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Examining fronto-limbic brain and sleep mechanisms of antidepressant effects in cognitive-behavioral therapy for insomnia

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Treating insomnia with Cognitive-Behavioral Therapy for Insomnia (CBT-I) improves depression symptoms, but the underlying mechanisms remain unknown. This single-arm mechanistic trial (ClinicalTrials.gov, NCT04424407) examined fronto-limbic and sleep mechanisms of CBT-I's antidepressant response in 48 participants (64% female; age 25–60) with insomnia and depression symptoms. Participants completed functional magnetic resonance imaging (fMRI), polysomnography (PSG), and symptom assessments before and after 6 CBT-I sessions. CBT-I resulted in reduced amygdala reactivity to fearful faces ($d = 0.55$, $p = 0.008$). Depression and sleep (objective and self-reported insomnia symptoms also improved. However, fMRI-assessed fronto-limbic changes were not associated with a reduction of depressive symptom severity. Instead, reduced depressive symptoms correlated with reduced self-reported insomnia symptoms ($p = 0.001$, $\eta^2p = 0.19$) and increased objective sleep efficiency ($p = 0.04$, $\eta^2p = 0.10$). Notably, pre-treatment PSG-assessed sleep efficiency, but not fronto-limbic function nor insomnia symptoms, predicted reduced depressive symptoms ($p = 0.007$, $\eta^2p = 0.16$), suggesting that lower objective sleep efficiency prior to treatment may be associated with greater antidepressant benefit from CBT-I.

Neuropsychopharmacology; https://doi.org/10.1038/s41386-026-02431-0

INTRODUCTION

Depression and insomnia disorders are both highly prevalent and debilitating conditions that frequently co-occur [1, 2]. Insomnia is a diagnostic feature of depression, a major risk factor for its development, and can exacerbate depressive symptom severity [1, 3]. Critically, insomnia increases suicide risk across the lifespan even when accounting for other symptoms [3–9], pointing to insomnia as a promising transdiagnostic target for alleviating depressive symptoms beyond sleep disturbances [10].

This overlap points toward shared underlying neurobiological mechanisms. Sleep problems may contribute to depression [11] by altering brain networks implicated in emotional processing and regulation. One promising neurobiological mechanism is fronto-limbic brain function. Emotional processing involves two parallel pathways [12, 13]: a direct, automatic pathway involving rapid bottom-up reactivity to emotional stimuli, and an explicit pathway involving conscious appraisal and contextual processing. The amygdala is at the core of both pathways. In the direct, automatic pathway, the amygdala works in concert with more ventral regions of the medial prefrontal cortex (mPFC), including the cingulate, to rapidly detect and respond to threat signals. In the explicit pathway, the amygdala engages with more dorsal regions of the mPFC during conscious emotional processing [14–22].

Neuroimaging studies can probe these parallel pathways using tasks designed to isolate automatic and explicit emotional processing. Nonconscious presentation of emotional stimuli isolates the automatic, bottom-up pathway [23], while conscious emotional tasks engage both bottom-up reactivity and explicit appraisal processes involving the mPFC [14–19]. The functional connectivity between the amygdala and mPFC regions reflects coordinated activity between these structures, suggesting modulatory interactions between these regions, consistent with top-down regulation.

Dysfunction in this fronto-limbic circuit has been observed in major depressive disorder (MDD) [24–36] and is related to poor emotion processing. Both amygdala hyper-reactivity and altered amygdala-mPFC connectivity are theorized to contribute to negative affective bias and threat sensitivity in some forms of depression [37–41].

These same emotion processing mechanisms are also altered by sleep disturbances. Most prior neuroimaging research using fMRI has examined experimental sleep deprivation or restriction paradigms that reduce sleep duration, often in healthy individuals. These studies show that experimental acute sleep

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Received: 17 November 2025 Revised: 26 March 2026 Accepted: 20 April 2026
Published online: 07 May 2026

deprivation and sleep restriction, and poor habitual self-reported sleep quality (including insomnia disorder) amplify amygdala reactivity to negative experiences [42–48]. For example, Motomura et al. [47] used chronic partial sleep restriction (4 h/night for 5 nights), which more closely approximates cumulative sleep debt than acute total deprivation, and found increased amygdala reactivity and decreased amygdala-cingulate connectivity associated with worse mood. Conversely, there is evidence that recovery sleep following sleep deprivation normalizes amygdala reactivity and re-establishes amygdala-mPFC connectivity [49]. Additionally, inter-individual differences in amygdala-mPFC connectivity following sleep deprivation correlate with concurrent anxiety increases [47].

However, clinical insomnia disorder differs importantly from experimental sleep deprivation. Insomnia is characterized by poor sleep despite adequate opportunity for sleep, and its diagnosis is based on subjective experience rather than objective sleep measurements. Moreover, not all individuals with insomnia show objectively short sleep duration.

Neuroimaging research specifically in insomnia populations remains very limited. Prather et al. [48] found that among poor sleepers, assessed using the Pittsburgh Sleep Quality Index questionnaire, depressive symptoms were associated with heightened amygdala reactivity, demonstrating that naturally occurring sleep disturbances relate to altered amygdala functioning. Baglioni et al. [50] reported increased amygdala reactivity to insomnia-related stimuli in individuals with insomnia disorder but without depression. While limited, this literature suggests that amygdala reactivity may be involved across several sleep disturbance profiles.

Critically, if sleep disturbance alters fronto-limbic function in ways that contribute to depression, this process may be reversible with targeted sleep intervention, such as cognitive-behavioral therapy for insomnia (CBT-I). CBT-I is the first-line non-pharmacological treatment for insomnia with established efficacy [51–54]. As recently outlined [55], controlled trials or longitudinal studies examining neuroimaging and objective sleep measurements together in treatment contexts are limited, particularly in clinical insomnia populations. The current two-phase trial addresses this gap by integrating multi-modal sleep and brain assessments to examine mechanisms of treatment response in CBT-I. This includes employing emotional processing tasks designed to probe automatic nonconscious reactivity, as well as explicit, conscious appraisal, allowing for identification of which specific fronto-limbic pathways are responsive to treatment.

Notably, CBT-I not only improves insomnia symptoms but also reduces comorbid depressive symptoms, including suicidal ideation [56, 57], but the mechanism remains unknown. This two-phased clinical trial tests whether impaired fronto-limbic brain function causally links insomnia and depression, specifically determining whether CBT-I improves depressive symptoms by reducing amygdala emotional reactivity and increasing amygdala-mPFC connectivity during emotional processing. Understanding whether CBT-I, the first-line intervention for insomnia disorder, operates directly through specific emotion processing pathways or indirectly through improved sleep can help provide mechanistic interpretability of how CBT-I reduces depressive symptoms.

The primary goal of the current report is to present results from the first phase of the two-phase clinical trial. This mechanistic, single-arm phase established whether CBT-I engages proposed fronto-limbic brain targets in individuals with comorbid insomnia and depression. We hypothesized that following CBT-I treatment, participants would experience reduced amygdala emotional reactivity and an increase in amygdala-mPFC functional connectivity, representing normalization of fronto-limbic emotional brain function.

We also hypothesized that CBT-I would be associated with improvements in both depression and sleep outcomes. Our primary clinical hypothesis was that CBT-I would reduce depressive symptom severity, with suicidal ideation as a secondary outcome. For sleep, we evaluated objective sleep efficiency as the primary outcome and self-reported insomnia severity as the secondary outcome. We selected polysomnography (PSG)-derived sleep efficiency as the primary objective outcome because sleep restriction is a component of CBT-I that aims to increase sleep efficiency, which is reduced in both insomnia and depression [58–60], and it is the most commonly used objective sleep quality measure [61, 62].

Building on these primary hypotheses, we also examined neural correlates of clinical improvement, testing whether the fronto-limbic normalization and sleep improvements were associated with reduced depressive symptoms. Additionally, we identified baseline predictors of antidepressant treatment response by examining whether pre-treatment differences in fronto-limbic function or sleep predicted which participants experienced the greatest antidepressant benefit from CBT-I.

To our knowledge, this is the first study examining a neurobiological model connecting depressive symptoms and sleep through their overlap in affective brain systems, elucidating the mechanisms by which CBT-I treatment improves depression and sleep.

METHODS

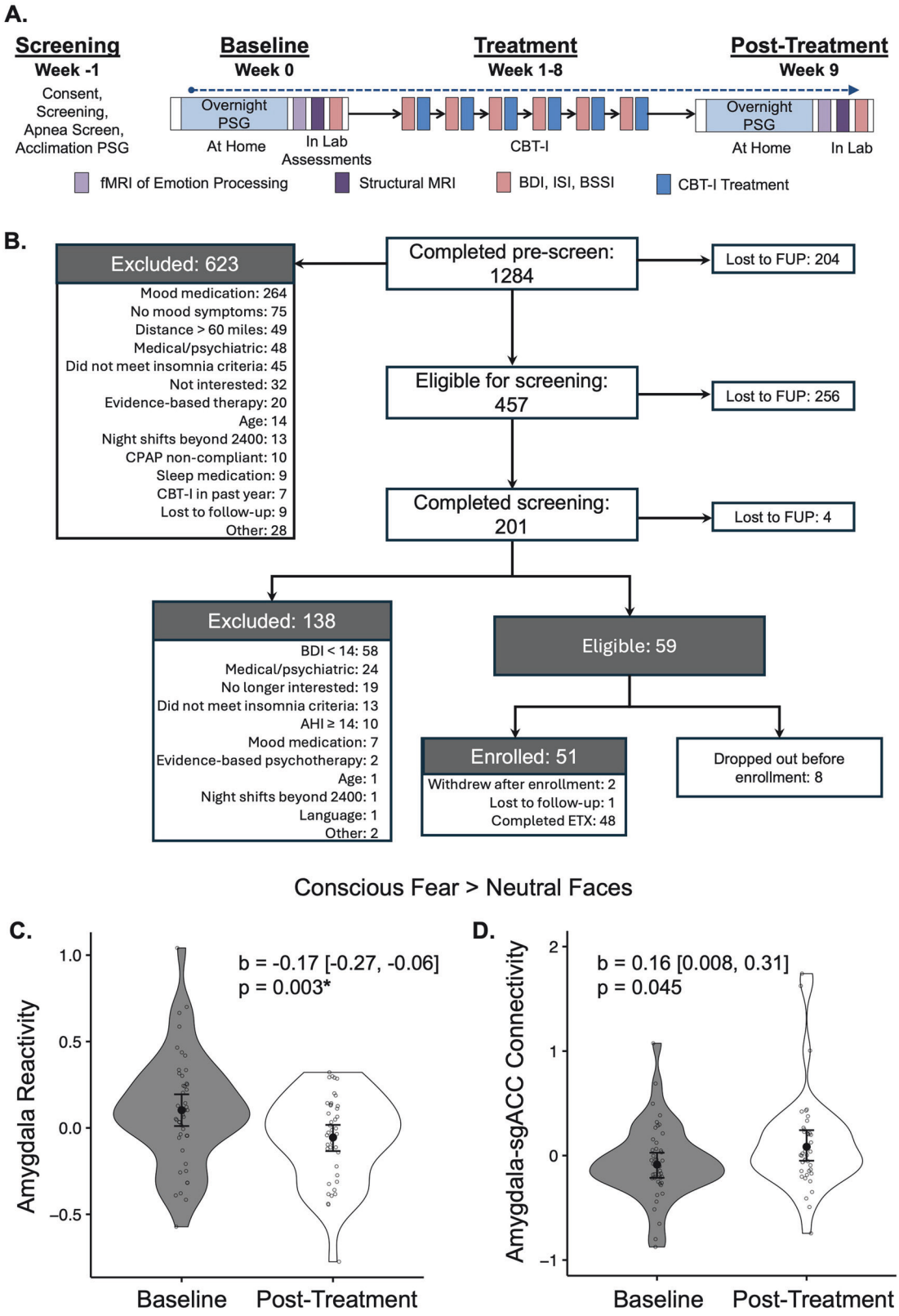
This manuscript presents primary results from the mechanistic clinical trial ClinicalTrials.gov NCT04424407 conducted at Stanford University. The overall trial aims to test the mechanisms of an established sleep intervention (CBT-I) in reducing depressive symptoms through improved fronto-limbic emotional brain function in individuals with elevated depressive symptoms and sleep disturbance. The current single-arm R61 phase primarily aims at establishing fronto-limbic target engagement. Target engagement is defined as the treatment effect reducing amygdala reactivity and increasing amygdala-mPFC connectivity during emotion reactivity and regulation paradigms. The study protocol was approved by the Institutional Review Board at Stanford.

Participants

Participants were recruited from within 60 miles of Stanford University. All participants exhibited clinically meaningful insomnia and depression symptoms (Beck Depression Inventory, BDI≥14), operationalized as having complaints of sleep disturbance for at least 3 months (assessed during structured clinical interviews) but not at imminent risk for suicide, as assessed by the Columbia-Suicide Severity Rating Scale. The eligibility criterion for insomnia symptoms, initially set at an Insomnia Severity Index (ISI) score of ≥15, was revised to ≥10 to align with recent trials [63] and to reflect an optimal cutoff for detecting clinical insomnia [64]. Participants previously excluded solely for ISI scores of 10-14 were recontacted and reassessed for study enrollment, but none were subsequently enrolled due to not meeting other eligibility criteria or loss to follow-up. All participants were fluent and literate in English and provided written informed consent.

The study excluded participants according to the following: other sleep/circadian disorders, medications affecting sleep/alertness/mood, >14 alcoholic drinks/week or >4 drinks/occasion, medical diagnoses interfering with assessments, substance abuse/dependence, traumatic brain injury, severe sensory/motor impediments, pregnancy/breastfeeding, current/lifetime bipolar disorder/psychosis, current/expected psychotherapy for other conditions, CBT-I within past year, acute/unstable chronic illness, recent trauma exposure, rotating shift work, untreated moderate-severe sleep apnea (AHI ≥ 15). Forty-eight participants were included in the current analyses.

Prospective participants underwent two-stage screening: remote video calls with consent, questionnaires, and clinical interviews assessing sleep and mood, followed by in-person screening with overnight at-home ambulatory PSG (Compumedics Siesta 802, BrainVision Easycap) and sleep apnea screening (ResMed Apnealink Air). Participants completed three overnight ambulatory PSG recordings at screening/habituation, pre-treatment baseline, and post-treatment (Fig. 1A). At baseline and post-treatment, participants completed overnight PSG, symptom questionnaires, and fMRI scans the following morning. MRI



scans were collected at identical times at each timepoint, 3 h post-wake, to control circadian and sleep inertia confounds. Daily sleep diaries confirmed CBT-I adherence, and actigraphy (MicroMotionlogger) corroborated sleep timing.

Insomnia treatment

Participants received six sessions of therapist-delivered CBT-I over 8 weeks. CBT-I is the gold-standard treatment for insomnia [65], utilizing behavioral therapy (sleep restriction and stimulus control), cognitive therapy

Fig. 1 Study design, consort flow diagram, primary fronto-limbic outcomes. A Fifty-one participants were enrolled in the study, which included a screening session, pre-treatment baseline, a period of weekly therapist-guided CBT-I treatment, and a post-treatment session. Overnight PSG was collected before and after CBT-I treatment using at-home ambulatory recordings, followed by fMRI scanning and clinical outcomes assessments the next morning in the laboratory. **B** CONSORT flow diagram of participant progression through the trial. The primary analysis was based on an intention-to-treat principle and included all 51 participants who completed pre-treatment baseline, and 48 participants completed the study in its entirety. Pre-treatment baseline and post-treatment values for **C** amygdala reactivity and **D** subgenual anterior cingulate cortex (sgACC) connectivity when viewing fearful relative to neutral faces in the conscious condition of the Faces task. Regression coefficients [95% CI] are from linear mixed-effect models. P-values are uncorrected, and the asterisk (*) marks significance following FDR-correction. Error bars represent 95% confidence intervals. PSG, polysomnography; CBT-I, cognitive-behavioral therapy for insomnia; fMRI, functional magnetic resonance imaging; BDI, Beck Depression Inventory; ISI, Insomnia Severity Index; BSSI, Beck Scale for Suicide Ideation; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; FUP, follow-up; ETX, end of treatment.

addressing maladaptive sleep-related thoughts, and sleep education. Daily sleep diaries were used for time-in-bed adjustments and determining PSG sleep period times.

Study outcomes

Fronto-limbic brain function. Primary outcomes of fronto-limbic emotional brain function include amygdala reactivity as well as amygdala-mPFC connectivity, as measured by psychophysiological interaction [66] (PPI), assessed using validated neuroimaging tasks of emotional reactivity and regulation. We focused on the amygdala and mPFC due to prior findings that they are sensitive to sleep status and are altered in depression. Cortical ROIs were defined a priori [13] (see Supplement). Briefly, clinically-relevant circuits were generated through a meta-analytic search using Neurosynth [67] (RRID:SCR_006798) to create a "Negative Affect" uniformity map. Five regions of the mPFC were selected for the current analyses, including the dorsal anterior cingulate (dACC), ventromedial prefrontal (vmPFC), dorsomedial prefrontal (dmPFC), subgenual anterior cingulate (sgACC), and pregenual anterior cingulate (pACC) cortices. The sgACC did not meet quality control metrics for temporal signal-to-noise ratio, but given the difficulty of imaging this region, its importance to defining the negative affect circuit, and prior imaging findings in depression, we included the region in the current analyses. For the subcortical amygdala, an anatomical definition from the AAL atlas was used [68].

Depression and sleep

The Beck Depression Inventory-II [69] total score, excluding the sleep item, was the primary outcome measure of depression symptoms, assessed at pre-treatment baseline, weekly before treatment sessions, and post-treatment. The BDI is a 21-item self-report scale assessing depression severity. The 'changes in sleeping pattern' item was removed to assess changes in depression symptoms independently from the established CBT-I efficacy on sleep symptoms [56, 70].

The Beck Scale of Suicidal Ideation was the secondary outcome of emotional distress. The BSSI is a 21-question evaluation measuring a broad spectrum of attitudes and behaviors related to suicide [71].

The primary objective sleep outcome was PSG-assessed sleep efficiency (percent of total sleep opportunity spent asleep), measured pre- and post-treatment.

Self-reported insomnia symptoms were measured using the ISI total score [72], administered at pre-treatment baseline, weekly before treatment sessions, and post-treatment.

Imaging tasks

The Facial Expressions of Emotion Task reliably activates the amygdala [12, 22, 29, 73, 74], described fully in Korgaonkar et al. [75] (see Supplement), with two conditions: conscious (500 ms presentation) and nonconscious (16.7 ms presentation with neutral face mask) [22]. The Emotion Regulation Scenes Task asked participants to "look" or "decrease" their emotional response to negative or neutral valence images from the International Affective Picture System [76], described fully in Fonzo et al. [77] and Minkel et al. [78].

Polysomnography

PSG was used to measure sleep using a 32-channel system (see Supplement). Sleep staging was performed in accordance with standardized techniques [79].

Sample size

We initially targeted enrollment of 70 participants. However, due to recruitment-related challenges arising from the COVID-19 pandemic, this enrollment target was adjusted to at least 50 participants. The final sample size of 51 enrolled participants provides 80% power to detect treatment effects on fronto-limbic activation and connectivity of Cohen's $d = 0.40$ (small to medium effect sizes) at Type 1 error α=0.05.

Statistical analyses

We conducted a modified intent-to-treat analysis, including all data unless artifactual or corrupted. The primary analysis examined treatment-associated changes in amygdala reactivity across tasks with FDR correction applied for each task [80]. For tasks/contrasts showing significant amygdala reactivity reductions, we tested whether these corresponded to parallel increases in mPFC connectivity. We applied linear mixed-effects (LME) models with random intercepts at the participant level, including age and sex as covariates.

Treatment-related clinical changes were tested using LME models with random intercepts. Given the zero-inflation in suicidal thinking (BSSI), we used generalized LME models for the negative binomial family.

Neural correlates of clinical improvement were examined using linear regression with change scores (post minus pre-treatment). For models with BSSI outcomes where residuals violated normality (Shapiro-Wilk test, $p < 0.05$), we used non-parametric bootstrap with 5000 resamples (R package "boot"), reporting original OLS coefficients with 95% bias-corrected and accelerated confidence intervals and two-sided p-values.

Relationships between insomnia and depression improvements were studied using OLS regression, with bootstrap methods for BSSI outcomes.

Finally, we tested whether pre-treatment, inter-individual differences in fronto-limbic function and sleep predicted depression improvement using residualized change models [81].

RESULTS

Intention-to-treat study sample

The study cohort consisted of 51 participants, recruited between May 2021 and March 2024, who completed pre-treatment time-points (64.4% female; age 40.6 ± 10.8 years) with at least moderate depressive symptoms (Mean ± SD Pre-treatment BDI Total Score: 18.8 ± 6.4) and at least mild insomnia symptoms (Pre-treatment ISI Score: 15.6 ± 3.8). Objective sleep disturbances were confirmed by low pre-treatment sleep efficiency assessed with PSG (Pre-treatment Sleep Efficiency: 78.8% ± 15.4%). The cohort exhibited low attrition (3 of the 51 withdrawn or lost to follow-up, 5.9%). No serious adverse events were reported, and the trial phase concluded as planned. Demographic and clinical characteristics of the final sample for analysis are presented in Table 1, and the CONSORT chart (Fig. 1B) shows recruitment, enrollment and retention details. None of the primary outcomes differed by age or sex (all $p > 0.10$).

Treatment effects on fronto-limbic brain function

Amygdala reactivity to emotional faces. Consistent with the overarching hypothesis that CBT-I treatment would be associated with a reduction in fMRI-assessed limbic reactivity, participants experienced reduced amygdala reactivity following CBT-I treatment when consciously viewing fearful faces (Conscious Fear vs.

Table 1. Demographic sample characteristics.

Final Sample $n = 48$	**%**	***n***	**M**	**SD**
Sex assigned at birth (female)	66.7	32		
Gender				
Woman	64.6	31		
Man	33.3	16		
Non-binary	2.1	1		
Age (years)			40.1	10.8
Ethnicity				
Hispanic	8.3	4		
Non-Hispanic	91.7	44		
Race				
Asian	37.5	18		
Black	2.1	1		
White	52.1	25		
More than one race	4.2	2		
Prefer not to answer	4.2	2		
Marital Status				
Single	39.6	19		
Married/Partnered	45.8	22		
Divorced/Separated/Widowed	16.7	8		
Prefer not to answer	2.1	1		
Education (Years)			18.6	2.8
Employment				
Full- or part-time/student	77.1	37		
Unemployed	22.9	11		
Berlin Questionnaire (OSA Risk)				
Low Risk	54.2	26		
High Risk	35.4	17		
Apnea-Hypopnea Index (High Risk Participants)			4.8	3.12

M mean, *SD* standard deviation

Neutral Faces: $b = -0.17$ [−0.27, −0.06], $p_{uncorrected} = 0.003$, $p_{adjusted} = 0.008$, Cohen's d = 0.55; Fig. 1C and Table 2). Reduced amygdala reactivity to threat-related faces was also observed (Conscious Threat vs. Neutral Faces: $b = -0.21$ [−0.42, 0.004], $P_{uncorrected} = 0.05$, $p_{adjusted} = 0.08$, Cohen's d = 0.40) though this did not survive FDR-correction. We did not observe changes in amygdala reactivity for the nonconscious condition of the Facial Expressions of Emotion task (all $p_{uncorrected} \geq 0.88$, $p_{adjusted} \geq 0.99$). Similarly, there were no changes in amygdala reactivity to negative emotional images while viewing or regulating emotion in the Emotion Regulation Scenes task (all $p_{uncorrected} \geq 0.64$, $p_{adjusted} \geq 0.65$).

Fronto-limbic connectivity

In addition to amygdala activity, we also tested initial support for the hypothesis that insomnia treatment is associated with increased task-modulated connectivity between amygdala and five a priori subregions of the mPFC during two different emotion paradigms. Focusing on the contrast and task that demonstrated significant treatment effects, amygdala-sgACC connectivity was increased post-treatment when viewing unmasked fearful faces (Conscious Fear vs. Neutral Faces: $b = 0.16$ [0.008, 0.31], $p_{uncorrected} = 0.045$, $p_{adjusted} = 0.23$, Cohens d = 0.28; Fig. 1D).

Together, CBT-I was associated with reduced amygdala reactivity to fearful faces and a trend towards increased amygdala-sgACC connectivity that was specific to the conscious condition (Table S1 for full connectivity results).

Treatment effects on clinical and sleep outcomes

CBT-I was associated with improved depression and sleep outcomes. First, depression symptoms (BDI total minus sleep item) were significantly reduced over the course of treatment ($b = -1.26$ [−1.47, −1.05], $p < 0.0001$, Cohen's d = 0.87; Fig. 2A), as was the severity of suicidal thoughts (BSSI total: $b = -0.29$ [−0.42, −0.17], $p < 0.0001$, Cohens d = 0.23; Fig. 2A).

Second, participants experienced a significant increase in PSG-measured sleep efficiency ($b = 1.1$ [0.42, 1.8], $p = 0.002$, Cohens $d = 0.54$; Fig. 2B). Complementing the increase in objective sleep efficiency, participants also experienced reduced self-reported insomnia symptom severity over the course of treatment (ISI: $b = -1.21$ [−1.3, −1.1], $p < 0.0001$, Cohens d = 2.0; Fig. 2B). Thus, CBT-I treatment was associated with improved depression symptoms, as well as objective and self-reported insomnia symptoms.

Associations between changes in depression, sleep, and fronto-limbic brain function

Associations between changes in depression and fronto-limbic function. We next evaluated whether changes in amygdala reactivity and its connectivity with sgACC when viewing unmasked fearful faces were associated with depression outcomes.

The treatment-related reduction in amygdala reactivity to unmasked fearful faces was not associated with the improvement in depression symptoms ($b = -2.9$ [−11.0, 5.12], $p = 0.47$, $\eta^2 p = 0.02$). Similarly, no association was found between amygdala reactivity to fearful faces and the presence of suicidal thinking ($b = -3.4$ [−12.2, 0.78], $p = 0.48$, $\eta^2 p = 0.05$). Therefore, while insomnia treatment was associated with reduced amygdala reactivity, these changes were unrelated to the parallel improvement in depression symptoms.

Next, we evaluated whether fronto-limbic connectivity, rather than activation, was associated with improved depression symptoms, again focusing on amygdala connectivity to the sgACC when viewing unmasked fearful faces. Amygdala-sgACC connectivity when viewing fearful faces was not associated with improved depression symptoms ($b = -1.6$ [−7.1, 3.8], $p = 0.54$, $\eta^2 p = 0.01$).

We repeated the above analyses for the secondary depression outcome. Decreased presence of suicidal thinking across treatment was not associated with increased amygdala-sgACC connectivity when viewing fearful faces (b = −0.08 [−2.6, 1.6], $p = 0.92$, $\eta^2 p < 0.01$).

Exploratory analyses revealed that changes in fronto-limbic activity and connectivity were also not significantly associated with improved objective sleep efficiency (see Supplement).

Taken together with the above, these initial results suggest that fronto-limbic brain connectivity may not be a mechanism of depression symptom improvement following CBT-I treatment.

Associations between changes in depression and sleep

Subsequently, we investigated whether CBT-I-associated improvements in objective (PSG-measured sleep efficiency) and self-reported (ISI total score) insomnia symptoms were related to improvement in depression symptoms. In contrast to fronto-limbic brain function, we found that sleep outcomes were significantly associated with depression improvement. More specifically, the reduction in depression symptom severity was significantly associated with the increase in objectively measured sleep efficiency from pre- to post-treatment ($b = -0.20$ [−0.39, −0.01], $p = 0.04$, $\eta^2 p = 0.10$; Fig. 2C). A similar effect was found for the reduction in self-reported insomnia symptoms ($b = 0.90$ [0.37, 1.4],

Table 2. Study Outcomes and Model Results.

	Pre-Treatment		Post-Treatment		LME Model Results			
	M	SD	M	SD	b (95% CI)	SE	*p*-value	Cohen's d
Beck Depression Inventory (total minus sleep item)	17.5	6.2	10.8	8.3	−1.3 (−1.5, −1.0)	0.11	<0.0001	0.87
Beck Depression Inventory (total score)	18.9	6.5	11.5	8.7	−1.3 (−1.6, −1.1)	0.11	<0.0001	0.92
Beck Scale for Suicide Ideation	1.7	3.9	0.66	2.7	−0.29 (−0.42, −0.17)	0.07	<0.0001	0.23
Sleep Efficiency (%)	78.9	15.1	86.2	8.3	1.1 (0.42, 1.77)	0.34	0.002	0.55
Insomnia Severity Index	15.7	3.83	7.66	3.53	−1.2 (−1.33, −1.11)	0.06	<0.0001	2.02
Amygdala Activation								
Conscious Facial Expressions of Emotion Task:								
Anger > Neutral	0.11	0.36	0.05	0.26	−0.05 (−0.18, 0.08)	0.07	0.49	0.17
Fear > Neutral	0.11	0.32	−0.05	0.25	−0.17 (−0.27, −0.06)	0.05	0.003[a]	0.55
Threat > Neutral	0.22	0.60	−0.002	0.41	−0.21 (−0.42, 0.004)	0.10	0.051	0.40
Nonconscious Facial Expressions of Emotion Task:								
Anger > Neutral	0.02	0.22	0.02	0.23	0.007 (−0.08, 0.09)	0.05	0.89	0.004
Fear > Neutral	−0.01	0.24	−0.03	0.25	−0.006 (−0.10, 0.09)	0.05	0.91	0.03
Threat > Neutral	0.009	0.41	−0.01	0.41	0.001 (−0.16, 0.16)	0.08	0.99	0.02
Emotion Regulation Scenes Task:								
Negative > Neutral	0.35	0.56	0.41	0.55	0.05 (−0.16, 0.26)	0.11	0.64	0.07
Look Negative > Decrease Negative	−0.05	0.28	−0.02	0.26	0.03 (−0.08, 0.14)	0.06	0.65	0.08

M mean, *SD* standard deviation, *b* unstandardized coefficient, *CI* confidence interval, *SE* standard error.
Linear mixed effect (LME) model results all represent the effect of treatment with age and sex as covariates. Cohen's d values reflect pre-to-post change effect sizes (paired comparisons) and are distinct from the LME-modeled treatment effects.
[a]Significant following FDR correction ($p_{adjusted} \leq 0.05$). Corrections for multiple comparisons were applied across contrasts within each task (3 contrasts for Conscious and Nonconscious tasks, 2 contrasts for the Emotion Regulation Scenes task).

$p = 0.001$, $\eta^2 p = 0.19$; Fig. 2D). Parallel analyses using diary-derived sleep efficiency showed similar patterns (see Supplement).

These analyses were then repeated using the secondary depression outcome of suicidal thinking. The reduction in suicidal thinking was not associated with objective sleep efficiency ($b = -0.03$ [−0.18, 0.05], $p = 0.56$, $\eta^2 p < 0.01$) or with improved self-reported insomnia symptom severity ($b = 0.35$ [0.02, 0.96], $p = 0.47$, $\eta^2 p = 0.08$). Thus, depression symptom severity improvement, as assessed using the BDI after removing the sleep item, is associated with treatment-related reductions in insomnia symptoms, measured both objectively and by self-report, while more specific suicidal thinking was not.

Moderators of depression symptom improvement

Pre-treatment fronto-limbic moderators. Finally, we examined whether inter-individual pre-treatment differences in fronto-limbic brain activity and connectivity, objective sleep efficiency and self-reported insomnia symptoms were predictive of the magnitude of improved clinical depression outcomes. Pre-treatment levels of amygdala reactivity and sgACC connectivity did not predict subsequent improvements in either depression or suicidal thinking (all $p > 0.27$; see Supplement for full results, which include tasks, contrasts, and mPFC target regions not engaged by CBT-I treatment).

Pre-treatment sleep moderators

In contrast, pre-treatment objective sleep efficiency, measured with PSG, was significantly predictive of the reduction in depressive symptoms ($b = 0.21$ [0.06, 0.36], $p = 0.007$, $\eta^2 p = 0.16$), such that participants with the lowest objective sleep efficiency prior to treatment experienced greater improvements in depression symptoms. On the other hand, pre-treatment self-reported insomnia symptoms, measured using the ISI questionnaire, showed no such predictive relationship ($b = -0.02$ [−0.64, 0.46], $p = 0.93$, $\eta^2 p < 0.01$; Fig. 3). This suggests that objective, but not self-reported, insomnia symptoms predict which participants will experience the greatest benefit of CBT-I for depression symptoms.

In predicting improvements in the secondary depression outcome of suicidal thinking, no such predictive relationship was found for either objective ($b = 0.02$ [−0.01, 0.13], $p = 0.50$, $\eta_2 p < 0.01$) or self-reported insomnia symptoms ($b = -0.0006$ [−0.38, 0.14], $p = 0.99$, $\eta^2 p < 0.01$).

DISCUSSION

In this R61 study phase, we found initial evidence that nonpharmacological insomnia treatment alters fronto-limbic emotion processing circuits. CBT-I was associated with reduced bilateral amygdala reactivity to unmasked fearful faces and marginally increased emotion-modulated amygdala-sgACC connectivity. However, there were no significant changes in fronto-limbic function during the masked (nonconscious) condition of the Facial Expressions of Emotion Task or during explicit emotion regulation conditions in the scenes task. Replicating prior work, CBT-I was associated with large within-subject improvements in depression and insomnia symptoms, including both self-reported and objectively measured sleep disturbances. Counter to our hypotheses, depression symptom improvements were not associated with changes in amygdala reactivity or amygdala-sgACC connectivity. Instead, depression improvement was associated with improved insomnia symptoms and objectively measured sleep efficiency. However, only baseline objective sleep efficiency derived from PSG, not baseline self-reported insomnia severity, predicted subsequent depression response. Collectively, these findings indicate that CBT-I-associated effects on fronto-limbic

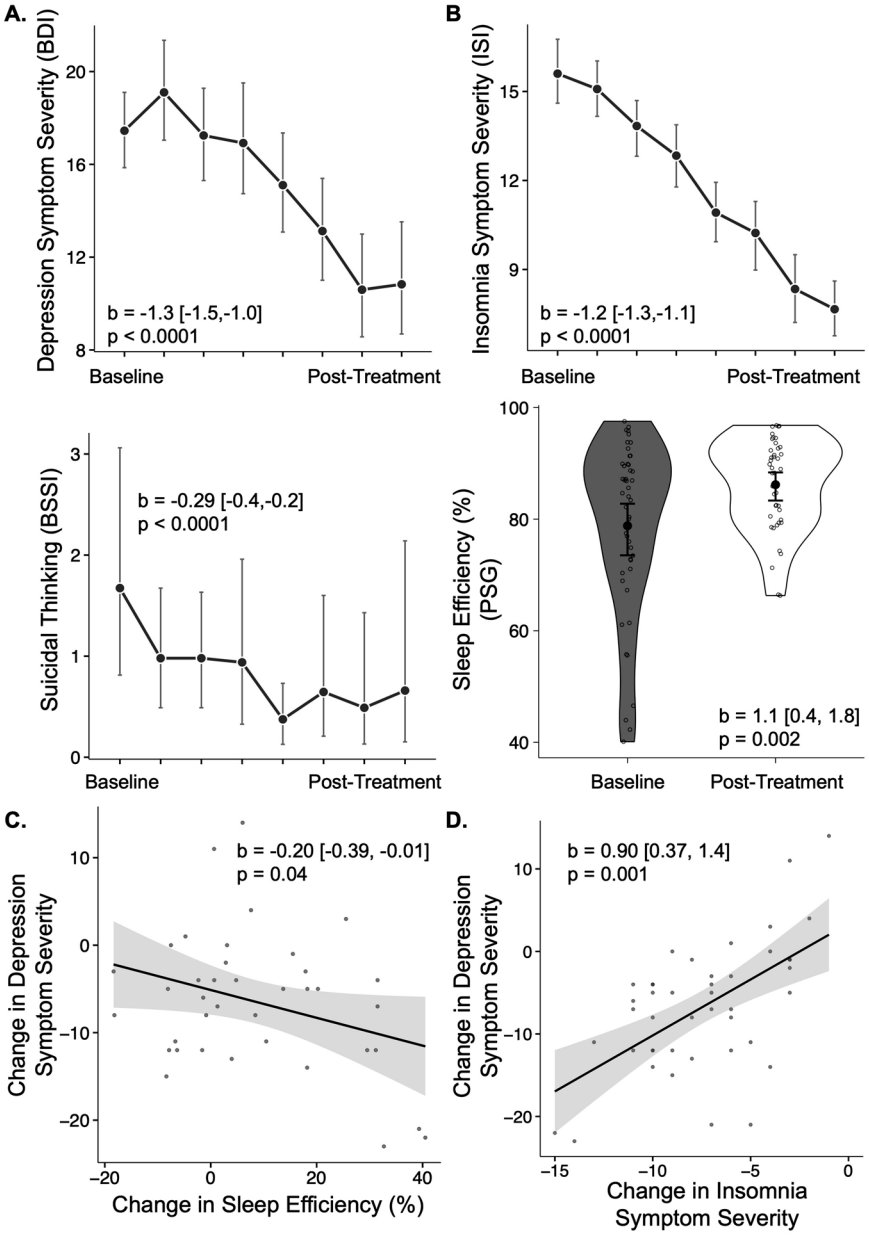


Fig. 2 Depression and insomnia symptoms are improved following CBT-I. Lineplots show week-to-week changes in **A** depression symptom severity measured using the Beck Depression Inventory (BDI), suicidal thinking measured using the Beck Scale for Suicidal Ideation (BSSI), **B** self-reported insomnia symptom severity measured using the insomnia severity index (ISI), and sleep efficiency objectively measured using polysomnography (PSG) before and after treatment. Regression coefficients [95% CI] and p-values are from linear mixed-effect models. **C**, **D** Post- minus pre-treatment changes in objective sleep efficiency and self-reported insomnia symptoms are associated with the improvement in depressive symptoms. Regression coefficients [95% CI] and p-values are from linear regression models. The shaded areas represent 95% CI.

function are task-specific and dissociable from clinical depression benefits, while highlighting the importance of sleep symptoms, particularly objective sleep efficiency, as correlates and potential prognostic indicators of antidepressant response.

The first aim was to determine whether fronto-limbic circuits were modulated following CBT-I treatment in emotion reactivity and regulation task paradigms. We found that CBT-I was associated with reduced amygdala emotional reactivity and increased amygdala-sgACC connectivity for consciously presented fear-expressing faces. While most changes in amygdala reactivity and connectivity did not reach statistical significance, the observed effect sizes suggest potential treatment-related changes worth examining in larger samples. Specifically, the effect size for amygdala reactivity to consciously presented faces was moderate-large (Cohen's d = 0.55), with moderate effect sizes for amygdala-sgACC connectivity ($d = 0.25$-0.31) and small-moderate effect sizes for amygdala-dmPFC ($d = 0.27$) and amygdala-vmPFC ($d = 0.24$) connectivity in the conscious task condition. These findings should be interpreted cautiously as preliminary evidence requiring replication. These results are broadly consistent with a normalization of the amygdala hyperreactivity and impaired prefrontal regulatory control observed in depression [32–36]. Hyperreactivity in negative affect circuits, including the amygdala, characterizes mood-congruent emotion processing bias in depression

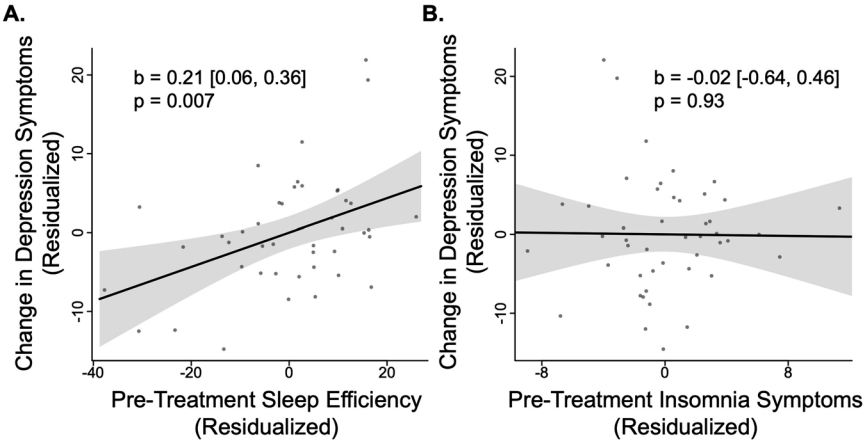


Fig. 3 Objective sleep efficiency predicts antidepressant response following CBT-I. Added variable plots illustrating the unique relationships between the change in depression symptom severity and pre-treatment **A** objective sleep efficiency and **B** self-reported insomnia symptoms. Following a residualized change model approach, the y-axes represent post-treatment depression symptoms after accounting for baseline depression levels, age, and sex. The x-axis represents pre-treatment sleep efficiency and pre-treatment insomnia symptom severity after accounting for the same covariates. The solid line indicates the partial regression slope, with the shaded area showing the 95% CI.

(sensitivity to negative emotion that accompanies negative mood). Previous studies also report normalization of amygdala emotional reactivity following antidepressant treatment [82–87], though not always [88, 89]. The current results are the first to demonstrate that CBT-I, a behavioral sleep intervention known to improve depression symptoms, also modifies fronto-limbic function associated with mood-congruent emotional biases and threat dysregulation.

Several factors contextualize these findings. First, reduced amygdala reactivity occurred only in the conscious condition, suggesting amygdala treatment-engagement is specific to the conscious appraisal of canonical threat cues (fearful faces) rather than automatic responses or complex scene stimuli. While previous studies found similar patterns [24, 25, 85, 90], others identified effects only for masked faces [86, 87, 91], suggesting different pathways of antidepressant effects in CBT-I compared to other treatments. Second, we observed reduced reactivity only to fear-expressing faces, overlapping with previous reports of normalization following depression treatment [20, 21, 82, 85, 90–94]. This specificity may relate to mood-congruent emotional biases in comorbid insomnia and depression, where hyperarousal and threat sensitivity [95] may produce bias towards arousing fear-expressing faces.

We did not observe changes in fronto-limbic function when explicitly regulating emotional responses in the Scenes task. Emotionally intense scenes may drive amygdala activity too strongly, overwhelming downregulation compared to face images. Alternatively, the post-treatment assessment may have been conducted too early to detect emotion regulation changes that emerge more slowly, particularly as participants continue stabilizing sleep [96]. Additionally, CBT-I's antidepressant benefits may not operate through improved emotion regulation as measured by amygdala-mPFC function. A recent meta-analysis found emotion regulation differences in the insula and lateral PFC rather than the amygdala-mPFC regions [97]. Future work should investigate additional neurobiological mechanisms (e.g., salience network [98–100]).

Although this phase primarily targeted fronto-limbic mechanisms, the findings also support CBT-I's clinical effects on depressive symptoms. As expected, there was a large reduction in depressive symptom severity as measured by the BDI scored without the "changes in sleeping pattern" item, indicating improvement beyond sleep complaints. Treatment was also associated with a small effect size reduction in suicidal thinking, emphasizing the clinical importance of insomnia treatment in depression, as both conditions are associated with increased suicide risk. Thus, insomnia treatment may yield broad antidepressant effects, and the second study phase will examine whether certain depression symptom profiles are more sensitive to CBT-I's antidepressant effect.

There were large reductions in self-reported insomnia symptoms and medium increases in objective sleep efficiency. Objectively measured sleep disturbances are not always observed in insomnia disorder [101, 102] and are inconsistently affected by CBT-I [103, 104]. Our results contribute evidence that CBT-I may improve objective PSG-assessed sleep efficiency. Sleep efficiency may better correlate with subjective sleep quality [105], suggesting improvements in sleep efficiency are the objective change that patients perceive during treatment, potentially preceding downstream insomnia and mood benefits.

We hypothesized that improved depression symptoms would be associated with both fronto-limbic and sleep changes. However, despite parallel improvements, we found no associations between them, suggesting target brain mechanisms were not related to symptom improvements. This may reflect a temporal lag wherein neural changes precede depressive symptom improvements, which the single post-treatment assessment could not test. Pharmacological antidepressant treatments show similar patterns, with rapid neural changes [84] but delayed symptom effects [106]. Fronto-limbic mechanisms may be causally involved but operate early in treatment.

Changes in fronto-limbic function and symptom improvements may simply be independent, with other brain mechanisms accounting for symptom changes. Arnone et al. [82] reported a lack of correlation between depression severity and amygdala activation changes following pharmacological treatment, though the parahippocampal gyrus was related to depression severity change. Depression and insomnia are heterogeneous conditions, and different neural mechanisms may operate for different subsets of treatment response.

In contrast, depression improvements were associated with reductions in self-reported insomnia and increases in objective sleep efficiency, suggesting greater sleep benefits predicted greater antidepressant effects. Given that CBT-I specifically targets sleep, this is consistent with sleep improvements as mediating mechanisms. Few studies examined both self-reported and

objective sleep in CBT-I for depression [107, 108], and many relied on actigraphy, a method with drawbacks [109]. The association with objective sleep efficiency suggests that biological pathways relating to sleep consolidation may link sleep disturbances to depression. The second phase will clarify causal roles and temporal ordering using mediation frameworks enabled by the larger sample and control treatment.

Finally, only pre-treatment objective sleep efficiency predicted the improvement in depressive symptoms, with lower pre-treatment sleep efficiency associated with greater antidepressant benefits. This finding suggests that individuals with lower objective sleep efficiency may derive greater benefit from CBT-I [110]. While the ISI is a well-validated measure of insomnia symptom severity, capturing sleep symptoms, distress, and daytime impairment, PSG-derived sleep efficiency may be more sensitive to the specific neurobiological or physiological processes that link sleep improvements to depression improvements. This preliminary finding requires replication, but if confirmed, it may have important clinical implications. While PSG is not practical for routine clinical assessment and is not part of diagnostic criteria for insomnia disorder, these findings suggest that objective sleep measures may offer distinct value beyond self-report in predicting which patients may experience the greatest antidepressant benefit from CBT-I. More accessible approaches, such as consumer-grade wearable EEG devices, could potentially serve this role, informing treatment. This is the first study examining predictors of depression response to CBT-I. Troxel et al. [111] found both objective sleep onset latency and self-reported insomnia predicted depression remission in psychotherapy/pharmacotherapy for depression, but did not examine objective sleep efficiency. The current results also suggest that predictors may differ by treatment type.

Some study limitations necessitate caution. As the first phase of a two-phase trial, the absence of a control group is a significant limitation. Without a control treatment, we cannot definitively attribute the observed improvements to CBT-I rather than natural symptom course or non-specific therapeutic factors. The two-phase clinical trial is designed to address this by including an additional active control treatment arm in the second phase, which will allow us to isolate the specific effects of CBT-I treatment. Regarding participant characteristics, while all participants experienced insomnia symptoms for at least 3 months prior to enrollment, we did not require a specific duration of depression symptoms. Additionally, the relatively small sample overrepresents females and includes a highly educated sample, potentially impacting generalizability. The sample size also limits the ability to detect smaller effects, particularly for the fronto-limbic analyses involving multiple comparisons. This may explain why several fronto-limbic associations showed moderate effect sizes but did not reach statistical significance after FDR-correction. These findings should be considered preliminary and require replication in larger samples in the next trial phase. Furthermore, while PSG is the gold-standard measure of objective sleep physiology, it is limited by the single-night collection at each time point. Adaptation effects or natural night-to-night variability may limit the representativeness of this measure, and the pre-treatment moderator findings should be interpreted as preliminary. Future studies may employ multi-night PSG or wearable EEG to address this. Finally, the a priori mechanistic brain targets do not rule out other neurobiological mechanisms.

Despite limitations, these results advance knowledge of antidepressant mechanisms of insomnia treatment for comorbid insomnia and depression. Fronto-limbic emotion processing mechanisms are engaged by treatment, but may not account for the depression response. Instead, sleep improvements may be more closely tied to depression response, with baseline sleep disturbance as a potential predictor of subsequent response.

Collectively, these findings offer initial support for a mechanism-informed framework for understanding the antidepressant benefits of insomnia treatment and reinforce the need for the randomized controlled trial design in the next phase to disentangle brain and sleep mediators and predictors of treatment response.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

REFERENCES

1. Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia is a risk factor for developing anxiety and depression. Sleep. 2007;30:873–80.
2. Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, et al. Insomnia comorbidity and impact, and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep. 2006;29:1391–7.
3. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 2008;10:329–36.
4. Bernert RA, Turvey CL, Conwell Y, Joiner TE. Association of poor subjective sleep quality with risk for death by suicide during a 10-year period: a longitudinal, population-based study of late life. JAMA Psychiatry. 2014;71:1129–37.
5. Gowin JL, Stoddard J, Doykos TK, Sammel MD, Bernert RA. Sleep disturbance and subsequent suicidal behaviors in preadolescence. JAMA Netw Open. 2024;7:e2433734.
6. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. Curr Psychiatry Rep. 2015;17:554.
7. Morphy H, Dunn KM, Lewis M, Boardman HF, Croft PR. Epidemiology of insomnia: a longitudinal study in a UK population. Sleep. 2007;30:274–80.
8. Bernert RA, Luckenbaugh DA, Duncan WC, Iwata NG, Ballard ED, Zarate CA. Sleep architecture parameters as a putative biomarker of suicidal ideation in treatment-resistant depression. J Affect Disord. 2017;208:309–15.
9. Sabo E, Reynolds CF, Kupfer DJ, Berman SR. Sleep, depression, and suicide. Psychiatry Res. 1991;36:265–77.
10. Harvey AG, Murray G, Chandler RA, Soehner A. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. Clin Psychol Rev. 2011;31:225–35.
11. Carney CE, Ulmer C, Edinger JD, Krystal AD, Knauss F. Assessing depression symptoms in those with insomnia: an examination of the Beck Depression Inventory Second Edition (BDI-II). J Psychiatr Res. 2009;43:576–82.
12. Williams LM, Das P, Liddell BJ, Kemp AH, Rennie CJ, Gordon E. Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. J Neurosci. 2006;26:9264–71.
13. Goldstein-Piekarski AN, Ball TM, Samara Z, Staveland BR, Keller AS, Fleming SL, et al. Mapping neural circuit biotypes to symptoms and behavioral dimensions of depression and anxiety. Biol Psychiatry. 2022;91:561–71.
14. Amting JM, Greening SG, Mitchell DGV. Multiple mechanisms of consciousness: the neural correlates of emotional awareness. J Neurosci. 2010;30:10039–47.
15. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research-past, present, and future. Biol Psychiatry. 2006;60:376–82.
16. Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. Biol Psychiatry. 2002;51:68–80.
17. Milad MR, Quirk GJ. Neurons in the medial prefrontal cortex signal memory for fear extinction. Nature. 2002;420:70–74.
18. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 2004;43:897–905.
19. Rosenkranz JA, Moore H, Grace AA. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. J Neurosci. 2003;23:11054–64.
20. Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety. 2017;34:9–24.
21. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3:472–80.
22. Williams LM, Liddell BJ, Kemp AH, Bryant RA, Meares RA, Peduto AS, et al. Amygdala-prefrontal dissociation of subliminal and supraliminal fear. Hum Brain Mapp. 2006;27:652–61.
23. Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto A, et al. A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. Neuroimage. 2005;24:235–43.

24. Peluso MA, Glahn DC, Matsuo K, Monkul ES, Najt P, Zamarripa F, et al. Amygdala hyperactivation in untreated depressed individuals. Psychiatry Res. 2009;173:158–61.
25. Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Max JE, et al. Adolescents with major depression demonstrate increased amygdala activation. J Am Acad Child Adolesc Psychiatry. 2010;49:42–51.
26. Killgore WD, Britton JC, Schwab ZJ, Price LM, Weiner MR, Gold AL, et al. Corticolimbic responses to masked affective faces across ptsd, panic disorder, and specific phobia. Depress Anxiety. 2014;31:150–9.
27. Bishop SJ, Duncan J, Lawrence AD. State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci. 2004;24:10364–8.
28. Stein MB, Simmons AN, Feinstein JS, Paulus MP. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry. 2007;164:318–27.
29. Bryant RA, Kemp AH, Felmingham KL, Liddell B, Olivieri G, Peduto A, et al. Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. Hum Brain Mapp. 2008;29:517–23.
30. Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, et al. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron. 2004;44:1043–55.
31. Bryant RA, Felmingham K, Whitford TJ, Kemp A, Hughes G, Peduto A, et al. Rostral anterior cingulate volume predicts treatment response to cognitive-behavioural therapy for posttraumatic stress disorder. J Psychiatry Neurosci. 2008;33:142–6.
32. Ho TC, Yang G, Wu J, Cassey P, Brown SD, Hoang N, et al. Functional connectivity of negative emotional processing in adolescent depression. J Affect Disord. 2014;155:65–74.
33. Kong L, Chen K, Tang Y, Wu F, Driesen N, Womer F, et al. Functional connectivity between the amygdala and prefrontal cortex in medication-naive individuals with major depressive disorder. J Psychiatry Neurosci. 2013;38:417–22.
34. Prater KE, Hosanagar A, Klumpp H, Angstadt M, Phan KL. Aberrant amygdala-frontal cortex connectivity during perception of fearful faces and at rest in generalized social anxiety disorder. Depress Anxiety. 2013;30:234–41.
35. Hahn A, Stein P, Windischberger C, Weissenbacher A, Spindelegger C, Moser E, et al. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. Neuroimage. 2011;56:881–9.
36. Demenescu LR, Kortekaas R, Cremers HR, Renken RJ, van Tol MJ, van der Wee NJ, et al. Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. J Psychiatr Res. 2013;47:1024–31.
37. Habermas T, Ott L-M, Schubert M, Schneider B, Pate A. Stuck in the past: negative bias, explanatory style, temporal order, and evaluative perspectives in life narratives of clinically depressed individuals. Depress Anxiety. 2008;25:E121–132.
38. Robinson OJ, Overstreet C, Allen PS, Letkiewicz A, Vytal K, Pine DS, et al. The role of serotonin in the neurocircuitry of negative affective bias: serotonergic modulation of the dorsal medial prefrontal-amygdala 'aversive amplification' circuit. Neuroimage. 2013;78:217–23.
39. Dannlowski U, Kersting A, Lalee-Mentzel J, Donges US, Arolt V, Suslow T. Subliminal affective priming in clinical depression and comorbid anxiety: a longitudinal investigation. Psychiatry Res. 2006;143:63–75.
40. Yancey JR, Vaidyanathan U, Patrick CJ. Aversive startle potentiation and fear pathology: mediating role of threat sensitivity and moderating impact of depression. Int J Psychophysiol. 2015;98:262–9.
41. Banks DM, Scott BG, Weems CF. Anxiety, hostile attributions, and differences in heart rate response to ambiguous situational vignettes in adolescents. Emotion. 2018;18:248–59.
42. Goldstein AN, Greer SM, Saletin JM, Harvey AG, Nitschke JB, Walker MP. Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. J Neurosci. 2013;33:10607–15.
43. Goldstein-Piekarski AN, Greer SM, Saletin JM, Walker MP. Sleep deprivation impairs the human central and peripheral nervous system discrimination of social threat. J Neurosci. 2015;35:10135–45.
44. Yoo S-S, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep: a prefrontal amygdala disconnect. Curr Biol. 2007;17:R877–878.
45. Chuah LY, Dolcos F, Chen AK, Zheng H, Parimal S, Chee MW. Sleep deprivation and interference by emotional distracters. Sleep. 2010;33:1305–13.
46. Killgore WDS. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. Sleep. 2013;36:1597–608.
47. Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, et al. Sleep debt elicits a negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. PLoS ONE. 2013;8:e56578.
48. Prather AA, Bogdan R, Hariri AR. Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. Psychosom Med. 2013;75:350–8.
49. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol. 2011;21:2029–32.
50. Baglioni C, Spiegelhalder K, Regen W, Feige B, Nissen C, Lombardo C, et al. Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. Sleep. 2014;37:1907–17.
51. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA. 1999;281:991–9.
52. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994;151:1172–80.
53. Okajima I, Komada Y, Inoue Y. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. Sleep Biol Rhythms. 2011;9:24–34.
54. Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann Intern Med. 2015;163:191–204.
55. Goldstein-Piekarski AN, Holt-Gosselin B, O'Hora K, Williams LM. Integrating sleep, neuroimaging, and computational approaches for precision psychiatry. Neuropsychopharmacol. 2020;45:192–204.
56. Manber R, Buysse DJ, Edinger J, Krystal A, Luther JF, Wisniewski SR, et al. Efficacy of cognitive-behavioral therapy for insomnia combined with antidepressant pharmacotherapy in patients with comorbid depression and insomnia: a randomized controlled trial. J Clin Psychiatry. 2016;77:e1316–e1323.
57. Manber R, Bernert RA, Suh S, Nowakowski S, Siebern AT, Ong JC. CBT for insomnia in patients with high and low depressive symptom severity: adherence and clinical outcomes. J Clin Sleep Med. 2011;7:645–52.
58. Baglioni C, Regen W, Teghen A, Spiegelhalder K, Feige B, Nissen C, et al. Sleep changes in the disorder of insomnia: a meta-analysis of polysomnographic studies. Sleep Med Rev. 2014;18:195–213.
59. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: a meta-analysis of polysomnographic research. Psychol Bull. 2016;142:969–90.
60. Pillai V, Kalmbach DA, Ciesla JA. A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. Biol Psychiatry. 2011;70:912–9.
61. Jung DW, Lee YJ, Jeong D-U, Park KS. New predictors of sleep efficiency. Chronobiol Int. 2017;34:93–104.
62. Åkerstedt T, Hume K, Minors D, Waterhouse J. The meaning of good sleep: a longitudinal study of polysomnography and subjective sleep quality. J Sleep Res. 1994;3:152–8.
63. Asarnow LD, Bei B, Krystal A, Buysse DJ, Thase ME, Edinger JD, et al. Circadian preference as a moderator of depression outcome following cognitive behavioral therapy for insomnia plus antidepressant medications: a report from the TRIAD study. J Clin Sleep Med. 2019;15:573–80.
64. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34:601–8.
65. Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17:255–62.
66. McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gppi): a comparison to standard approaches. Neuroimage. 2012;61:1277–86.
67. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods. 2011;8:665–70.
68. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002;15:273–89.
69. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67:588–97.
70. Osorno RA, Ahmadi M, O'Hora KP, Solomon NL, Lopez M, Morehouse AB, et al. The effects of a sleep intervention in the early COVID-19 pandemic on insomnia and depressive symptoms: results of a randomized controlled pilot study. J Psychiatr Res. 2025;182:319–28.
71. Beck AT, Steer RA, Ranieri WF. Scale for Suicide Ideation: psychometric properties of a self-report version. J Clin Psychol. 1988;44:499–505.
72. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med. 2001;2:297–307.

73. Williams LM, Mathersul D, Palmer DM, Gur RC, Gur RE, Gordon E. Explicit identification and implicit recognition of facial emotions: I. Age effects in males and females across 10 decades. J Clin Exp Neuropsychol. 2009;31:257–77.
74. Goldstein-Piekarski AN, Korgaonkar MS, Green E, Suppes T, Schatzberg AF, Hastie T, et al. Human amygdala engagement moderated by early life stress exposure is a biobehavioral target for predicting recovery on antidepressants. Proc Natl Acad Sci USA. 2016;113:11955–60.
75. Korgaonkar MS, Grieve SM, Etkin A, Koslow SH, Williams LM. Using standardized fMRI protocols to identify patterns of prefrontal circuit dysregulation that are common and specific to cognitive and emotional tasks in major depressive disorder: first wave results from the iSPOT-D study. Neuropsychopharmacol. 2013;38:863–71.
76. Bradley MM, Lang, PJ. The International Affective Picture System (IAPS) in the study of emotion and attention. In Handbook of emotion elicitation and assessment, pp. 29–46, Oxford University Press; New York:2007.
77. Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, et al. Selective effects of psychotherapy on frontopolar cortical function in PTSD. Am J Psychiatry. 2017;174:1175–84.
78. Minkel JD, McNealy K, Gianaros PJ, Drabant EM, Gross JJ, Manuck SB, et al. Sleep quality and neural circuit function supporting emotion regulation. Biol Mood Anxiety Disord. 2012;2:22.
79. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM scoring manual updates for 2017 (Version 2.4). J Clin Sleep Med. 2017;13:665–6.
80. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B. 1995;57:289–300.
81. Castro-Schilo L, Grimm KJ. Using residualized change versus difference scores for longitudinal research. J Soc Personal Relatsh. 2018;35:32–58.
82. Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, et al. Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. Am J Psychiatry. 2012;169:841–50.
83. Ruhé HG, Booij J, Veltman DJ, Michel MC, Schene AH. Successful pharmacologic treatment of major depressive disorder attenuates amygdala activation to negative facial expressions: a functional magnetic resonance imaging study. J Clin Psychiatry. 2012;73:451–9.
84. Godlewska BR, Norbury R, Selvaraj S, Cowen PJ, Harmer CJ. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol Med. 2012;42:2609–17.
85. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry. 2004;61:877–89.
86. Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC. Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. Arch Gen Psychiatry. 2010;67:1128–38.
87. Williams LM, Korgaonkar MS, Song YC, Paton R, Eagles S, Goldstein-Piekarski A, et al. Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the Randomized iSPOT-D trial. Neuropsychopharmacology. 2015;40:2398–408.
88. Townsend JD, Eberhart NK, Bookheimer SY, Eisenberger NI, Foland-Ross LC, Cook IA, et al. fMRI activation in the amygdala and the orbitofrontal cortex in unmedicated subjects with major depressive disorder. Psychiatry Res. 2010;183:209–17.
89. Demenescu LR, Renken R, Kortekaas R, van Tol MJ, Marsman JB, van Buchem MA, et al. Neural correlates of perception of emotional facial expressions in outpatients with mild-to-moderate depression and anxiety. A multicenter fMRI study. Psychol Med. 2011;41:2253–64.
90. Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, et al. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry. 2005;57:201–9.
91. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 2001;50:651–8.
92. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am J Psychiatry. 2012;169:693–703.
93. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev. 2013;37:152–63.
94. Stuhrmann A, Suslow T, Dannlowski U. Facial emotion processing in major depression: a systematic review of neuroimaging findings. Biol Mood Anxiety Disord. 2011;1:10.
95. Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev. 2021;101:995–1046.
96. Goldstein-Piekarski AN, Wielgosz J, Xiao L, Stetz P, Correa CG, Chang SE, et al. Early changes in neural circuit function engaged by negative emotion and modified by behavioural intervention are associated with depression and problem-solving outcomes: a report from the ENGAGE randomized controlled trial. EBioMedicine. 2021;67:103387.
97. Wu D, Li J, Wang J. Altered neural activities during emotion regulation in depression: a meta-analysis. J Psychiatry Neurosci. 2024;49:E334–E344.
98. Spiegelhalder K, Regen W, Baglioni C, Nissen C, Riemann D, Kyle SD. Neuroimaging insights into insomnia. Curr Neurol Neurosci Rep. 2015;15:9.
99. Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 2015;16:55–61.
100. Chen MC, Chang C, Glover GH, Gotlib IH. Increased insula coactivation with salience networks in insomnia. Biol Psychol. 2014;97:1–8.
101. Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J Sleep Res. 1997;6:179–88.
102. Edinger JD, Fins AI, Glenn DM, Sullivan RJ Jr, Bastian LA, Marsh GR, et al. Insomnia and the eye of the beholder: are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? J Consult Clin Psychol. 2000;68:586–93.
103. Mitchell LJ, Bisdounis L, Ballesio A, Omlin X, Kyle SD. The impact of cognitive behavioural therapy for insomnia on objective sleep parameters: a meta-analysis and systematic review. Sleep Med Rev. 2019;47:90–102.
104. Chan WS, McCrae CS, Ng AS-Y. Is cognitive behavioral therapy for insomnia effective for improving sleep duration in individuals with insomnia? A meta-analysis of randomized controlled trials. Ann Behav Med. 2023;57:428–41.
105. Krystal AD, Edinger JD, Wohlgemuth WK, Marsh GR. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. Sleep. 2002;25:630–40.
106. Thompson C. Onset of action of antidepressants: results of different analyses. Hum Psychopharmacol. 2002;17:S27–32.
107. Gebara MA, Siripong N, DiNapoli EA, Maree RD, Germain A, Reynolds CF, et al. Effect of insomnia treatments on depression: a systematic review and meta-analysis. Depress Anxiety. 2018;35:717–31.
108. Carney CE, Edinger JD, Kuchibhatla M, Lachowski AM, Bogouslavsky O, Krystal AD, et al. Cognitive behavioral insomnia therapy for those with insomnia and depression: a randomized controlled clinical trial. Sleep. 2017;40:zsx019.
109. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med. 2001;2:389–96.
110. Rezaie L, Fobian AD, McCall WV, Khazaie H. Paradoxical insomnia and subjective-objective sleep discrepancy: a review. Sleep Med Rev. 2018;40:196–202.
111. Troxel WM, Kupfer DJ, Reynolds CF, Frank E, Thase ME, Miewald JM, et al. Insomnia and objectively measured sleep disturbances predict treatment outcome in depressed patients treated with psychotherapy or psychotherapy-pharmacotherapy combinations. J Clin Psychiatry. 2012;73:478–85.

AUTHOR CONTRIBUTIONS

ANG-P, RAB, LMW, JJG, JM, LCL, JAY, RM, and JMS contributed to the conceptualization and study design. AJK and ANG-P developed the methodology. RO, NS, MA, PL, OM, EB-S, LNH, SSI, and MB conducted the investigation. AJK performed the formal analysis and visualization. JMS provided software. ANG-P supervised the study and acquired funding. AJK and ANG-P prepared the original draft. AJK, ANG-P, RO, RAB, LMW, JJG, JM, RM, JMS, and LNH contributed to the review and editing of the manuscript.

FUNDING

This work was supported by the National Institutes of Health under grant numbers R61MH120245 and P20GM139743.

COMPETING INTERESTS

LMW declares US patent applications 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data. JM serves as an editor for an Oxford University Press journal. The remaining authors have nothing to disclose.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-026-02431-0.

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