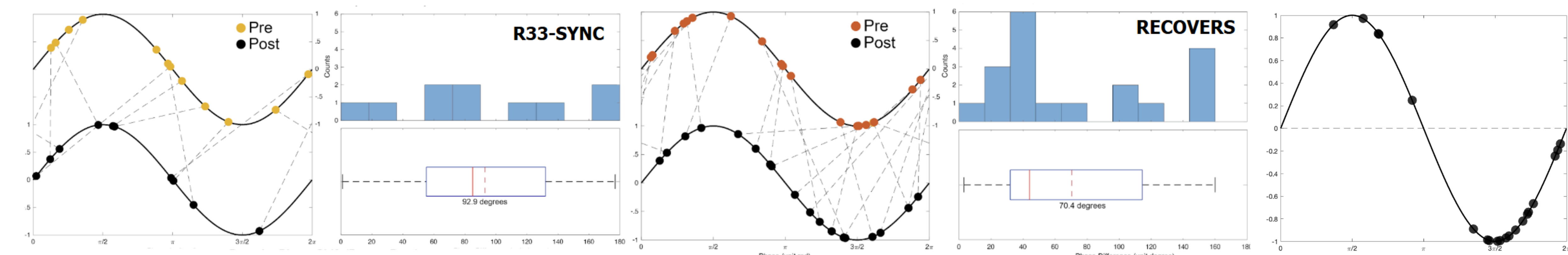
Generalized Anxiety Disorder-7 GAD-7



After 5 days of treatment 85% no longer meet diagnostic threshold for major depression. The three patients above threshold are both mild and experienced 67%-74% reduction.

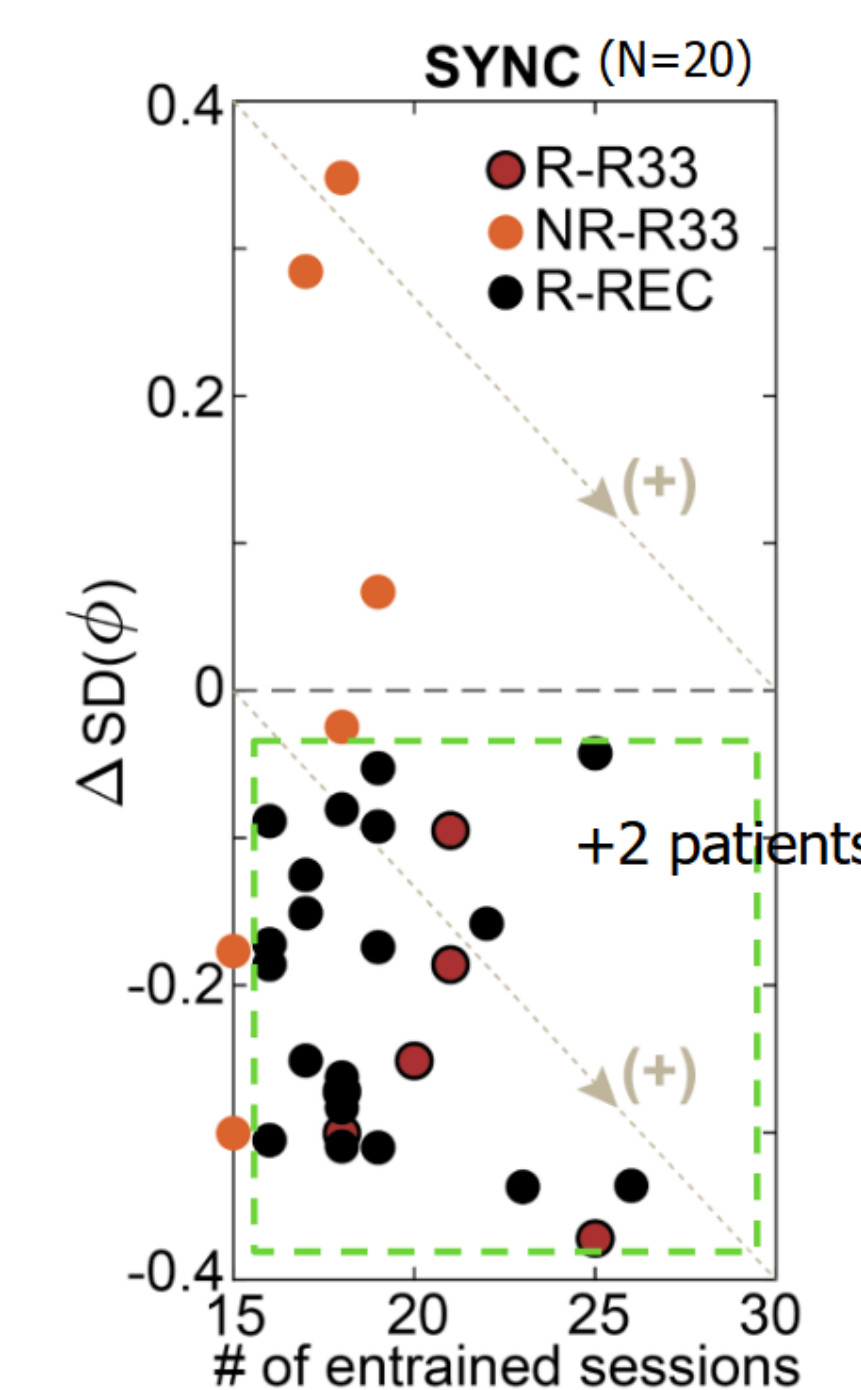
Immediately following 5 days of treatment, 95% responders, 55% are remitted. At 1 month follow up, 58% of completers attained remission.

Across the whole sample, inclusive of no to mild elevations at baseline, immediately following 5 days of treatment, 85% were responders in anxiety severity after 5 days of treatment.

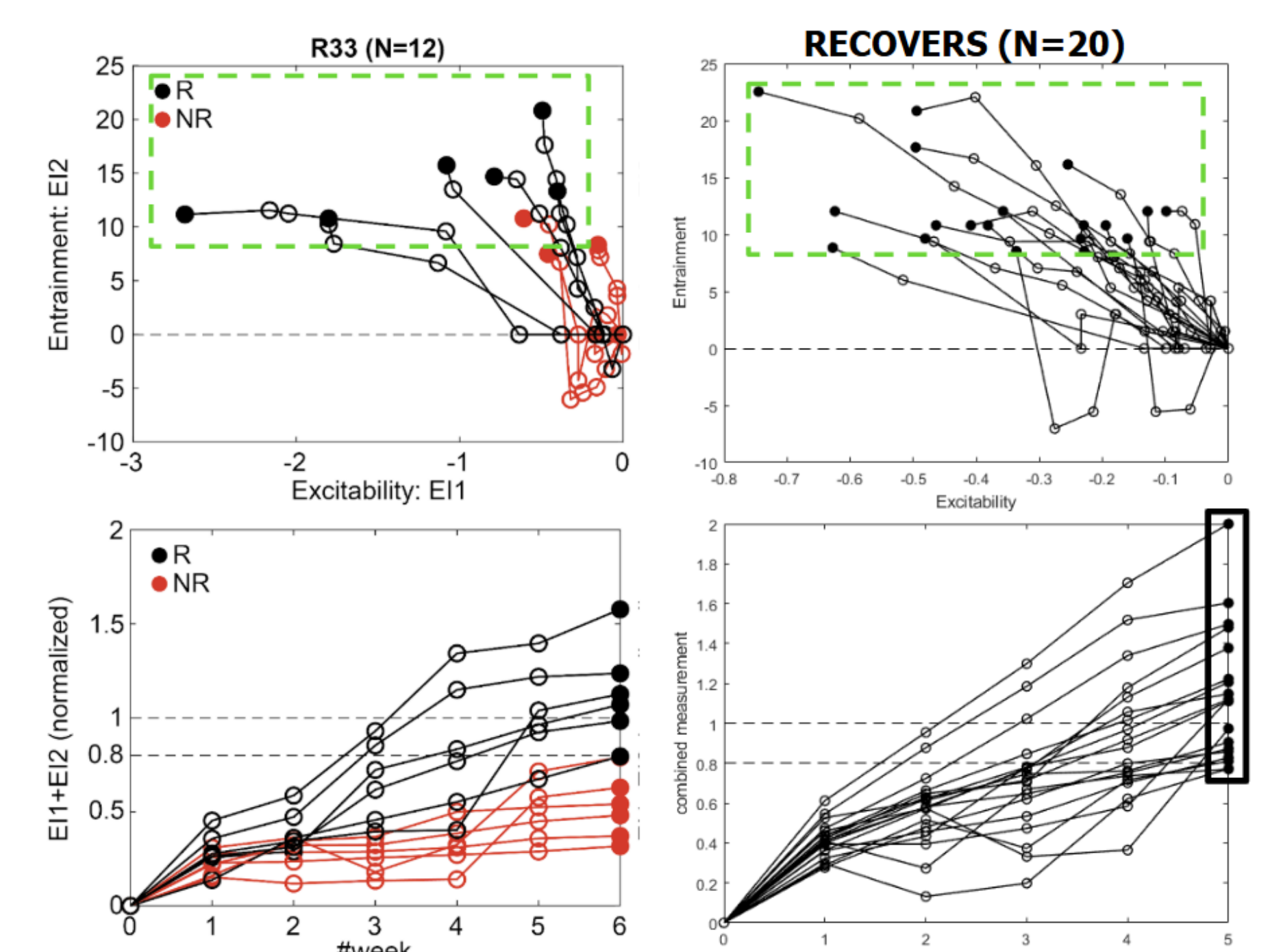
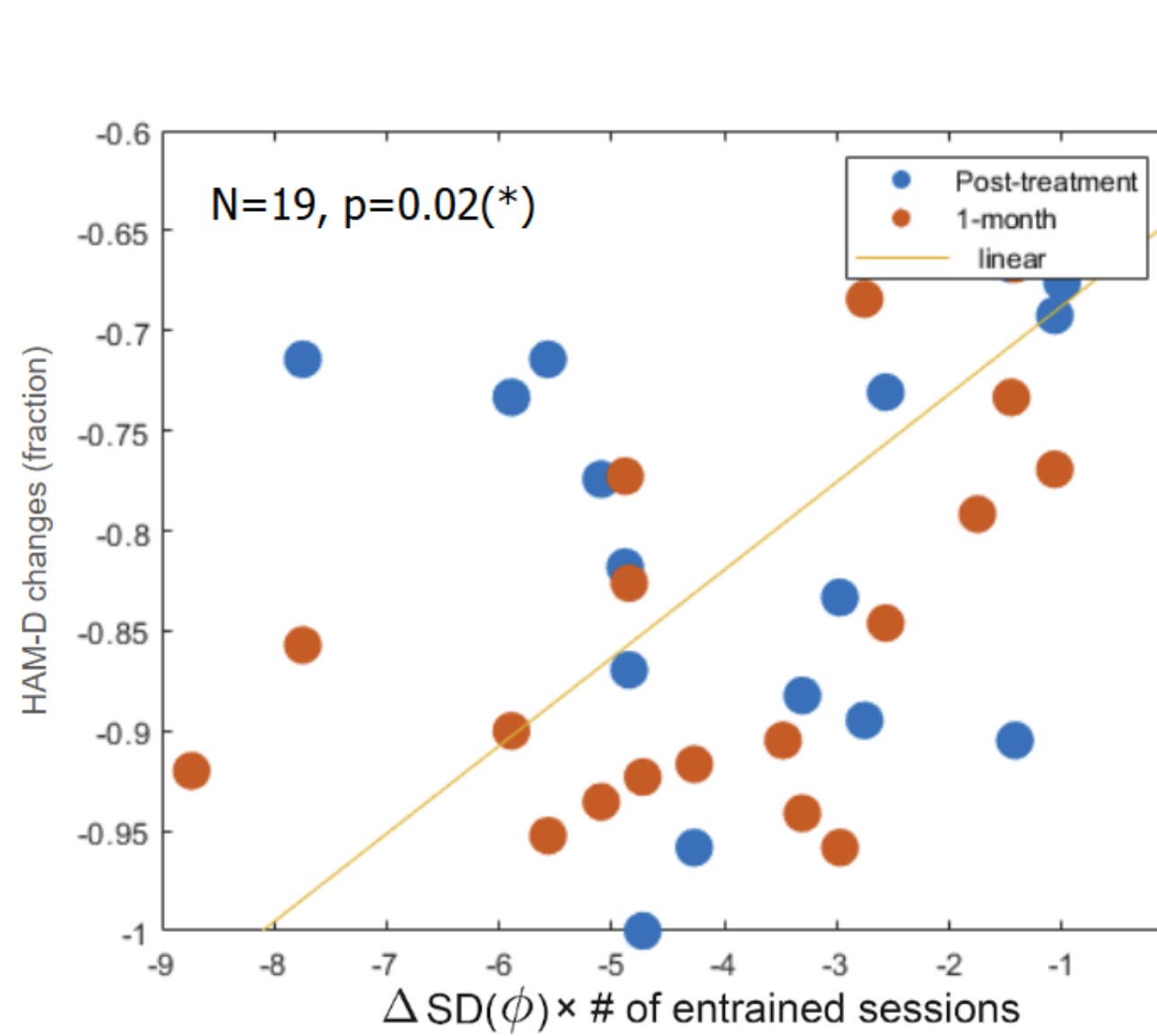


Preferred Phase from MRI+EEG+TMS: There was a smaller preferred phase change between pre and post treatment in the RECOVERS trial (mean 70.4 degrees) compared to a prior R33 trial that delivered treatment across 6 weeks (mean 92.9 degrees)

EEG Entrainment Phase clusters near the trough of alpha



Correlation between Entrainment and HAM-D decrease



Global Entrainment and Excitability: (Left): There is a significant correlation between entrainment and HAMD-D decrease. (Right): Weekly / Daily changes of each patient in Excitability (GMFP) and Entrainment (ITPC phase alignment) are shown. In the prior R33 trial, when those 2 indices were combined, there is a clear separation between treatment responders (R) and non-responders (NR) who received synchronized treatment. In the RECOVERS trial, responders also show consistent changes in their neurophysiological biomarkers.

CONCLUSIONS

An accelerated closed-loop rTMS treatment, interleaved with CBT, was effective in treating clinical symptomology in the clinically depressed.

Global entrainment and excitability show a clear separation for treatment responders and non-responders across two different clinical trials, suggesting potential value as a prognostic biomarker.

The preferred alpha phase shifted changed less in the RECOVERS trial with treatment delivered in a week compared to a prior trial with treatment delivered across six weeks. This suggests more consistent phase targeting leads to greater clinical efficacy. The EEG entrainment phase was found to cluster near the trough of alpha, suggesting future trials could target at the trough rather than a personalized phase to simplify the clinical workflow.

ACKNOWLEDGEMENTS

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