The Relationship of Anxious Arousal With Treatment of Dysphoria Using Virtual Reality Mindfulness and 2 Accelerated Transcranial Magnetic Stimulation Protocols

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Abstract

Objective: This secondary analysis investigated the relationship of anxious arousal, as measured by the Tension-Anxiety subscale of the Profile of Mood States (TA-POMS), to treatment outcome across diagnoses for each phase of the study. Sequential treatment phases of virtual reality (VR) mindfulness followed by left dorsolateral prefrontal cortex (dlPFC) accelerated transcranial magnetic stimulation (accel-TMS) and then dorsomedial prefrontal cortex (dmPFC) accel-TMS were used to treat dysphoria across diagnoses in an open trial from September 2021 to August 2023.

Methods: The change in the TA-POMS subscale was compared to the percent change in primary clinician scale scores using a bivariate analysis. Baseline TA-POMS subscales were compared to treatment response using linear regression models to assess anxious arousal's impact on treatment outcome for the 3 phases. Significance was defined as $P < .05$, 2-tailed.

Results: Twenty-three participants were enrolled in VR mindfulness, 19 in left dlPFC accel-TMS, and 12 in dmPFC accel-TMS. Although the change in TA-POMS scores did not significantly correlate with the percent change in primary clinician scale ratings for the VR phase, they did for both the dlPFC ($P = .041$) and the dmPFC ($P = .003$) accel-TMS treatment phases. Importantly, baseline anxious arousal levels as measured by TA-POMS were not predictive of treatment outcome in any treatment phase.

Conclusion: The outcome of accel-TMS treatment was not adversely affected by anxious arousal and similarly improved along with primary rating scales.

Trial Registration: ClinicalTrials.gov identifier: NCT05061745

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Dysphoria, defined as "a mood characterized by generalized discontent and agitation," is a symptom complex present in several medical conditions including major depressive disorder (MDD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and chronic pain.[1] Despite health conditions being dependent on the presentation of specific criteria to direct treatment, treatments are being developed that seek to alleviate dysphoria across multiple diagnostic conditions. Identifying treatments for dysphoria demonstrates patient-centeredness due to the commonality of these comorbidities in mental health disorders. For example, 65% of patients with MDD experience one or more pain complaints,[2] 90% of patients with anxiety disorders have MDD,[3] and 19.1% of patients with chronic pain meet criteria for PTSD.[4] In consideration of these comorbidities, understanding how these comorbidities impact outcome across conditions becomes clinically important.

One symptom cluster that has demonstrated a negative impact on treatment outcome of neuropsychiatric disorders in various treatment modalities is anxiety.[5–8] Anxiety has been associated with reduced clinical improvement using cognitive behavioral

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Clinical Points

- Anxious arousal, although a negative predictor of success in antidepressant trials, has not been explored as a predictor of accelerated transcranial magnetic stimulation (accel-TMS) outcome.
- Participant improvement via accel-TMS correlated with decreases in anxious arousal, and anxious arousal was not a negative predictor of treatment success.
- Accel-TMS may be a viable intervention for those indicated to not be responsive to medication.

therapy in chronic pain patients,[9] and patients with higher levels of anxiety were found to have more severe depression and pain 1 year later.[10] A dimension of anxiety that has been previously implicated to affect treatment outcomes is anxious arousal, as measured by the Tension-Anxiety subscale of the Profile of Mood States (TA-POMS). Studies have demonstrated that higher TA-POMS scores are associated with severity of depression[11] and insomnia.[12] Anxious arousal has been shown to negatively impact pharmacologic treatment outcomes in depression,[13] but less is known about anxious arousal's impact on treatment outcome with neuromodulation treatments. Studies have found a correlation between improvement in anxious arousal as measured by the TA-POMS subscale and improved treatment outcomes with neuromodulation.[14,15]

As a secondary analysis, this study investigates data collected from participants that underwent protocols outlined in Senda 2023.[16] Briefly, participants were treated with up to 2 weeks of virtual reality (VR) mindfulness, followed by 25 treatments of over 5 days of accelerated transcranial magnetic stimulation (accel-TMS) of the left dorsolateral prefrontal cortex (dlPFC), followed by 25 treatments of over 5 days of accel-TMS of the dorsomedial prefrontal cortex (dmPFC). Participants that demonstrated meaningful improvement in each phase were followed weekly for an additional 5 weeks, while those that did not improve were offered the next treatment. Those that completed the 5 weeks of follow-up but still met criteria for entry into the study based on clinical severity were also allowed to proceed to the next treatment phase.

In the dlPFC accel-TMS treatment phase, participants received intermittent theta-burst stimulation (iTBS), which is triplet 50-Hz bursts repeated at 5 Hz. Stimulation intervals were repeated for 2 seconds on and 8 seconds off. In total, 1,800 pulses were delivered per session, which occurred over a 9.5-minute timespan. There were 50-minute intervals between treatment sessions. In the dmPFC treatment phase, the same iTBS protocol was delivered for 600 pulses over a 3-minute and 10-second interval. Immediately following iTBS, 10-Hz TMS was delivered for 4 seconds on and 11 seconds off for an additional 1,200 pulses lasting 7.5 minutes. Each treatment session was separated by 50-minute intervals. Both treatment phases received stimulation at 110% of a participant's resting motor threshold for hand (dlPFC) or leg (dmPFC).

Based on the results of Senda 2023, which found that accel-TMS has great potential for addressing symptoms of dysphoria in patients with transdiagnostic depression, anxiety, and PTSD, this post hoc analysis seeks to better understand which populations with dysphoria would benefit the most from accel-TMS. As demonstrated by previous studies, anxious arousal may represent an important predictor of outcome to psychiatric treatment. This study seeks to determine whether change in anxious arousal as measured by TA-POMS was correlated with improvement in dysphoria. The impact of baseline anxious arousal on treatment outcome was also investigated. The relationship of anxious arousal to clinical outcome was examined in response to 3 treatments of dysphoria as part of a recent clinical trial. The treatment study used a sequential approach in which participants with dysphoria who met criteria for MDD, GAD, PTSD, and/or chronic pain proceeded to the next neuromodulation treatment if symptoms were not resolved with the prior treatment (for complete details, see Senda 2023).[16] Increased change in anxious arousal throughout each phase was hypothesized to be significantly correlated with increased change in primary clinician scale ratings. In addition, analyses were conducted to investigate whether the TA-POMS subscale had predictive capability in determining treatment impact across each phase. Exploratory analyses were also performed to determine whether changes in other POMS subscales were significantly correlated with changes in clinician ratings or had predictive capability in determining treatment impact across each phase.

METHODS

Approval and Consent

The study was approved by The Florida State University Investigation Review Board, and the protocol was registered on ClincialTrials.gov (Neuromodulation for Dysphoria: NCT05061745) prior to participant enrollment. Verbal consent was acquired over the phone for prescreening purposes regarding eligibility and safety. Written consent was collected from participants at the beginning of each phase, prior to any study procedures. This study was conducted from September 2021 to August 2023.

Inclusion/Exclusion Criteria

Inclusion criteria for this study included minimum symptoms of dysphoria based on self-rated scales [Patient Health Questionnaire-9 ≥10, GAD-7 ≥10, PTSD Checklist for *DSM-5* ≥45, or average pain ≥4/10 for >3 months], at least 18 years of age, and no changes in medication for at least 1 month. Exclusion criteria

included taking any medications that increased the risk for seizure, diagnosis of a substance use disorder, severe neurological disorder, psychotic disorder, history of severe traumatic brain injury, metal within the head, pregnancy, or unstable medical conditions.

Recruitment

Participants were recruited through community word of mouth, flyers, health care provider referrals, and Facebook advertisements. Many of the individuals were directed to our participant registry to indicate their interest in being contacted about applicable research opportunities by providing their contact information, areas of study interested in participating, and basic demographic information.

Rating Scale Assessments

An appropriate dysphoria scale to use in this study was not found. As such, validated scales for specific psychiatric disorders associated with dysphoria (ie, MDD, GAD, PTSD, and chronic pain) were utilized for assessing dysphoria. For this analysis, the VR mindfulness POMS score and clinician-rated scales from the first visit and tenth visit were utilized. If participants dropped out before the tenth visit, the POMS results and the clinician-rated scale from the fifth visit were used. If participants dropped out before the fifth visit, the POMS results and the clinician-rated scale from the first visit of the dlPFC accel-TMS treatment phase were used if participants began the phase within 60 days of concluding VR mindfulness. For the dlPFC accel-TMS and dmPFC accel-TMS treatment phases, POMS and clinician-rated scales were completed at the start of the first treatment visit and first follow-up visit. The clinician-rated scales used in this trial included Montgomery-Asberg Depression Rating Scale (MADRS) for MDD,[17] Hamilton Anxiety Rating Scale (HARS) for GAD,[18] Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) for PTSD,[19] and Patient-Reported Outcome Measurement Information System (PROMIS) Pain Interference for chronic pain.[20] Treatment response was defined as a ≥50% decrease in MADRS or HARS or a ≥30% decrease in CAPS-5 or PROMIS Pain Interference. Diagnostic remission was defined as a score ≤10 on the MADRS, a score ≤7 on the HARS, no diagnosis of PTSD based on CAPS-5 criteria, and a ≥50% decrease in PROMIS Pain Interference score. For further details on measures and outcomes, see Table 1 and Figure 3 of Senda 2023.[16]

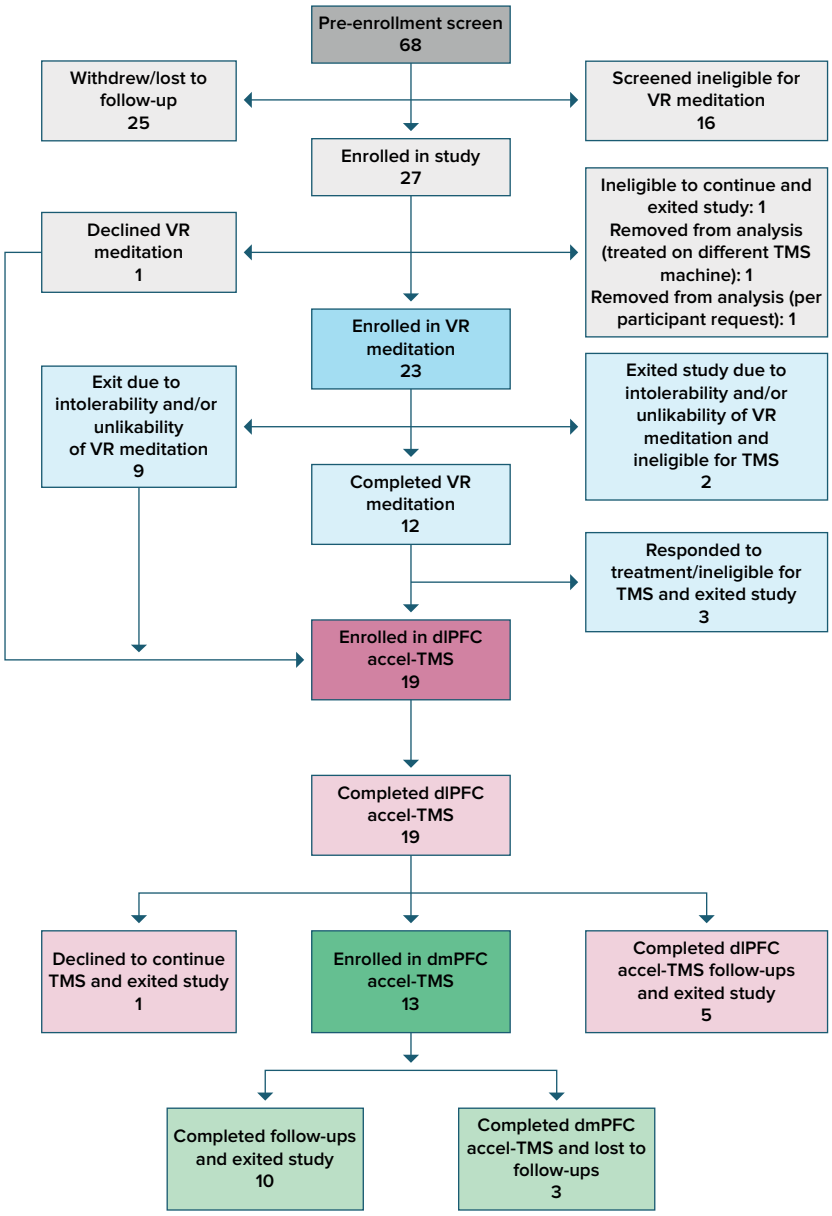
The TA-POMS was selected a priori as the primary assessment of anxious arousal. The POMS is a 60-question self-survey originally developed as a clinical instrument to measure mood states and mood change in outpatient psychiatric populations.[21] POMS is a widely accepted measure of psychological distress in healthy,[22] physically ill,[23] and psychiatric populations,[24] having been used in over 5,000 studies and translated into over 40 languages.[25] POMS consists of subscales (Fatigue-Inertia, Vigor-Activity, Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Confusion-Bewilderment) and yields a total score (Total Mood Disturbance). The specific version of POMS used in this analysis is an abbreviated, 40-question POMS survey that added one subscale (Esteem) while maintaining internal validity.[26] Correlation between the full version and the abbreviated form has been found to exceed .95 across all subscale and

Table 1.
Demographics of Study Sample

Variables	N	Percent	Mean	SD
Age	22	92	43.6	15.8
Undisclosed[a]	2	8		
Biological sex				
Male	9	38		
Female	15	63		
Other	0	0		
Marital status				
Single	8	33		
Married	12	50		
Divorced	0	0		
Widowed	2	8		
Domestic partner	0	0		
Significant other	2	8		
Race				
American Indian or Alaska Native	0	0		
Asian	1	4		
Black or African American	0	0		
Native Hawaiian or Pacific Islander	0	0		
White	21	92		
More than one race	1	0		
Unknown or not reported	1	4		
Ethnicity				
Hispanic or Latino	1	4		
Not Hispanic or Latino	21	88		
Unknown or not reported	2	8		
Veteran	1	4		
Education				
Less than high school diploma	0	0		
High school graduate/GED	1	4		
Some college but no degree	4	17		
Associate degree	2	8		
Bachelor's degree	7	29		
Master's degree	6	25		
PhD, JD, or other professional degree	4	17		
Household income				
$0–25,000	1	4		
$25,001–50,000	5	21		
$50,001–75,000	7	29		
$75,001–100,000	4	17		
$100,001–150,000	2	8		
$150,001–200,000	3	13		
$200,001+	1	4		
Undisclosed	1	4		
Handedness				
Left	3	12		
Ambidextrous	0	0		
Right	21	88		

[a]Specific age unknown but clearly greater than 18 years old.
Abbreviation: GED = General Educational Development.

Figure 1.
CONSORT Diagram With Participants Enrollment



Abbreviations: accel-TMS = accelerated transcranial magnetic stimulation, CONSORT = Consolidated Standards of Reporting Trials, dPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, VR = virtual reality.

Total Mood Disturbance scores.[27] Total Mood Disturbance is a combined score of positive subscales (Vigor and Esteem) subtracted from negative subscales (Tension, Fatigue, Anger, Confusion, and Depression).

Data Analysis

Participants were excluded from data analysis if applicable rating scales were not available. To determine whether anxious arousal symptoms were correlated with treatment response, the change in TA-POMS was calculated by determining the change in subscale score between pre- and posttreatment. The change in primary clinician scale ratings, which was used as the primary indicator of response to treatment, was also calculated using the same visits for each trial. Changes in clinician scores were used to calculate percentage change, which standardized data from different clinician-rated scales. Pearson correlation coefficients were generated using SPSS Statistics 29 to compare the change in TA-POMS to the percent change in primary clinician scale rating. To

Table 2.

Outcomes by Primary Diagnosis Group

Clinical response and remission of primary diagnosis[a]				
Treatment	**Primary diagnosis**	**Participants**	**Clinical response**	**Clinical remission**
VR mindfulness	MDD	9	0	0
	GAD	6	0	0
	PTSD	5	0	0
	Chronic pain	2	1	0
	Total	22	1	0
dlPFC accel-TMS	MDD	8	1	1
	GAD	7	2	2
	PTSD	4	1	0
	Chronic pain	0	0	0
	Total	19	4	3
dmPFC accel-TMS	MDD	4	1	0
	GAD	4	2	2
	PTSD	3	1	2
	Chronic pain	1	0	0
	Total	12	4	4

[a]Primary diagnosis was decided based on clinical scores at the beginning of each phase.
Abbreviations: accel-TMS = accelerated transcranial magnetic stimulation, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, GAD = generalized anxiety disorder, MDD = major depressive disorder, PTSD = posttraumatic stress disorder, VR = virtual reality.

explore whether the changes in other POMS subscales were associated with treatment outcomes, the changes in each subscale and Total Mood Disturbance scores were compared to clinical outcome based on the diagnosis-specific clinician rating scales using the same procedure as for TA-POMS above. No corrections for multiple comparisons were performed as the primary outcomes were hypothesized to be unrelated. SPSS Statistics 29 was also used to generate linear regression models to assess whether TA-POMS baseline scores had an impact on treatment outcome for all 3 phases. Linear regression models were used to explore whether baseline scores of other subscales and Total Mood Disturbance had an impact on treatment outcome. Significance was defined as $P < .05$, two-sided.

RESULTS

A significant number of participants were referred specifically for TMS due to their treatment-resistant nature, despite an attempt to broadly recruit from the community. The average participant in this study tried more than 2 antidepressants, 36% had been prescribed 3 or more antidepressants, and 72% previously trialed psychotherapy. Of the 27 participants that were eligible for the VR mindfulness treatment phase (see Table 1 demographics), 1 participant was deemed ineligible to continue the study, 1 participant declined to undergo the VR mindfulness protocol, 1 participant was removed from analysis per participant request, and 1 participant who completed Phase 1 was treated on a different TMS machine and was excluded from all data analysis for continuity. Thus, there were 23 participants that entered the VR mindfulness treatment phase (see Figure 1 Consolidated Standards of Reporting Trials [CONSORT] diagram). One participant was excluded from the analysis because the time between starting the VR mindfulness and dlPFC accel-TMS treatment phases was greater than 60 days. Primary diagnoses included MDD (n = 9), GAD (n = 6), PTSD (n = 5), and chronic pain (n = 2). Of the 22 participants included in the analysis, 1 achieved a clinical response of their primary diagnosis after VR treatment, but none met criteria for clinical remission (see Table 2 outcomes by primary diagnosis group). Scores from a participant's fifth visit of VR mindfulness or first visit of the dlPFC accel-TMS treatment phase were used in 9 of the 22 participants in this phase, as these participants chose to exit the phase prior to the tenth visit.

In the dlPFC accel-TMS treatment phase, 19 participants were enrolled and included in the analysis. Primary diagnoses included MDD (n = 8), GAD (n = 7), and PTSD (n = 4). Four of the 19 participants in the dlPFC accel-TMS treatment phase achieved a clinical response of their primary diagnosis, and 3 met criteria for clinical remission. Of the 19 participants that completed dlPFC accel-TMS, 5 completed this phase and exited the study, and 1 declined to continue TMS and exited the study. Thirteen participants enrolled in the dmPFC accel-TMS treatment phase, and 1 was excluded from the analysis due to incomplete data. The other 12 participants were included in the data analysis. Primary diagnoses included MDD (n = 4), GAD (n = 4),

Table 3.

Correlation of POMS Subscales and Total Mood Disturbance With Clinical Outcome Using Pearson Correlation

Change in POMS subscale scores vs change in primary clinician scale rating			
Treatment	**POMS subscale**	***P***	***r***
VR mindfulness	Tension-Anxiety	.606	0.014
	Fatigue	.335	0.216
	Anger	**.022**	0.486
	Vigor	.860	−0.040
	Esteem	.136	0.328
	Confusion	.094	0.336
	Depression	.321	0.222
	Total Mood Disturbance Score	**.033**	0.455
dlPFC accel-TMS	Tension-Anxiety	**.041**	0.473
	Fatigue	.355	0.225
	Anger	.408	0.202
	Vigor	.066	0.431
	Esteem	.027	0.507
	Confusion	.333	−0.235
	Depression	.143	0.349
	Total Mood Score	.447	0.185
dmPFC accel-TMS	Tension-Anxiety	**.003**	0.772
	Fatigue	.917	−0.034
	Anger	.193	0.404
	Vigor	.186	0.409
	Esteem	.100	0.497
	Confusion	.216	0.385
	Depression	.372	0.283
	Total Mood Disturbance Score	.096	0.503

Boldface indicates statistical significance.
Abbreviations: accel-TMS = accelerated transcranial magnetic stimulation, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, POMS = Profile of Mood States, VR = virtual reality.

PTSD (n = 3), and chronic pain (n = 1). Four of the 12 participants showed a clinical response of their primary diagnosis, and 4 met criteria for clinical remission. Each participant in the dlPFC accel-TMS and dmPFC accel-TMS treatment groups completed all treatment sessions.

Correlation of Anxious Arousal With Clinical Outcome

The TA-POMS was not found to be significantly associated with changes in primary clinician scale ratings in the VR mindfulness treatment phase (N = 22, $P = .606$, $r = 0.014$). However, TA-POMS was found to be significantly correlated with primary clinician scale ratings in the dlPFC accel-TMS (N = 19, $P = .041$, $r = 0.473$) and the dmPFC accel-TMS (N = 12, $P = .003$, $r = 0.772$) treatment phases (see Table 3).

Correlation of POMS Subscales and Total With Clinical Outcome

Generated linear regression models for changes in other subscales across clinician ratings were not found to be statistically significant, except for the Anger subscale and Total Mood Disturbance in the VR mindfulness treatment phase (N = 22, $P = .022$, $r = 0.486$ and N = 22, $P = .033$, $r = 0.455$) and Esteem subscale in the dlPFC accel-TMS treatment phase (N = 19, $P = .027$, $r = 0.507$) (see Table 3). Although these subscales reached significance, due to the multiple comparisons, these findings will need to be replicated in future studies.

Table 4.

Baseline POMS Subscales and Total Impacting Clinical Outcome

Baseline POMS subscale scores vs change in primary clinician scale rating				
Treatment	**POMS subscale**	**β**	***P***	***r*²**
VR mindfulness	Tension	−1.169	.185	0.086
	Fatigue	−1.232	.131	0.110
	Anger	−0.286	.732	0.006
	Vigor	2.232	.122	0.116
	Esteem	0.855	.651	0.010
	Confusion	−0.203	.846	0.002
	Depression	−0.185	.771	0.004
	Total Mood Score	−0.211	.275	0.059
dlPFC accel-TMS	Tension	1.172	.226	0.085
	Fatigue	0.992	.430	0.037
	Anger	0.483	.736	0.007
	Vigor	−0.751	.703	0.009
	Esteem	0.807	.632	0.014
	Confusion	−0.151	.925	0.001
	Depression	0.082	.929	0.000
	Total Mood Score	0.062	.852	0.002
dmPFC accel-TMS	Tension	6.585	.097	0.275
	Fatigue	−3.726	.241	0.149
	Anger	3.738	.299	0.119
	Vigor	2.277	.855	0.004
	Esteem	−6.814	.051	0.360
	Confusion	3.657	.419	0.074
	Depression	1.665	.536	0.044
	Total Mood Score	0.212	.818	0.006

Abbreviations: accel-TMS = accelerated transcranial magnetic stimulation, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, POMS = Profile of Mood States, VR = virtual reality.

Baseline Anxious Arousal and Other POMS Subscales Impact on Clinical Outcome

A linear regression model found that anxious arousal as measured by TA-POMS was not significantly predictive (VR mindfulness: β = −1.169, $P = .185$; dlPFC accel-TMS: β = 1.172, $P = .226$; dmPFC accel-TMS: β = 6.585, $P = .097$) of clinical outcome in all 3 phases of treatment. In addition, all other baseline scores of POMS subscales and Total Mood Disturbance were not predictive of treatment outcome across all phases (see Table 4).

DISCUSSION

In our primary analysis, changes in anxious arousal were found to be significantly correlated with changes in

clinician scale ratings in the accel-TMS treatment groups, but baseline severity of anxious arousal did not significantly impact the clinical outcome of treatment. This is the first report of which we are aware that anxious arousal's lack of a negative impact on clinical outcome has been demonstrated in an accel-TMS protocol. Our preliminary data indicates that individuals with anxious arousal can have quite positive treatment responses to TMS. Demonstrating these findings with accel-TMS therapies warrants further investigation to better understand the role neuromodulation has in treating dysphoria.

Change in TA-POMS did not correlate with changes in primary clinician-rated scales in the VR mindfulness treatment phase, possibly due to limited treatment response in the group or due to a small sample size. In addition, data from 9 of 22 participants elected to enter the dlPFC accel-TMS treatment phase prior to the completion of the VR mindfulness phase. This large attrition rate likely reflected the frustration of participants due to lack of treatment effects for VR mindfulness. The benefit from VR mindfulness may also be due to reductions in dimensions of dysphoria other than anxious arousal. While studies have demonstrated mixed results for predicting the degree of anxious arousal based on the level of mindfulness,[28–30] there is limited information on the effects of mindfulness-based treatment on the severity of anxious arousal. Further research is needed to determine the relationship between mindfulness interventions and anxious arousal.

Dissimilar to pharmacologic intervention studies,[5,13,31] baseline anxious arousal was not found to be predictive of treatment success in the neuromodulation therapies used in this study. These findings contribute to ongoing discussions about the impact of comorbid anxiety on TMS treatment for MDD. Hernandez et al[32] found anxiety to be a slightly negative predictor of TMS treatment for depression using some rating scales but not others. Lisanby et al[33] found anxiety to potentially be a negative predictor of treatment outcome for MDD using standard TMS protocols. Conversely, Clarke et al[34] found no significant difference between MDD-treated groups with and without anxiety in repetitive TMS, and Philip et al[35] found anxiety to be a positive predictor of TMS response in a very different version (synchronized) of TMS. TMS is actually Food and Drug Administration–cleared for "anxious depression" based on significant improvement in depressive and anxiety symptoms across randomized trials and a registry database. For the registry analysis, the groups with and without anxious depression had equivalent improvements in depressive scores, but the categorical responses and remission for depression were lower for the anxious depressed group.[36] Inconsistent results have been reported in the literature regarding anxiety in TMS, and further work will be needed to clarify accel-TMS's role in treating dysphoria.

With respect to response and remission rates in this study, several factors should be considered. Many participants would be considered "treatment-resistant," as they had experienced periods of dysphoria throughout their lifetime and have tried numerous medical interventions. In addition, most participants met criteria for more than 1 diagnosis. The response and remission rates included in the secondary data analysis purposefully did not take this into consideration, as we focused on the primary clinician scale rating. For example, a participant with a primary diagnosis of depression may have experienced a 40% reduction in their MADRS score and now met criteria for PTSD remission based on their CAPS-5 score. Although the participant would not be considered in this analysis to have achieved a clinical response or remission, the participant still significantly benefited from treatment. Data in Senda 2023 account for patients across all 4 diagnostic spectrums used in this study.[37]

As anxious arousal is not predictive of treatment outcomes in the neuromodulation interventions used in this study and correlates with participant improvement in accel-TMS treatment groups, we conclude that anxious arousal is not a negative predictor of participant outcome for accel-TMS. With the added context of previous pharmacologic studies concluding that anxious comorbidities, specifically anxious arousal, lead to worse patient outcomes, the result of this trial contributes to other studies that TMS is not as negatively affected by anxious symptoms and represents an effective intervention for some medication-resistant anxious conditions.[5,13,31,36] For example, recent meta-analyses have concluded that TMS is an efficacious treatment modality for obsessive-compulsive disorder, panic disorder, and PTSD.[38–40] Notably, the accel-TMS protocols used in this study correspond with the findings of Siddiqi, 2021,[41] in which dysphoric (left dlPFC) and anxiosomatic (dmPFC) circuits were identified as distinct biotypes of MDD. Our study demonstrates that anxious arousal is not a negative predictor of treatment outcome in either of these locations.

Limitations of this study include a small sample size, which is a consequence of a longitudinal, sequential pilot study. In addition, there was no randomized control group to test the role of TMS vs other benefits of participating in a clinical trial as this was an initial testing of a novel treatment approach to treat dysphoria. However, the limited response of the VR mindfulness phase would argue that other factors were likely involved than just participation in a clinical trial. The follow-up period was limited in this study to an acute treatment period. This analysis utilized a last-observation-carried-forward method, which assumes that a participant did

not experience a worsening or improvement in dysphoria after declining to continue VR mindfulness. Future investigations on dysphoria and neuromodulation should consider a sham-controlled arm as well as long-term follow-up data collection to better understand the impact of these treatment modalities.

CONCLUSION

Change in anxious arousal was not found to be correlated with participant's response for VR mindfulness but was determined to be correlated with response in the left dlPFC and dmPFC accel-TMS treatment groups. Anxious arousal was not found to be a significant predictor of clinical outcome of accel-TMS for dysphoria. These results support existing literature that anxiety is not a negative predictor of neuromodulation treatment outcome, unlike pharmacologic interventions, and add to ongoing discussion on the potential of TMS to treat numerous psychiatric conditions. Future studies are needed to better understand these relationships.

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References

1. American Psychological Association. *APA Dictionary of Psychology*. American Psychological Association. Accessed Februrary 9, 2023. https://dictionary.apa.org/dysphoria
2. Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433–2445.
3. Tiller JWG. Depression and anxiety. *Med J Aust*. 2013;199(S6):S28–S31.
4. Fishbain DA, Pulikal A, Lewis JE, et al. Chronic Pain types Differ in their reported prevalence of post-traumatic stress disorder (PTSD) and there is consistent evidence that chronic pain is associated with PTSD: an evidence-based structured systematic review. *Pain Med*. 2017;18(4):711–735.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917.
6. Tunvirachaisakul C, Gould RL, Coulson MC, et al. Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis. *J Affect Disord*. 2018;227:164–182.
7. Cavicchioli FL, Maes M, Roomruangwong C, et al. Associations between severity of anxiety and clinical and biological features of major affective disorders. *Psychiatry Res*. 2018;260:17–23.
8. Steiner AJ, Boulos N, Mirocha J, et al. Quality of life and functioning in comorbid posttraumatic stress disorder and major depressive disorder after treatment with citalopram monotherapy. *Clin Neuropharmacol*. 2017;40(1):16–23.
9. Cunningham NR, Jagpal A, Tran ST, et al. Anxiety adversely impacts response to cognitive behavioral therapy in children with chronic pain. *J Pediatr*. 2016;171:227–233.
10. Bair MJ, Poleshuck EL, Wu J, et al. Anxiety but not social stressors predict 12-month depression and pain severity. *Clin J Pain*. 2013;29(2):95–101.
11. Sundermann EE, Tang B, Kim M, et al. Neuropsychiatric predictors of cognitive functioning over a one-year follow-up period in HIV. *J Affect Disord*. 2023;336:92–96.
12. Passos GS, Youngstedt SD, Rozales AARC, et al. Insomnia severity is associated with morning cortisol and psychological health. *Sleep Sci*. 2023;16(1):92–96.
13. Saveanu R, Etkin A, Duchemin AM, et al. The International Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment. *J Psychiatr Res*. 2015;61:1–12.
14. Xu J, Fregni F, Brody AL, et al. Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. *Front Psychiatry*. 2013;4:112.
15. Roh HT, So WY. Cranial electrotherapy stimulation affects mood state but not levels of peripheral neurotrophic factors or hypothalamic– pituitary–adrenal axis regulation. *Technol Health Care*. 2017;25(3):403–412.
16. Senda MC, Johnson KA, Taylor IM, et al. A pilot trial of stepwise implementation of virtual reality mindfulness and accelerated transcranial magnetic stimulation treatments for dysphoria in neuropsychiatric disorders. *Depress Anxiety*. 2023;2023:1–16.
17. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
19. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess*. 2018;30(3):383–395.
20. Reeve BB, Hays RD, Bjorner JB, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). *Med Care*. 2007;45(5 suppl 1):S22–S31.
21. McNair DM, Lorr M, Droppleman LF. Profile of mood states. Educational and Industrial Testing Service; 1971.
22. Comotto S, Bottoni A, Moci E, et al. Analysis of session-RPE and profile of mood states during a triathlon training camp. *J Sports Med Phys Fitness*. 2015;55(4):361–367.
23. Hoffman CJ, Ersser SJ, Hopkinson JB, et al. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: a randomized, controlled trial. *J Clin Oncol*. 2012;30(12):1335–1342.
24. Meyer JD, Koltyn KF, Stegner AJ, et al. Influence of exercise intensity for improving depressed mood in depression: a dose-response study. *Behav Ther*. 2016;47(4):527–537.
25. McNair DM, Heuchert JWP, Shilony E. *Profile of Mood States manual: Bibliography 1964–2002*. Multi- Health Systems Inc; 2003.
26. Grove JR, Prapavessis H. Preliminary evidence for the reliability and validity of an abbreviated Profile of Mood States. *Int J Sport Psychol*. 1992;23(2):93–109.
27. Curran SL, Andrykowski MA, Studts JL. Short Form of the Profile of Mood States (POMS-SF): psychometric information. *Psychol Assess*. 1995;7(1):80–83.

28. Tobin R, Dunkley DM. Self-critical perfectionism and lower mindfulness and self-compassion predict anxious and depressive symptoms over two years. *Behav Res Ther*. 2021;136:103780.
29. Vujanovic AA, Zvolensky MJ, Bernstein A, et al. A test of the interactive effects of anxiety sensitivity and mindfulness in the prediction of anxious arousal, agoraphobic cognitions, and body vigilance. *Behav Res Ther*. 2007;45(6): 1393–1400.
30. Zvolensky MJ, Bakhshaie J, Garza M, et al. Anxiety sensitivity and mindful attention in terms of anxiety and depressive symptoms and disorders among Latinos in primary care. *Psychiatry Res*. 2015;229(1–2):245–251.
31. Fava M, Uebelacker LA, Alpert JE, et al. Major depressive subtypes and treatment response. *Biol Psychiatry*. 1997;42(7):568–576.
32. Hernandez MJ, Reljic T, Van Trees K, et al. Impact of comorbid PTSD on outcome of repetitive Transcranial Magnetic Stimulation (TMS) for veterans with depression. *J Clin Psychiatry*. 2020;81(4):19m13152.
33. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522–534.
34. Clarke E, Clarke P, Gill S, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of depression with comorbid anxiety disorders. *J Affect Disord*. 2019;252:435–439.
35. Philip NS, Leuchter AF, Cook IA, et al. Predictors of response to synchronized transcranial magnetic stimulation for major depressive disorder. *Depress Anxiety*. 2019;36(3):278–285.
36. Hutton TM, Aaronson ST, Carpenter LL, et al. The anxiolytic and antidepressant effects of transcranial magnetic stimulation in patients with anxious depression. *J Clin Psychiatry*. 2023;84(1):22m14571.
37. Senda MC, Johnson, KA, Taylor, IM, et al. A pilot trial of stepwise implementation of virtual reality mindfulness and accelerated transcranial magnetic stimulation treatments for dysphoria in neuropsychiatric disorders. *Depress Anxiety*. Forthcoming 2023.
38. Fitzsimmons SMDD, van der Werf YD, van Campen AD, et al. Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: a systematic review and pairwise/network meta-analysis. *J Affect Disord*. 2022;302: 302–312.
39. Parikh TK, Strawn JR, Walkup JT, et al. Repetitive transcranial magnetic stimulation for generalized anxiety disorder: a systematic literature review and meta-analysis. *Int J Neuropsychopharmacol*. 2022;25(2):144–146.
40. Cirillo P, Gold AK, Nardi AE, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: a systematic review and meta-analysis. *Brain Behav*. 2019;9(6):e01284.
41. Siddiqi SH, Taylor SF, Cooke D, et al. Distinct symptom-specific treatment targets for circuit-based neuromodulation. *Am J Psychiatry*. 2020;177(5):435–446.