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Cognitive, Behavioral, and Circadian Rhythm Interventions for Insomnia Alter Emotional Brain Responses

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ABSTRACT

BACKGROUND: The highest risk of depression is conveyed by insomnia. This risk can be mitigated by sleep interventions. Understanding brain mechanisms underlying increased emotional stability following insomnia treatment could provide insight relevant to the prevention of depression. Here, we investigated how different sleep interventions alter emotion-related brain activity in people with insomnia at high risk of developing depression.

METHODS: Functional magnetic resonance imaging was used to assess how the amygdala response to emotional stimuli (negative facial expression) in 122 people with insomnia disorder differed from 36 control subjects and how the amygdala response changed after 6 weeks of either no treatment or internet-based circadian rhythm support (CRS), cognitive behavioral therapy for insomnia (CBT-I), or their combination (CBT-I+CRS). Effects on depression, insomnia and anxiety severity were followed up for 1 year.

RESULTS: Only combined treatment (CBT-I+CRS) significantly increased the amygdala response, compared with no treatment, CBT-I, and CRS. Individual differences in the degree of response enhancement were associated with improvement of insomnia symptoms directly after treatment ($r = -0.41$, $p = .021$). Moreover, exclusively CBT-I+CRS enhanced responsiveness of the left insula, which occurred in proportion to the reduction in depressive symptom severity ($r = -0.37$, $p = .042$).

CONCLUSIONS: This functional magnetic resonance imaging study on insomnia treatment, the largest to date, shows that a combined cognitive, behavioral, and circadian intervention enhances emotional brain responsiveness and might improve resilience in patients with insomnia who are at high risk of developing depression.

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The most important risk factor for developing a depressive disorder is conveyed by insomnia (1,2), not only because of the odds but also because of the high prevalence of insomnia disorder (ID), estimated at ±10% of the general population (3). Patients with ID frequently report emotional distress (4) and have difficulty resolving their emotional distress overnight (5,6). The first-line treatment of insomnia is cognitive behavioral therapy for insomnia (CBT-I). While this intervention alleviates both sleep and mood complaints (7,8), overall remission rates for CBT-I stay below 40% (9). Some studies therefore evaluated whether intervention effectiveness could be boosted by extending CBT-I with circadian rhythm support (CRS), such as bright light exposure, physical activity, and body warming (10,11). This multimodal approach showed the strongest long-term improvement, both for sleep and for mood (11,12). Neurobiological mechanisms underlying therapy-induced sleep improvement and emotional stabilization remain unknown. Understanding how insomnia treatment changes emotional brain processes is highly relevant beyond insomnia and could reveal insight in the brain mechanisms underlying emotional stability and resilience to depressive disorders.

A few functional magnetic resonance imaging (fMRI) studies have indicated that insomnia treatment can alter brain activity. Some of these studies addressed brain activity during executive cognitive task performance (13–17). For example, individual differences in clinical improvement in insomnia severity from pre- to post–CBT-I treatment were associated with the degree of increase in activation of the left supramarginal gyrus during executive task performance (15). Studies that combined CBT-I with CRS found that the combined intervention increased activation in the medial and inferior prefrontal cortices during executive tasks (16) but could not restore the patients' insufficient recruitment of the head of the left caudate nucleus during such tasks (17). Aside from these studies that investigated executive functioning, two studies addressed brain responses specifically to sleep-related stimuli, based on the idea that such stimuli might have acquired a distressful connotation in people with insomnia. CBT-I reduced the response of the precentral,

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prefrontal, fusiform, and posterior cingulate cortices to sleep-related pictures (13) and reduced the response of the left middle temporal and left middle occipital gyrus to sleep-related sounds (14).

Previous studies in people currently experiencing major depressive disorder (MDD) reported amygdala reactivity to be increased (18,19), blunted (20–22), or unchanged (23,24). The association of amygdala reactivity with MDD is complex and may be modulated, for example, by the ability to regulate emotion and by neuroticism. Moreover, opposing findings on amygdala reactivity have been reported for people at risk of MDD versus those that currently experience an episode of depression: Two studies on the familiar or genetic risk of developing depression in currently nondepressed people reported attenuated amygdala activation (22,25). Thus, in order to develop a better understanding of the complex and possibly changing role of the amygdala in the development of, persistence of, and recovery from depression, it is important to study it across all these facets. While insomnia is known to be a major risk factor for the development of MDD, no previous studies investigated amygdala activation in insomnia in relation to MDD. Therefore, the current sample specifically targeted people with insomnia with an increased risk of developing MDD, while excluding current depression.

To date, no study has investigated the effect of insomnia treatment on brain activity elicited specifically by emotional stimuli, despite resting-state fMRI studies suggesting that CBT-I changes functional connectivity in regions known to be involved in emotional processing (26). Therefore, the aim of the current study was to evaluate the effect of insomnia interventions on brain activity elicited by emotional stimuli. To facilitate wide interpretability, we chose the Hariri faces/shapes emotion task (27), which has been implemented in the large cohort studies of the Human Connectome Project (28) and the UK Biobank (29) and was specifically designed to assess the amygdala response, which is key to emotion processing (30). We assessed how the amygdala response to emotional stimuli in 122 people with ID differed from activation in 36 control subjects without sleep problems, and how the response changed after 6 weeks of either no treatment (NT) or therapist-guided digital CRS, CBT-I, or combined CBT-I+CRS. We furthermore evaluated whether individual differences in intervention-induced changes in brain responses to emotional stimuli were correlated with changes in clinical variables, notably the severity of insomnia, depression, and anxiety. When designing our study, only one neuroimaging study reported on amygdala reactivity to emotional stimuli in individuals with insomnia versus good-sleeper control subjects (31). People with insomnia showed enhanced amygdala reactivity to sleep-related stimuli but attenuated reactivity to negative non–sleep-related stimuli. Given this restricted prior knowledge, we did not phrase a directional hypothesis favoring, at baseline, either increased reactivity (as in MDD) or attenuated reactivity as reported for insomnia and the risk it conveys for developing depression, although the latter may be somewhat more likely in our selected sample of particpants with insomnia at high risk of developing depression. We furthermore hypothesized that effective intervention would normalize altered amygdala reactivity. Findings could have relevance beyond insomnia and provide insight into resilience to depression.

METHODS AND MATERIALS

Participants

Assessments were integrated within a randomized controlled trial (12,32). Inclusion criteria for participants with ID were 1) meeting the criteria of ID according to the DSM-5 (33) and the International Classification of Sleep Disorders, Third Edition (34); 2) Insomnia Severity Index (ISI) score $\geq$10 [based on Morin *et al.* (35)]; and 3) age between 18 and 70 years. Moreover, we prioritized inclusion of participants with ID of a subtype with an increased lifetime risk of depression (36). We complemented the data with baseline fMRI assessments in 36 control subjects without sleep complaints (ISI score $<$10 and not meeting ID DSM-5 criteria). Exclusion criteria for all participants were 1) a current diagnosis of major depression (past diagnosis of depression was allowed); 2) current antidepressant treatment; 3) current CBT-I treatment; 4) a severe sleep disorder other than insomnia (i.e., sleep apnea, restless legs syndrome, periodic limb movement disorder); 5) a current diagnosis of any other severe psychiatric or neurological disorder; 6) a severe physical or mental impairment due to stroke or head injury; 7) night work or rotating shift work; 8) an eye condition incompatible with light exposure; 9) a history of light-induced migraine or epilepsy, or severe sensitivity to bright light; or 10) MRI contraindications. See the study protocol and the Supplement for more details (32). Participants were recruited through the Netherlands Sleep Registry (www.sleepregistry.org), media advertisements, and flyers. The final sample included 122 patients with ID and 36 control subjects without sleep complaints. Another 10 possible participants could not be included in the analyses due to MRI contraindications, excessive head motion, or otherwise incomplete fMRI data. The study was approved by the Medical Ethics Committee of the VU University Medical Center (NL63139.029.17) and registered with the International Clinical Trial Registry Platform (NTR7567). Participants provided written informed consent.

Interventions

Details about the interventions are provided elsewhere (12,32). In brief, participants with ID were randomized to either no treatment (NT) or 6 weeks of digital therapist-guided CRS, CBT-I, or combined CBT-I+CRS. The CRS intervention module addressed 1) psychoeducation about circadian rhythms and light exposure including daily use of a Philips EnergyUp HF3430/01 light, scheduled for use shortly after awakening, for 30 minutes; 2) consolidating the light schedule and commencing with physical activity for at least 30 minutes at a fixed time of day; 3) consolidating scheduled physical activity and increasing its intensity; 4) half an hour of body warming between 2 and 3 hours before bedtime, by taking a warm bath with a temperature of 37 to 39 °C (or a hot shower if no bath was available), approximately 3 times a week; and 5) revisiting schedules to optimize feasibility and to secure continued adherence (see Supplement for more information). The CBT-I intervention module (37–39) addressed 1) psychoeducation, 2) stimulus control and sleep restriction, 3) worrying and relaxation, 4) erroneous cognitions about sleep, and 5) plans to

secure continuation. Participants randomized to combined CBT-I+CRS received both CBT-I and CRS simultaneously.

Symptom Severity Assessments

Symptom severity was assessed prior to treatment (week 0 [T0]) and at 4 follow-up assessments at week 7 (T1), week 26 (T2), week 39 (T3), and week 52 (T4). Insomnia, depression, and anxiety severity were measured with the ISI (35); Inventory of Depressive Symptomatology, Self-Report (IDS-SR) (40); and Beck Anxiety Inventory (41), respectively.

Emotion fMRI Task

The emotional faces task (27,28) recruits emotional brain areas (e.g., amygdala, hippocampus, medial and lateral orbitofrontal cortices) with moderate test-retest reliability across time (42,43). Participants were presented with pictures of emotional faces (angry or fearful) or neutral shapes and were instructed to indicate which of two faces or shapes matched the target image. Alertness level was measured by the accuracy of the matching task. The task consisted of 12 blocks (6 shape blocks, 6 face blocks), each consisting of 6 trials of the same condition (face or shape). The shape and face blocks were presented alternately in a fixed order. Each stimulus was presented for 2 seconds, with an interstimulus interval of 1 second. Every block was preceded by a task cue (face or shape) for 3 seconds. The total duration of the task was 4.30 minutes. fMRI data were obtained prior to treatment (week 0 [T0]) and after completion of the 6-week intervention period (week 7 [T1]).

Image Acquisition and Preprocessing

The Supplement provides image acquisition parameters and a detailed description of image preprocessing using fMRIPrep 20.1.0rc2 (44).

fMRI Data Analysis

Subject-level general linear model analyses were conducted for each participant and each session using FEAT (FMRIB Software Library; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT). White matter, cerebrospinal fluid regressors (derived from fMRIPrep), and temporal derivatives were included in the general linear model. Autocorrelation correction was applied using FILM (FMRIB Software Library; https://www.fmrib.ox.ac.uk/datasets/techrep/tr04ss2/tr04ss2/node3.html) (45). The contrast of interest, face versus shape, was defined to determine voxels that were more activated during the presentation of emotional faces than shapes. The group-level design to evaluate differences between patients with ID and control subjects included 2 dummy regressors for patients with insomnia and control subjects, respectively, and 2 regressors for demeaned values of age and sex. The group-level design to assess the intervention effects included 4 dummy regressors for each of the intervention groups (e.g., NT, CRS, CBT-I, CBT-I+CRS), demeaned values of age and sex, and a voxel-based regressor consisting of each person's baseline face versus shape activity map prior to intervention. The voxel-based regressor corrects for the face versus shape activation at baseline, i.e., prior to intervention. Nonparametric permutation testing (5000 permutations) was performed voxelwise using Randomiseh (FMRIB Software Library; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise) (46) to test differences between patients with ID and control subjects, and similarly to test the interventions effects. Intervention effects were tested by comparing the postintervention brain activity, corrected for baseline brain activity, between each intervention group combination (e.g., CBT-I vs. CRS, CBT-I vs. NT, CBT-I vs. CBT-I+CRS). All results were corrected for multiple comparisons with threshold-free cluster enhancement with familywise error correction at $p < .05$. For the region-of-interest (ROI) analysis, a mask of the bilateral amygdala was obtained from the Harvard-Oxford subcortical atlas (threshold >50%) and used as prethreshold mask. Whole-brain analyses were conducted to explore results in other regions.

In case significant changes were observed in a group, ancillary analyses were conducted to evaluate associations between individual differences in the pre-to-post change in brain activity and individual differences in the pre-to-post changes (from T0 to T1) in insomnia, depression, and anxiety severity. For each individual and each scanning session (pre- and posttreatment), the mean contrast of parameter estimate was extracted with featquery (FMRIB Software Library; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/UserGuide#Featquery_-_FEAT_Results_Interrogation) from each significant cluster. Pre-to-post changes in contrast to parameter estimate values were correlated with pre-to-post changes in ISI, IDS-SR, and Beck Anxiety Inventory scores.

RESULTS

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics. The mean age of the 122 patients with ID was 48.1 years (SD = 12.7 years; range 21–69 years; 73% female), and they had an average insomnia severity (ISI) score of 16.0 (SD = 3.8). The mean age of the 36 matched control subjects was 48.3 years (SD = 13.1 years; range 20–69 years; 72% female). Their average ISI score was 3.0 (SD = 3.7). Within the ID sample, there were no significant baseline differences between the 4 intervention conditions in age, sex, education, alcohol use, smoking status, handedness, sleep medication usage, and insomnia duration, nor were there baseline differences in insomnia severity and depressive and anxiety symptoms (all *p*s > .216) (see Table 1).

Effects of Interventions on Insomnia and Depression

Intervention effects on the severity of insomnia and depressive symptoms have been reported previously (12), including patients with ID both with and without fMRI data ($N = 132$). For the 122 participants with complete fMRI data reported here, intervention effects were, as expected, similar (see Table S1). In brief, CBT-I and CBT-I+CRS induced a significantly stronger reduction during the 1-year follow-up (T1 to T4) in ISI and IDS-SR scores as compared with NT (ISI for CBT-I and CBT-I+CRS vs. NT: Cohen's $d = -0.93$, $p < .001$ and $d = -0.87$, $p < .001$, respectively; IDS-SR for CBT-I and CBT-I+CRS vs.

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Sample			Intervention				
	ID, *n* = 122	Control, *n* = 36	*p* Value	NT, *n* = 30	CRS, *n* = 32	CBT-I, *n* = 29	CBT-I + CRS, *n* = 31	*p* Value
Age, Years, Mean (SD)	48.1 (12.7)	48.3 (13.1)	.932	46.9 (12.1)	50.1 (13.0)	48.0 (13.5)	47.1 (12.4)	.756
Sex, Female, *n* (%)	89 (73.0%)	26 (72.2%)	.999	20 (66.7%)	24 (75.0%)	21 (72.4%)	24 (77.4%)	.805
Education, Years, Mean (SD)	16.5 (3.0)	18.2 (2.9)	.004	15.6 (3.5)	16.9 (2.6)	16.5 (2.5)	17.1 (3.1)	.216
Alcohol Consumption per Week			.135					.745
0 units of alcohol, *n* (%)	26 (21.3%)	4 (11.1%)		8 (26.7%)	8 (25.0%)	5 (17.2%)	5 (16.1%)	
1–14 units of alcohol, *n* (%)	86 (70.5%)	29 (23.8%)		20 (66.7%)	21 (65.6%)	23 (79.3%)	22 (71.0%)	
>14 units of alcohol, *n* (%)	10 (8.2%)	3 (2.5%)		2 (6.7%)	3 (9.4%)	1 (3.4%)	4 (12.9%)	
Smoker, *n* (%)	4 (3.3%)	0 (0.0%)	.619	1 (3.3%)	2 (6.2%)	1 (3.4%)	0 (0.0%)	.584
Handedness, Right, *n* (%)	108 (88.5%)	33 (91.7%)	.789	26 (86.7%)	28 (87.5%)	24 (82.8%)	30 (96.8%)	.387
Sleep Medication User, *n* (%)	27 (22.1%)	0 (0.0%)	.002	8 (26.7%)	8 (25.0%)	5 (17.2%)	6 (19.4%)	.789
Mild Sleep Apnea, *n* (%)	7 (5.7%)	1 (2.8%)	.780	2 (6.7%)	3 (9.4%)	1 (3.5%)	1 (3.2%)	.688
Mild Restless Legs Syndrome, *n* (%)	17 (13.9%)	4 (11.1%)	.874	3 (10.0%)	4 (12.5%)	5 (17.2%)	5 (16.1%)	.842
Insomnia Duration, Years, Mean (SD)	9.5 (10.8)	–		10.8 (11.3)	8.7 (11.2)	9.1 (10.3)	9.4 (10.7)	.888
Insomnia Severity (ISI), Mean (SD)	16.0 (3.8)	3.0 (3.7)	<.001	16.1 (4.5)	15.9 (3.2)	16.1 (4.1)	15.8 (3.7)	.995
Sleep Quality (PSQI), Mean (SD)	10.7 (2.4)	3.3 (2.6)	<.001	10.4 (3.4)	10.9 (3.2)	10.7 (3.5)	10.9 (3.4)	.921
Depression Severity (IDS-SR), Mean (SD)	18.8 (7.3)	5.2 (4.9)	<.001	18.7 (6.3)	18.6 (7.5)	18.9 (7.9)	18.9 (7.6)	.998
Past MDD Diagnosis (CIDI Interview), *n* (%)	69 (56.6%)	9 (25.0%)	.002	16 (53.3%)	19 (59.4%)	17 (58.6%)	17 (54.8%)	.957
Anxiety (BAI), Mean (SD)	7.7 (5.8)	1.9 (2.4)	<.001	7.9 (4.9)	7.6 (7.0)	7.6 (5.8)	7.7 (5.7)	.996

BAI, Beck Anxiety Inventory; CBT-I, cognitive behavioral therapy for insomnia; CIDI, Composite International Diagnostic Interview; CRS, circadian rhythm support; ID, insomnia disorder; IDS-SR, Inventory of Depressive Symptomatology, Self-Report; ISI, Insomnia Severity Index; MDD, major depressive disorder; NT, no treatment; PSQI, Pittsburgh Sleep Quality Index.

NT: $d = -0.79$, $p = .001$ and $d = -0.97$, $p < .001$, respectively). Stand-alone CRS did not significantly reduce ISI ($d = -0.44$, $p = .107$) or IDS-SR ($d = -0.27$, $p = .221$) scores as compared with NT. Beneficial effects on the IDS-SR seemed to last longer for CBT-I+CRS, as indicated by larger effect sizes for CBT-I+CRS at 9 and 12 months ($d = -1.44$ and $d = -0.77$, respectively) than for stand-alone CBT-I ($d = -0.76$ and $d = -0.55$, respectively) (Table S1). Information about treatment adherence is provided in the Supplement.

Behavioral Performance on Emotion Task

Details on task performance are provided in the Supplement. Patients with ID performed slightly, but not significantly, more accurately than good-sleeper control subjects (patients with ID: 98.4%; control subjects: 97.7%) ($p = .060$) and did not differ with respect to reaction time (patients with ID: 820 ms; control subjects: 840 ms) ($p = .565$). Among the patients with ID, there were no differences in accuracy or reaction time between the 4 intervention conditions ($p = .680$ and $p = .441$, respectively), nor were there significant time-by-intervention-condition interaction effects in accuracy or reaction time ($p = .767$ and $p = .963$, respectively).

Comparison of Brain Response With Emotional Stimuli Between Patients With ID and Control Subjects

There were no significant baseline differences between patients with insomnia and good-sleeper control subjects in the differential response to emotional versus nonemotional stimuli (face > shape) in the bilateral amygdala ROI or at whole-brain level.

Intervention Effect on Brain Response to Emotional Stimuli in ID

At baseline, the 4 intervention groups (CBT-I, CRS, CBT-I+CRS, NT) did not differ in their differential response to emotional versus nonemotional stimuli (face > shape) in the bilateral amygdala ROI or at the whole-brain level.

ROI analysis revealed that CBT-I+CRS significantly increased the differential emotional response of the bilateral amygdala from baseline to posttreatment, as compared with all other conditions (stand-alone CBT-I, stand-alone CRS, NT) (Table 2; Figure 1; Figure S1). One-by-one group comparisons showed that CBT-I+CRS enhanced the differential response in 3 overlapping clusters in the left amygdala significantly more than NT, CRS, and CBT-I did, and enhanced the response difference in the right amygdala significantly more than CBT-I did (Table 2; Figure 1; Figure S1). No other comparison reached significance (e.g., CBT-I vs. CRS, CRS vs. NT, etc.).

Whole-brain analysis showed that CBT-I+CRS significantly increased the differential response to emotional stimuli in 2 distinct clusters in the left insula and a cluster in the right inferior frontal gyrus, as compared with all other conditions. One-by-one group comparisons revealed that the enhanced differential response after CBT-I+CRS in the right temporal parietal junction and the right angular gyrus reached significance when compared with NT. One-by-one group

Table 2. Intervention Effects Showing Significant Clusters for ROI and Whole-Brain Analyses

	Cluster Size, Voxels	CBT-I+CRS Increased Compared With	MNI Coordinates			*t*	*p* Value
			x	y	z		
ROI: Bilateral Amygdala							
Left amygdala	85	All other groups	−16	−4	−20	3.14	.002
	9	NT	−16	−4	−22	3.24	.033
	113	CBT-I	−16	−4	−16	3.35	<.001
	8	CRS	−18	−4	−14	2.97	.035
Right amygdala	5	All other groups	30	−2	−26	3.48	.037
	18	CBT-I	30	−2	−26	3.13	.016
Whole Brain							
Left amygdala	3	CBT-I	−16	−4	−16	4.82	.031
Left insula	33	All other groups	−38	4	−14	3.92	.033
	24	All other groups	−38	−10	−12	3.84	.038
	93	CBT-I	−38	4	−12	3.73	.048
Right inferior frontal gyrus	7	All other groups	42	16	26	3.86	.048
Right temporoparietal junction	158	NT	60	−48	6	3.79	.021
Right angular gyrus	22	NT	54	−50	52	3.96	.042

Results were corrected for multiple comparisons with threshold-free cluster enhancement with familywise error correction at $p < .05$.

CBT-I, cognitive behavioral therapy for insomnia; CRS, circadian rhythm support; MNI, Montreal Neurological Institute; NT, no treatment; ROI, region of interest.

comparisons also showed that the enhanced differential response after CBT-I+CRS in the left amygdala (overlapping with clusters found in the ROI analysis) and the left insula reached significance when compared with stand-alone CBT-I. In no other brain area did groups differ with respect to pre-to-post changes in the differential emotional response. A past MDD diagnosis did not change or confound our results (see Supplement).

Correlation Between Pre-to-Post Changes in Brain Activity and Changes in Symptom Severity in ID

To investigate the functional relevance of the pre-to-post changes in brain activity that only emerged after CBT-I+CRS, we calculated whether individual changes in pre-to-post brain response correlated with individual changes in pre-to-post (from T0 to T1) insomnia (ISI), depression (IDS-SR), and anxiety (Beck Anxiety Inventory) symptom severity within the CBT-I+CRS group.

Participants with a larger pre-to-post reduction in insomnia severity showed a larger pre-to-post increase in the differential response to emotional versus nonemotional stimuli in all 4 significant clusters in the left amygdala (range of $r = -0.38$ to -0.46, all $p < .033$) (Table 3; Figure 2), while significance was not reached in the right amygdala, left insula, right inferior frontal gyrus, right temporoparietal junction, or right angular gyrus (Table 3).

Likewise, participants with a larger reduction in depression severity showed a larger pre-to-post increase in the differential response in 2 of the significant clusters in the left insular cortex (range of $r = -0.36$ to -0.37, $p < .042$) (Table 3; Figure 2), while significance was not reached in the third insula cluster, bilateral amygdala, right inferior frontal gyrus, right temporoparietal junction, or angular gyrus (Table 3). There were no significant correlations between changes in brain activity and anxiety severity. Although pre-to-post change correlation analyses within the other groups are less telling because of absence of pre-to-post changes in brain activity, results are provided in Figure S2 for completeness.

DISCUSSION

This study is the largest to date to investigate the effect of sleep interventions on brain activation in ID. We compared different sleep interventions and found that only combined CBT-I+CRS led to a significant pre- to postintervention increase in bilateral amygdala activation in response to emotional stimuli, which was paralleled by the longest-lasting favorable effect on mood resulting from this intervention. Within the CBT-I+CRS group, increased responsiveness of the left amygdala correlated with improvement of insomnia symptoms directly after treatment, while increased responsiveness of the left insula correlated with improvement of depression symptoms.

Contrary to the undirectional hypothesis of altered amygdala reactivity in insomnia, baseline differences between patients with insomnia and good sleeper control subjects did not reach significance. While the sample size of the control group was too small for small case-control differences to reach significance, the larger sample size of the insomnia group was sufficient to reveal within-subject pre–post changes. Concurrently, the nonsignificant case-control differences and significant pre–post changes suggest a slightly attenuated amygdala reactivity in currently nondepressed people at risk of developing depression (see Figure S4 and Table S2 for post hoc analyses with lower statistical threshold $z = 1.96$), in line with 2 previous studies (22,25). In partial support of our hypothesis on the normalizing effect of intervention, our most elaborate and effective combined sleep intervention boosted amygdala reactivity from the lower to the upper range of reactivity observed in healthy control subjects (see Figure S4 and Table S2 for post hoc analysis). This

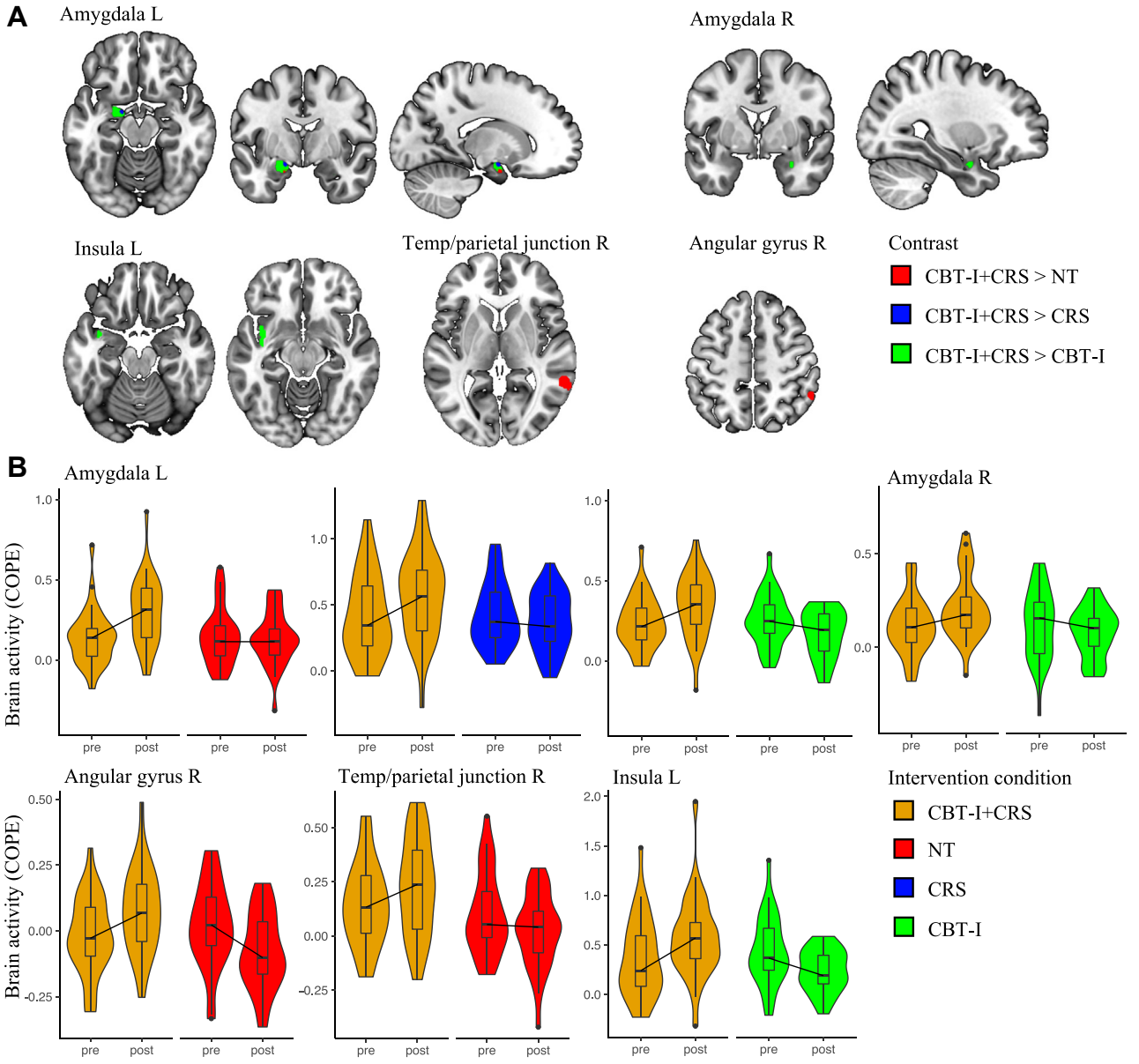

Figure 1. Significant clusters for region-of-interest (ROI) and whole-brain analyses showing increased brain response to emotional stimuli in patients with insomnia receiving combined cognitive behavioral therapy for insomnia and circadian rhythm support (CBT-I+CRS). **(A)** Locations of significant clusters. **(B)** Violin plots and box plots showing the distribution of individual brain activity (contrast of parameter estimate [COPE]) pre- and postintervention for significant clusters for CBT-I+CRS (orange), no treatment (NT) (red), CRS (blue), CBT-I (green). Note that each plot shows the significant difference in brain activity between the CBT-I+CRS group and the NT, CRS, or CBT-I group. L, left; R, right; temp/parietal, temporoparietal.

change may be involved in ameliorating the risk of people with insomnia to develop depression. Long-term follow-up studies in large cohorts like the UK Biobank could evaluate whether, among a heterogeneous sample of people with insomnia complaints, the people who will develop future depression are more likely to be in the lower range of the normal distribution of the amygdala response to negative facial expression (47), while those in the higher range may be more resilient. Heterogeneity is an important factor complicating the assessment of amygdala activation in insomnia and its involvement in the risk and resilience for depression. While insomnia is characterized more by fragmented sleep than by a lack of sleep, some people experiencing insomnia in addition obtain <6 hours of sleep when polysomnographically recorded. In these cases, subtle attenuated amygdala activation related to insomnia and the risk of depression might be overridden by enhancement of amygdala activation due to sleep deprivation (48–50).

Table 3. Correlation in CBT-I+CRS Group Between Pre-to-Post Changes in Brain Activity (COPE) and Pre-to-Post (T0 to T1) Changes in Insomnia, Depression, and Anxiety Severity

		Correlation ΔISI		Correlation ΔIDS-SR		Correlation ΔBAI	
	Cluster Size, Voxels	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value
Bilateral Amygdala ROI							
Left amygdala	85	−0.41	.021	0.12	.537	−0.25	.186
	9	−0.46	.010	0.16	.397	−0.19	.306
	113	−0.38	.033	0.10	.603	−0.21	.268
	8	−0.38	.033	−0.09	.612	−0.32	.085
Right amygdala	5	−0.08	.679	−0.15	.407	−0.17	.358
	18	−0.19	.309	−0.17	.367	−0.17	.371
Whole Brain							
Left amygdala	3	−0.31	.084	−0.06	.752	−0.29	.126
Left insula	33	−0.12	.531	−0.37	.042	−0.06	.751
	24	−0.11	.543	−0.33	.068	−0.05	.776
	93	−0.15	.421	−0.36	.044	−0.11	.575
Right inferior frontal gyrus	7	−0.03	.887	−0.15	.409	−0.20	.289
Right temporoparietal junction	158	−0.26	.159	−0.13	.492	−0.25	.189
Right angular gyrus	22	−0.28	.128	−0.20	.292	−0.14	.472

BAI, Beck Anxiety Inventory; CBT-I, cognitive behavioral therapy for insomnia; COPE, contrast of parameter estimate; CRS, circadian rhythm support; IDS-SR, Inventory of Depressive Symptomatology, Self-Report; ISI, Insomnia Severity Index; NT, no treatment; ROI, region of interest; T, time.

CBT-I+CRS elicited the strongest pre- to posttreatment change in amygdala responsiveness and also resulted in the most favorable long-term effects on mood in patients with insomnia. Several studies in MDD likewise reported a stronger amygdala response to be predictive of a better long-term outcome: Those with a more pronounced amygdala response to emotional words (51) or faces (52) at baseline subsequently showed a stronger decrease in depressive symptom severity assessed after respectively 3 and 8 months. In treatment-resistant depression, individuals with a stronger amygdala response to emotional faces also showed the strongest decrease in depressive symptom severity, specifically after 1 year (20). Similarly, we found in our sample of people with ID that the combined treatment that uniquely enhanced amygdala responsiveness also outperformed other treatments in reducing depressive symptoms on the long term (9 and 12 months) (Table S1). The diverging short- and long-term effects on insomnia and mood sorted by the

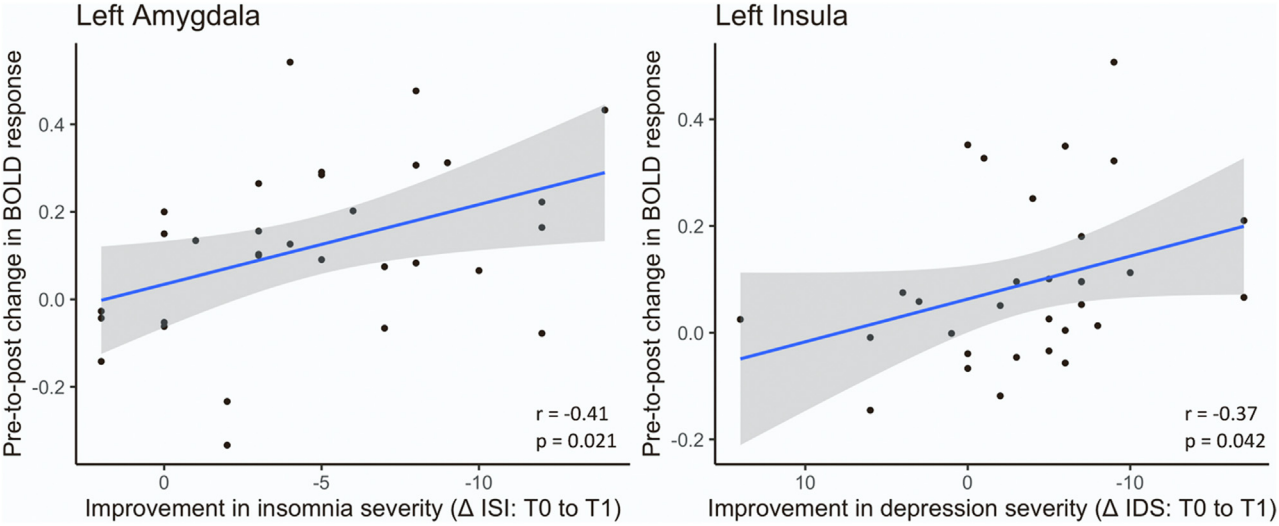

Figure 2. Correlation between pre-to-post change in brain activity and pre-to-post change (time 0 [T0] to T1) in insomnia and depression severity within the combined cognitive behavioral therapy for insomnia and circadian rhythm support (CBT-I+CRS) group for significant clusters found in the left amygdala and left insula for CBT-I+CRS compared with all other groups (no treatment [NT], CRS, CBT-I). Note that the horizontal axis runs from positive to negative to indicate the degree of improvement, defined by the reduction in severity. BOLD, blood oxygen level–dependent; IDS, Inventory of Depressive Symptomatology; ISI, Insomnia Severity Index.

interventions suggest that CBT-I is required for an initial response, the maintenance of which is supported by CRS, in line with a previous study (11). Meta-analysis has shown that sleep-improving effects of stand-alone CBT-I wane within a year (53). CRS might prevent this waning by supporting the diurnal expression of clock genes that is crucial to optimal functioning of brain circuits including the amygdala (54,55).

In depression, hyperreactivity of the amygdala to negative emotional stimuli may be mitigated by treatment with selective serotonin reuptake inhibitors (56). However, in treatment-resistant depression, the amygdala may be hyporesponsive, and intervention with psilocybin and psychological support shows the opposite effect: It increased the amygdala response to fearful faces in proportion to clinical improvement (57). Differing from these examples, the current study targeted prevention of depression in people with insomnia, rather than treatment of people currently experiencing depression.

While ID is a major risk factor for MDD, not all people with insomnia develop MDD. Identifying those individuals that are most likely to develop MDD is important because their selection would promote efficiency in studies on the effectiveness of interventions to prevent MDD. A recent study revealed 5 robust insomnia subtypes (36) based on their profiles of emotional, cognitive, and personality traits and life history. The subtypes differed markedly with respect to lifetime risk of depression, which had occurred in 8% of the least vulnerable subtype up to 54% in the most vulnerable subtype. The current study included only subtypes with increased risk of developing depression in order to more efficiently study prevention of MDD. Indeed, in our selected sample, depression increased in people who were not treated for insomnia, in contrast to previous studies in heterogeneous samples that were inconclusive on prevention, because on average also people with untreated insomnia showed a decrease in depressive symptoms (58–60).

A lifetime history of MDD was also observed in 25% of the control subjects, which may seem surprisingly high as compared with estimates of lifetime MDD in the general population. However, population estimates derived from self-reported retrospective surveys may shrink to half of the actual prevalence due to recall failure (61,62). Our Composite International Diagnostic Interview method previously yielded overall estimates of near 20% in the age range of participants in our study, and a higher prevalence in females (63,64). Indeed, we also observed this sex difference (27% of females, 20% of males), which due to the larger proportion of females led to the observed overall 25%. Possibly by excluding people with clinically relevant insomnia, MDD prevalence observed in our control group was actually lower than the estimated true lifetime prevalence in the Netherlands, which is 42% for females and 27% for males in the age range of participants in our study (65).

Limitations need to be considered. First, we only assessed the brain response to negative facial expressions and did not assess the brain response to positive emotional stimuli. We considered it valuable for comparison to choose a task used in the large studies of the Human Connectome Project (28) and the UK Biobank (66). Future studies could include positive stimuli. Second, it was not feasible to acquire fMRI data at a longer follow-up (e.g., 1 year after receiving initial treatment). Therefore, it remains unknown whether the increased amygdala response induced by CBT-I+CRS would be sustained in the long term and whether such a sustained response would be related to the long-term favorable effect of CBT-I+CRS on depressive symptomatology. Third, we did not systematically assess subjective experience of the emotional stimuli. Fourth, it remains unknown how the interventions would affect amygdala reactivity in good sleepers. A major strength of this study is our 4-arm design including 3 intervention groups and an untreated control group. This approach allows for comparison with both active treatment interventions and an untreated group. Several previous fMRI studies only compared pre-to-post differences in brain activity following CBT-I (13–15), without comparison with an untreated group, which made it difficult to disentangle therapy-related brain changes from those related to spontaneous recovery.

To conclude, our results indicate that CBT-I+CRS has the largest long-lasting effect on mood and enhances brain activity in several limbic-related brain regions in response to emotional stimuli. The findings contribute to understanding the effect of insomnia interventions on emotional brain circuits, which might be important for patients with insomnia to increase resilience to depression.

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International Clinical Trial Registry Platform: Effects of treatments for insomnia on depressive symptoms in persons with insomnia prone to depression; https://trialsearch.who.int/Trial2.aspx?TrialID=NTR7567; NTR7567.

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