Differential symptom cluster responses to repetitive transcranial magnetic stimulation treatment in depression

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Summary

Background Repetitive transcranial magnetic stimulation (rTMS) can target specific neural circuits, which may allow for personalized treatment of depression. Treatment outcome is typically determined using sum scores from validated measurement scales; however, this may obscure differential improvements within distinct symptom domains. The objectives for this work were to determine: (1) whether a standard depression measure can be represented using a four symptom cluster model and (2) whether these symptom clusters had a differential response to rTMS treatment.

Methods Data were obtained from two multi-centre randomized controlled trials of rTMS delivered to the left dorsolateral prefrontal cortex (DLPFC) for participants with treatment-resistant depression (TRD) conducted in Canada (THREE-D [Conducted between Sept 2013, and Oct 2016] and CARTBIND [Conducted between Apr 2016 and Feb 2018]). The first objective used confirmatory factor analytic techniques, and the second objective used a linear mixed effects model. Trial Registration: NCT01887782, NCT02729792.

Findings In the total sample of 596 participants with TRD, we found a model consisting of four symptom clusters adequately fit the data. The primary analysis using the THREE-D treatment trial found that symptom clusters demonstrated a differential response to rTMS treatment (F(3,5984) = 31.92, p < 0.001). The anxiety symptom cluster was significantly less responsive to treatment than other symptom clusters (t(6001) = -8.02, p < 0.001). These findings were replicated using data from the CARTBIND trial.

Interpretation There are distinct symptom clusters experienced by individuals with TRD that have a differential response to rTMS. Future work will determine whether differing rTMS treatment targets have distinct patterns of symptom cluster responses with the eventual goal of personalizing rTMS protocols based on an individual's clinical presentation.

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Keywords: Depressive disorders; Repetitive transcranial magnetic stimulation; Cluster analysis; Treatment outcomes

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Research in context

Evidence before this study
We conducted a search in MEDLINE using the Pubmed interface from January 1980 to July 2022 and included all articles (English and non-English) of studies including human participants using the following search terms: (1) repetitive transcranial magnetic stimulation (rTMS), (2) statistical methods to identify latent classes or clusters of symptoms (cluster analysis, bayes theorem, principal components analysis, and factor analysis), and (3) major depressive disorder.

There is minimal information on this topic available in the current literature. To date, there has been a single published study examining symptom cluster response with rTMS amongst individuals with depression. This study used an exploratory, data-driven approach and found that rTMS treatment results in a differential impact on distinct symptom clusters.

Added value of this study
This study used two large clinical trials of rTMS to conduct a confirmatory, hypothesis-driven study to determine if rTMS delivered to the left dorsolateral prefrontal cortex (DLFPC) had a differential response on symptom clusters in patients with treatment-resistant depression (TRD). This work found that patients with TRD referred for rTMS experience four distinct symptom clusters - mood, insomnia, somatic and anxiety symptoms - and that these clusters respond differently to rTMS. Consistent with prior work, mood symptoms were significantly more responsive than anxiety symptoms. These findings were independently replicated in both clinical trials supporting the robustness of results.

Implications of all the available evidence
There appear to be distinct symptom clusters amongst individuals experiencing treatment-resistant depression and these symptom clusters have a differential response to rTMS treatment. Future work will determine if rTMS protocols can be personalized to an individual's clinical presentation.

Introduction

Major depressive disorder (MDD) is a leading source of illness burden and disability worldwide. First line treatment for depression involves pharmacotherapy, psychotherapy or a combination of the two.[1] Unfortunately, many individuals do not respond to initial trials of medication or psychotherapy, and are diagnosed with treatment-resistant depression (TRD).[1] Novel treatments, such as repetitive transcranial magnetic stimulation (rTMS) have demonstrated effectiveness for achieving response and remission in TRD potentially through modulating dysfunctional neural circuits.[2–4]

Though response and remission in depression are typically characterized using the sum score of a psychometric scale, this approach has been heavily criticized.[5] Instead, depression is more accurately represented as a construct with multiple distinct symptom clusters, which is a characteristic known as multidimensionality.[6] Prior work using factor analyses has identified 2 to 5 symptom dimensions on standard depression measures.[6] Though the multidimensionality of depression (i.e., factor structure of standard depression measures) has been assessed in a variety of clinical samples of individuals with depression,[6,7] to our knowledge it has not been assessed in a sample of adults with TRD referred for rTMS.

Given that depression has also been conceptualized as a disorder of abnormal neural circuits, it is possible that these distinct symptom domains - or clusters - may each originate from dysfunction in specific neural circuits.[2] rTMS therefore has the potential, through its ability to focally stimulate cortical regions, to modulate specific dysfunctional neural circuits which may allow for targeting specific symptom clusters and achieve differential responses to treatment. Unfortunately, when sum scores of depression are used to examine treatment response, then differential responses of symptom clusters will go undetected.[8] Differential patterns of response have been assessed in a variety of pharmacological trials of individuals with depression and found that particular symptoms may have greater response to treatment such as the core emotional or mood symptoms of depression,[9,10] neurovegetative symptoms,[11] or particular symptom groupings.[12] Studies of differential symptom cluster response to brain stimulation including electroconvulsive therapy and transcranial direct current stimulation have also found that the core mood and dysphoric symptoms respond better to treatment than other symptom clusters.[13,14]

The knowledge of how rTMS treatment can differentially impact distinct symptom clusters in depression could eventually facilitate personalized delivery of rTMS based on an individual's presenting symptoms. However, to our knowledge, there has only been one study conducted examining differential symptom response to rTMS.[15] In this study, the authors examined clustering of MRI voxel-based connectivity in subjects with depression severity measured using the Beck Depression Inventory who received rTMS with a figure-of-eight coil to the left dorsolateral prefrontal cortex (DLPFC), and found that two symptom clusters best explained their findings - a dysphoric cluster and an anxiosomatic cluster. Importantly, they also found that rTMS had a differential impact on these symptom clusters

depending on the treatment target.[15] In particular, treatment delivered to the left DLPFC resulted in greater improvement of dysphoric symptoms compared to anxiosomatic symptoms.[15] While these results have potentially important implications, a notable caveat is that the results were based on two small samples (N = 30; N = 81) and a meta-analysis with heterogeneous rating scales.[15] Furthermore, this study, as well as other symptom cluster studies[10] typically use data-driven approaches to identify symptom clusters, such as exploratory factor analysis, which are suitable for hypothesis generation as opposed to hypothesis evaluation.[16]

To build on findings of prior work we used data from two large randomized controlled trials of rTMS delivered to the same MNI-152 coordinate in the left DLPFC and employed a hypothesis-driven approach to address two objectives.[17,18] First, we sought to determine the presence of distinct symptom clusters amongst adults with TRD referred for rTMS as measured on the Hamilton Depression Rating Scale using a hypothesis evaluative framework. We hypothesized that a multiple symptom cluster model of depression would more accurately fit the observed data compared to a single symptom cluster model. Second, we sought to determine whether rTMS treatment delivered in these trials would have a differential impact on the identified symptom clusters. We hypothesized, informed by prior work,[15] that the treatment target of these studies (i.e., left DLPFC) would result in significantly greater improvement in mood symptom clusters compared to anxiety symptom clusters. Confirmation of these hypotheses would therefore be an important advance in the delivery of rTMS and one step closer towards personalized treatment of depression.

Methods

Study procedures

This work was a secondary analysis combining data from two multi-centre randomized trials of rTMS delivered to the left DLPFC targeted using MRI-guided neuronavigation at the MNI-152 stereotaxic coordinate (x-38, y+44, z+26).[17,18] The first study (THREE-D) was a randomized non-inferiority trial comparing two rTMS protocols applied to the left DLPFC: standard (10 Hz) high frequency left (HFL) or intermittent theta-burst (iTBS) stimulation.[17] The second study (CARTBIND) was a randomized superiority trial of iTBS stimulation applied to the left DLPFC comparing once daily treatment with twice daily treatment.[18]

For both studies, participants were outpatients between the ages of 18–59 (up to 65 for THREE-D) with a diagnosis of unipolar MDD confirmed using the Mini International Neuropsychiatric Interview (MINI). They met the following inclusion criteria: current major depressive episode scoring ≥18 on the 17-item Hamilton Depression Rating Scale (HDRS-17)[19]; lack of response to at least one adequate or two inadequate antidepressant trials during the current episode; and receiving stable dosages of psychotropic medications for at least four weeks prior to screening. The exclusion criteria were: substance dependence/abuse <3 months preceding study entry; unstable medical/neurologic illness; acute suicidality; MINI diagnosis of bipolar I or II disorder, primary psychotic disorder, or psychotic symptoms in current episode; any rTMS contraindication (i.e., history of seizures; intracranial implant); lifetime history of failure to respond to an adequate course of ECT; previous rTMS treatment; receiving lorazepam >2 mg/day (or equivalent); receiving any anticonvulsant; pregnancy; or significant laboratory abnormalities. THREE-D excluded participants with >3 failed adequate trials of antidepressant medication, while CARTBIND did not. For both studies, local research ethics board approval was obtained for all three study sites and all participants provided written, informed consent.

In both cases, treatment was delivered daily for 5 days per week for either 20–30 days (THREE-D)[17] or 30 days (CARTBIND)[18] while individuals continued their psychotropic medications unchanged for the study duration. Randomization of participants was stratified by degree of medication resistance (>1 adequate vs 1 or fewer medication trials). While the design of both studies did not allow the rTMS technician or patient to be blinded during treatment, outcome assessors were blinded to treatment allocation.

Choice of primary measure

The primary outcome measure in both studies was the HDRS-17, which is the most commonly used clinician-rated psychometric measure of depression severity.[19] Of the 17 items, nine are scored between 0 (not present) and four points (severe), while the remaining eight are scored between 0 (not present) and two points (severe) for a total score ranging from 0 to 52. Outcome assessments were completed by trained research assistants blinded to treatment allocation in both studies. In THREE-D, the HDRS-17 was collected at baseline, and every week until study completion, while CARTBIND collected this at baseline, then weekly from weeks two until six. Further details regarding study procedures for both studies are available in the original publications.[17,18] A comprehensive review of the psychometric properties of HDRS-17 has previously been published.[6]

rTMS procedure

Before treatment, all participants underwent an anatomical MRI. rTMS treatments were guided using MRI-guided neuronavigation to optimize coil positioning. The left DLPFC was targeted using the MNI-152 stereotaxic coordinate (x-38, y+44, z+26).[17,18] A MagPro X100/R30 stimulator equipped with a B70

fluid-cooled coil (MagVenture, Farum, Denmark) was used for stimulation. The resting motor threshold (RMT) was determined using visual observation. For THREE-D, HFL was delivered with the FDA-approved treatment settings (120% RMT, 10 Hz, 4 s on, 26 s off, 3000 pulses/session over 37.5 min).[17] iTBS was delivered to the same site with the same intensity but used a different stimulation pattern (triplet 50 Hz bursts, repeated at 5 Hz, 2 s on, 8 s off, 600 pulses/session over 3 min).[17] For CARTBIND, iTBS was delivered to same location, but one treatment arm delivered 1200 pulses consecutively with the other treatment arm delivering 600 pulses separated by 1 h (1200 pulses total).[18]

Statistical analyses
Confirmatory factor analysis
To assess the dimensionality - or number of symptom clusters - present in the HDRS-17, we used confirmatory factor analysis (CFA) to test our hypotheses. We first conducted a CFA using a single factor model to test the hypothesis that the HDRS-17 is a unidimensional symptom measure. We then conducted a CFA using a previously described four-factor model,[20] which was a model obtained by meta-analyzing exploratory factor analyses of the HDRS published over a 30 year period. The factors present in this model were (1) mood, (2) anxiety, (3) insomnia, and (4) somatic factors, with factor loading available in the original publication.[20] This model was selected because, it is the most comprehensive meta-analysis of the HDRS-17 factor structure published to date. We modified the model a priori by excluding the insight item because of (1) poor conceptual fit with the primary factor (anxiety), (2) complex factor loading onto other factors, and (3) poor item reliability.[6]

CFA was conducted using the *lavaan* package (Version 0.6.11) in R (R version 4.1.3 (2022-03-10))[21] with HDRS-17 scores from THREE-D and CARTBIND pooled together to achieve sufficient sample size.[22] We estimated parameters for the factors using maximum likelihood estimators with heteroskedasticity-consistent standard errors. Visual inspection of the distribution of symptom cluster sum scores demonstrated an approximately normal distribution (appendix p5). In the event of inadequate model fit, we assessed for areas of localized strain (identified by modification indices >10), and made modifications to the factor model guided by theoretical and empirical considerations.[23] Where item loadings were negative on their assigned factor, these items were subtracted from (rather than added to) the symptom cluster sum score. We first assessed model fit at baseline in both studies. We next assessed for measurement invariance using data from baseline and weeks 2–4 (given these weeks had minimal non-random missing data) and sequentially assessed for configural,

metric and scalar invariance.[24] For the baseline model, we assessed global fit using both absolute indices (root mean square error of approximation [RMSEA] and standardized root mean squared residual [SRMR]) and relative fit indices (chi-square value, and comparative fit index [CFI]) interpreted using standard cutoffs (RMSEA≤0.06, SRMR≤0.05, CFI≥0.90).[25,26] For assessment of measurement invariance, we used previously recommended cutoffs for adequate samples (N ≥ 300) indicating measurement non-invariance: ΔCFI ≥ –0.01, ΔRMSEA≥0.015, ΔSRMR≥0.03 (metric invariance), ΔSRMR≥0.015 (scalar invariance).[27] Where applicable, we used robust fit measures.

Symptom cluster response
After confirming the four-factor model demonstrated adequate fit, we considered each of these dimensions to be a distinct symptom cluster and assessed whether there was a differential response within these clusters to rTMS treatment. For this analysis given its more exploratory nature, we used the THREE-D dataset for the primary analysis, and data from CARTBIND as an independent replication to assess reproducibility. To assess for differential symptom cluster response, we fit a linear mixed effects model using the *lmerTest* package (Version 3.1.3)[28] in which the outcome (dependent variable) was the sum score of a symptom cluster. As there were four symptom clusters, each participant contributed four outcome scores, one for each cluster (i.e., mood, anxiety, insomnia, and somatic). The sum score of each symptom cluster was scaled using the proportion of maximum possible scaling method to facilitate comparisons between symptom clusters.[29] This method transforms each scale to a metric ranging from 0 to 1, and avoids the problems inherent to z-standardization.[30] The model incorporated time, symptom cluster type and their interaction as fixed effects. The interaction between time and symptom cluster type allows for assessing whether the effect of time (i.e., duration of rTMS treatment) differs between distinct symptom clusters. We also included treatment allocation as a fixed effect to ensure any observed estimates controlled for treatment allocation. Time was modeled as a continuous variable as number of weeks since starting rTMS treatment. Symptom cluster type was modeled as a categorical variable with four levels: anxiety, mood, insomnia, and somatic. For random effects, we compared two different models using the likelihood ratio test: (1) random effect for subject intercept, and (2) random effect for subject intercept and subject specific slope. In the primary analysis using THREE-D, we analyzed the first four weeks of treatment, as there is non-random missing data after week four due to the study design.[17] In the replication analysis using CARTBIND, we analyzed the complete 6 weeks of treatment.[18]

The primary comparison of interest for this analysis was the interaction term between time and symptom

cluster, and whether it was statistically significant. Post hoc analyses examined which, if any, symptom clusters had a significant interaction with time, which would indicate the symptom clusters with greater (or lesser) response to rTMS treatment. In these post hoc analyses, the anxiety symptom cluster was used for the reference group. We conducted additional analyses to determine if there was a study effect on symptom response by combining THREE-D with CARTBIND data and including an additional covariate in the primary analytic model denoting study. To improve interpretability of the magnitude of differential symptom cluster response, we used the *emmeans* package (Version 1.7.3) to calculate standardized effect sizes of each cluster after rTMS treatment relative to the anxiety symptom cluster group (i.e., reference). We also calculated the standardized effect size of each symptom cluster at treatment completion relative to baseline. Model fit was assessed by visual inspection of a density plot of residuals and degrees of freedom were estimated using Satterthwaite's method. Statistical tests were two-tailed with α set to 0.05.

Role of funding

Results
Confirmatory factor analysis
Included in this analysis were 596 participants, 388 participants from THREE-D and 208 participants from CARTBIND. Baseline characteristics have been previously reported in the original publications.[17,18] In assessing the dimensionality of the HRSD-17 using the combined THREE-D and CARTBIND datasets, we found that a one-dimensional model had an inadequate model fit ($\chi^2 = 428.20$, CFI = 0.32, RMSEA = 0.07, SRMR = 0.07). Before a priori modifications (i.e., exclusion of insight item), the four-factor model did not meet prespecified cutoffs for adequate model fit ($\chi^2 = 223.90$, CFI = 0.76, RMSEA = 0.04, SRMR = 0.05). After a priori modifications to the four-factor model there was still poor relative and absolute model fit ($\chi^2 = 216.98$, CFI = 0.75, RMSEA = 0.05, SRMR = 0.05); however, this model fit was significantly improved compared to the one factor model (χ^2 (6) = 202.69,

p < 0.001). Examining the areas of local strain identified significant covariance between the psychomotor agitation and retardation items, consistent with the fact that both are observer-rated items (appendix p1). Since agitation and retardation are characteristics along the same spectrum, the decision was made to allow psychomotor disturbances to load onto both mood and anxiety factors. This resulted in a significant improvement in both local strain and global model fit such that the majority of model fit indices were adequate, though CFI was marginal ($\chi^2 = 179.55$, CFI = 0.82, RMSEA = 0.04, SRMR = 0.05) (appendix p1). This model also demonstrated a significantly improved fit compared to the a priori four-factor model (χ^2 (3) = 37.74, p < 0.001). These model modifications also resulted in negative factor loadings of psychomotor agitation onto the mood factor and psychomotor retardation onto the anxiety factor. Completely standardized factor loadings of the final model using measurements from baseline, and weeks 2–4 with factor loadings fixed at all time points are presented in Table 1 with graphical representation of our final latent variable model in the appendix (p4). In assessing measurement invariance, we found adequate model fit supporting configural invariance ($\chi^2 = 886.37$, CFI = 0.89, RMSEA = 0.05, SRMR = 0.04) in addition to support for metric invariance (ΔCFI = −0.013, ΔRMSEA = 0.00, ΔSRMR = 0.00), though ΔCFI was marginal, as well as support for scalar invariance (ΔCFI = 0.007, ΔRMSEA = 0.00, ΔSRMR = 0.00).

Symptom cluster response
Following confirmation of the multidimensionality of the HDRS-17 we conducted analyses assessing the differential symptom response to rTMS using linear mixed effects models in the THREE-D dataset. In assessing the mixed effects models with differing random effects, we found that the model incorporating subject-specific random slopes significantly improved model fit (χ^2 (9) = 2216.98, p < 0.001). Using this model, we found a significant interaction between time and symptom cluster (F(3,5984) = 31.92, p < 0.001). In post-hoc analyses, relative to the anxiety symptom cluster, there was a statistically significant greater reduction in severity for mood (t(6001) = -8.02, p < 0.001), insomnia (t(5980) = −8.83, p < 0.001) and somatic (t(5995) = -6.12, p < 0.001) symptom clusters over time. The pattern of symptom cluster responses in THREE-D over the course of rTMS treatment are presented in Fig. 1. Standardised effect sizes for each contrast after four weeks of treatment are presented in Table 2. The effect size for each symptom cluster relative to anxiety ranged from 0.14 to 0.21, while the other contrasts were smaller in magnitude and not statistically significant. The effect size of each symptom cluster from baseline to study completion was statistically significant (also Table 2). Visual inspection of the density plot of

	Estimate	Std. Err.	Z	p
Factor loadings				
Anxiety				
Psychic anxiety	0.67	0.06	11.78	0.000
Psychomotor agitation	0.17	0.04	4.21	0.000
Psychomotor retardation	−0.12	0.04	−2.62	0.009
Somatic anxiety	0.40	0.03	11.48	0.000
Hypochondriasis	0.16	0.03	6.07	0.000
Mood				
Depressed mood	0.51	0.03	17.03	0.000
Psychomotor agitation	−0.05	0.03	−1.82	0.069
Psychomotor retardation	0.21	0.03	7.17	0.000
Work and activity difficulties	0.46	0.03	16.70	0.000
Guilt	0.39	0.02	15.95	0.000
Suicidality	0.36	0.02	15.48	0.000
Insomnia				
Early insomnia	0.44	0.03	12.61	0.000
Middle insomnia	0.62	0.04	14.48	0.000
Late insomnia	0.45	0.04	12.77	0.000
Somatic				
Loss of sexual interest	0.27	0.03	7.99	0.000
Weight Loss	0.14	0.03	5.36	0.000
Somatic symptoms	0.38	0.05	8.44	0.000
Appetite loss	0.31	0.04	8.30	0.000
Residual variances				
Psychic anxiety	0.56	0.08	6.96	0.000
Psychomotor agitation	0.99	0.07	14.94	0.000
Psychomotor retardation	0.97	0.06	17.49	0.000
Somatic anxiety	0.81	0.05	17.40	0.000
Hypochondriasis	0.97	0.08	12.71	0.000
Depressed mood	0.68	0.05	12.71	0.000
Work and activity difficulties	0.82	0.06	12.86	0.000
Guilt	0.85	0.06	13.78	0.000
Suicidality	0.87	0.04	20.45	0.000
Early insomnia	0.83	0.05	18.18	0.000
Middle insomnia	0.60	0.05	10.87	0.000
Late insomnia	0.78	0.04	20.30	0.000
Loss of sexual interest	0.94	0.06	14.80	0.000
Weight Loss	0.96	0.07	14.20	0.000
Somatic symptoms	0.87	0.07	12.47	0.000
Appetite loss	0.88	0.03	26.85	0.000
Latent covariances				
Anxiety with Mood	0.25	0.08	2.96	0.003
Anxiety with Insomnia	0.10	0.08	1.32	0.188
Anxiety with Somatic	0.13	0.11	1.22	0.222
Mood with Insomnia	−0.05	0.08	−0.60	0.552
Mood with Somatic	0.32	0.11	2.87	0.004
Insomnia with Somatic	0.06	0.11	0.55	0.582

Std. Err.: Standard error; z: z-score; CFI: comparative fit index; RMSEA: Root mean square error of approximation; SRMR: standardized root mean squared residual.

Table 1: Confirmatory factor analysis of baseline and weeks 2–4 measurements with fixed factor loadings with completely standardized factor loadings.

residuals demonstrated a normal distribution suggesting adequate model fit (appendix pp6, 7).

Using the CARTBIND dataset as an independent replication, we found results consistent with our primary analysis supporting the replicability of our results. We found a significant interaction between symptom cluster and time (F(3,3800) = 33.02, p < 0.001). Post hoc analyses, relative to anxiety symptom cluster, also found a statistically significant greater reduction in severity over time for all other symptom clusters - mood (t(3808) = −6.36, p < 0.001), insomnia (t(3791) = −8.72, p < 0.001), and somatic (t(3809) = −8.43, p < 0.001) - but the magnitude of effects differed slightly (see Table 2). The pattern of symptom cluster responses over the course of rTMS treatment in CARTBIND is presented in Fig. 1. We did not find an effect of study on the pattern of symptom cluster response over the course of treatment (t(648) = −0.51, p = 0.608).

Discussion

In this novel analysis of two large rTMS clinical trials we found that depression experienced by patients with TRD referred for rTMS consists of multiple distinct symptom clusters, and these clusters have differential responses to rTMS treatment. This is also the first study to demonstrate that rTMS delivered to the left DLPFC using MRI-guided neuronavigation resulted in significantly greater improvements in mood, somatic, and insomnia symptoms compared to anxiety. This finding of differential symptom cluster response was independently replicated in a separate clinical trial of rTMS targeting the same treatment location with a different protocol, which lends support to the robustness of these findings.

Our finding that distinct symptom clusters have differential responses to rTMS treatment is consistent with similar analyses conducted in pharmacotherapy trials.[9–12] These studies consistently find that the core "emotional" or depressed mood symptoms are more responsive to pharmacotherapy treatment compared to other items[9] or symptom clusters.[10] However, due to differences in analytic techniques, the symptom clusters identified in other studies measure different constructs such as "atypical" symptoms,[10] or cognitive symptoms.[11] As a result, direct comparisons between the present and prior work is problematic. Comparative studies of pharmacotherapy with rTMS using consistent analytic techniques will be required to determine whether our findings are unique to rTMS or are consistent across depression treatment modalities. If there are unique effects observed by treatment modality, it will then be important to consider mechanisms of observed differences and whether side effects such as pain, which is associated with anxiety in rTMS,[31] mediate symptom cluster response. Similarly, it will also be important to determine whether differing rTMS treatment targets (i.e., right DLPFC or DMPFC), can achieve greater
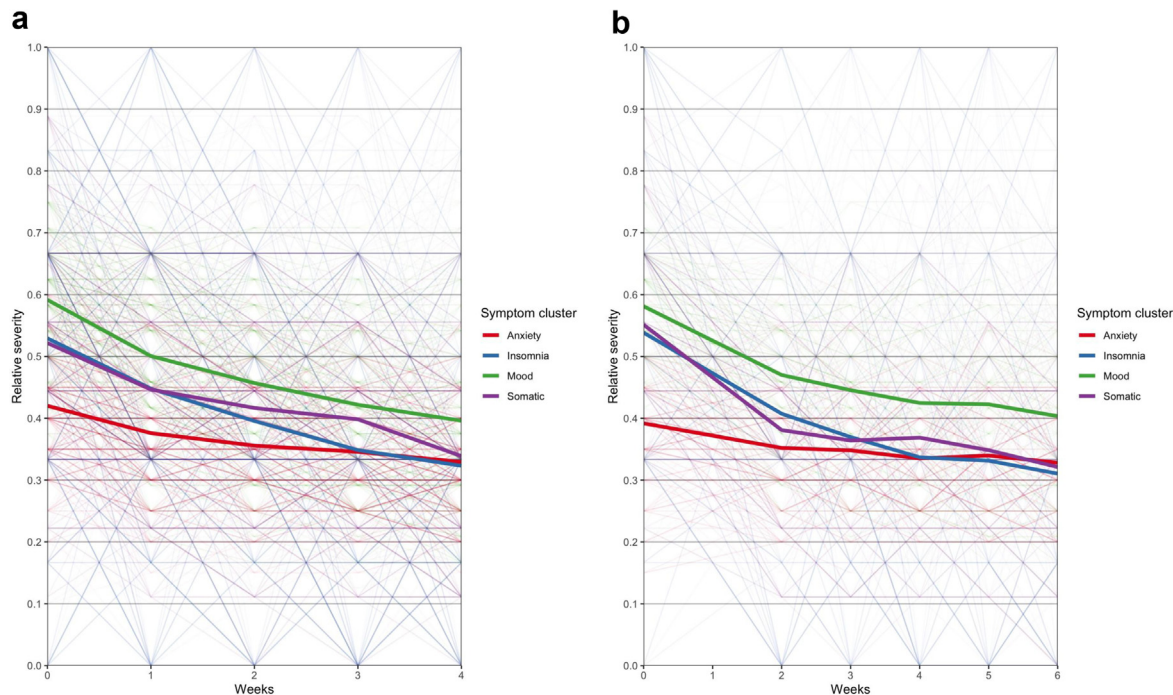
Fig. 1: Spaghetti plots of change in relative severity of symptom cluster with rTMS treatment in (a) THREE-D and (b) CARTBIND. Relative severity is the proportion of maximum possible value to facilitate comparisons between symptom clusters.

relative reductions in anxiety symptoms, as suggested by prior hypothesis generating work.[15] Regardless of future study findings, our work provides clinically relevant information that can inform the current decision-making process for patients with depression. For those considering rTMS treatment with a figure-of-eight coil applied to the left DLPFC, our work indicates that patients should expect less relative improvement in anxiety symptoms compared to core mood, insomnia, and somatic symptoms.

This is a timely and clinically relevant finding because the U.S. FDA recently approved the Brainsway Deep TMS system for treating depression with comorbid anxiety.[32] A possible explanation to account for the discrepancy between our findings and the approval of the Brainsway device may be related to the electric field

Symptom cluster	THREE-D effect size (95% CI)	CARTBIND effect size (95% CI)
Baseline to treatment completion		
Anxiety	0.66 (0.52, 0.81)	0.46 (0.26, 0.66)
Insomnia	1.45 (1.31, 1.60)	1.60 (1.40, 1.81)
Mood	1.42 (1.28, 1.57)	1.32 (1.12, 1.52)
Somatic	1.32 (1.18, 1.47)	1.72 (1.51, 1.92)
Weekly symptom cluster comparison		
Anxiety–insomnia	0.21 (0.16, 0.25)	0.18 (0.14, 0.23)
Anxiety–mood	0.19 (0.14, 0.23)	0.13 (0.09, 0.18)
Anxiety–Somatic	0.14 (0.10, 0.19)	0.18 (0.14, 0.22)
Insomnia–Mood	−0.02 (−0.06, 0.03)	−0.05 (−0.09, −0.01)
Insomnia–Somatic	−0.06 (−0.11, −0.02)	−0.01 (−0.05, 0.03)
Mood–Somatic	−0.04 (−0.09, 0.00)	0.04 (0.00, 0.09)

Effect sizes of individual symptom clusters are from baseline to treatment completion, while symptom cluster comparisons are weekly effect sizes. 95%CI: 95% confidence interval.

Table 2: Effect sizes of contrast with rTMS treatment.

distribution of the Brainsway coil compared to the figure-of-eight coil.[33] Modeling studies indicate that the Brainsway device, even when applied to the left DLPFC generates substantial electric field in the right DLPFC as well as smaller fields bilaterally in the prefrontal and medial prefrontal cortex, while the figure-of-eight coil was largely localized to the left DLPFC.[33]

These findings are also congruent with the neuro-imaging based findings of prior work demonstrating the differential response of symptom clusters with rTMS.[15] The authors of this previous study hypothesized that rTMS treatment delivered to the left DLPFC may have preferentially greater impact on mood/dysphoric symptoms compared to anxiety symptoms, a finding which was confirmed in our study. Our results also suggest that, given the similarity between the THREE-D and CARTBIND findings, the number and timing of stimulation pulses do not have a significant effect on differential response of symptom clusters. While the effect of rTMS on depression and mood symptoms is well-established,[17] the effect of rTMS on sleep distur-bances and insomnia is less understood.[34] To our knowledge there has been a single study examining the effect of rTMS treatment delivered to the left DLPFC on sleep disturbances related to depression, and found – consistent with our findings – that rTMS improved sleep quality independent of mood.[35]

Though there are strengths to our work including a large sample size, independent replication, and a hy-pothesis evaluation framework, there are also limita-tions to consider. First, while our hypotheses were guided by neuroimaging,[15] in our analysis we only considered clinical measures of depression and future work will incorporate neuroimaging data available for study participants. Second, the results of this analysis are specific to the protocols used in the trials and par-ticipants had treatment delivery based on structural imaging localization. While the replication of the symptom cluster response with THREE-D and CART-BIND studies is promising, future work will be required to assess the generalizability of these results to novel rTMS protocols.[36] Third, both studies included in-dividuals with TRD and how these findings may apply to other samples (i.e., bipolar depression or depression with anxious distress) is unknown. Fourth, our primary analysis of symptom cluster response was based on a trial using two different forms of rTMS, which while they have demonstrated non-inferiority,[17] could poten-tially differentially impact symptom clusters. However, we accounted for this analytically by including treatment allocation as a covariate in our analytic models, and also replicated these findings using an external dataset using the same form of rTMS treatment (iTBS).[18] Fifth, the present work made several modifications to a pre-existing factor model,[20] which while guided by theoret-ical and empirical considerations consistent with best practices for conducting CFA,[23] means that the factor

model developed in the current work requires replica-tion in independent datasets. While we used the current datasets to replicate the symptom cluster response analysis, we were unable to do so for the CFA, which require sample large sample sizes ranging from 300-500.[22] Therefore, we were required to pool data from both studies for the factor analysis such that replication analyses were not possible. Sixth, while we incorporated repeated measurements into our CFA, due to software limitations we were unable to model the multilevel na-ture of the observed data due to within-individual clus-tering and as a result the estimated standard errors should be interpreted cautiously. Last, while there were differences between the datasets in study design (e.g., non-inferiority vs superiority), duration (e.g. 4 vs 6 weeks), and selection criteria (e.g., ATHF criteria) between studies, the consistency of our symptom cluster analysis support the robustness of our findings.

In a hypothesis-driven analysis of two large rTMS clinical trials, we found that rTMS treatment delivered to the left DLPFC demonstrated a differential impact on the distinct symptom clusters of depression. In partic-ular we found evidence for a greater effect of rTMS on reducing mood, insomnia and somatic symptoms compared to anxiety symptoms, a finding that was replicated in an external dataset. Future work will determine whether differing rTMS treatment targets have distinct patterns of symptom cluster responses with the eventual goal of personalizing rTMS protocols based on an individual's clinical presentation.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi. org/10.1016/j.eclinm.2022.101765.

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