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Sleep System Sensitization: Evidence for Changing Roles of Etiological Factors in Insomnia

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Abstract

Objectives—To test for sensitization of the sleep system in response to insomnia development and major life stress. In addition, to evaluate the impact on depression and anxiety associated with sleep system sensitization.

Methods—A longitudinal study with three annual assessments. The community-based sample included 262 adults with no history of insomnia or depression who developed insomnia 1 year after baseline (67.6% female; 44.0±13.4y). Measures included the Ford Insomnia Response to Stress Test to assess sleep reactivity, Quick Inventory of Depressive Symptomatology, and Beck Anxiety Inventory. Insomnia classification was based on DSM-IV criteria. Sleep system sensitization was operationally defined as significant increases in sleep reactivity.

Results—Sensitization of the sleep system was observed from baseline to insomnia onset at 1-y follow-up among insomniacs with low premorbid vulnerability ($p<.001$), resulting in 68.3% of these individuals re-classified as highly sleep reactive. Major life stress was associated with greater sleep system sensitization ($p=.02$). Results showed that sleep reactivity at 2-y follow-up remained elevated among those with low premorbid vulnerability, even after insomnia remission ($p<.01$). Finally, analyses revealed that increases in sleep reactivity predicted greater depression ($p<.001$) and anxiety ($p<.001$) at insomnia onset. The impact of sensitization on depression was stable at 2-y follow-up ($p=.01$).

Conclusions—Evidence supports sensitization of the sleep system as consequence of insomnia development and major life stress among individuals with low premorbid sleep reactivity. Sleep system sensitization may serve as a mechanism by which insomnia is perpetuated. Harmful effects of the sensitization process may increase risk for insomnia-related depression and anxiety.

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Keywords

sleep reactivity; insomnia; FIRST; sleep system sensitization; depression; anxiety

1. Introduction

Prior literature on insomnia risk factors has largely focused on premorbid vulnerabilities such as sleep reactivity (i.e., the tendency to exhibit sleep disturbance in response to a sleep challenge),^{1, 2} parental insomnia history,^{3, 4} and poor physical and mental health.⁵⁻⁷ Comparatively, little is known about the evolution of potentially non-static premorbid risk factors as consequence of developing insomnia. Recent models suggest that exposure to stress and insomnia result in changes in cognitive and neurobiologic systems that modulate stress-response and sleep regulation associated with insomnia-vulnerability.^{8, 9} This proposal suggests that insomnia vulnerabilities are not stable and that changes in susceptibility may influence disease course and risk for commonly co-occurring psychiatric illnesses. Importantly, this framework is consistent with personal history of insomnia as a robust predictor of future sleep and mood pathology,^{5, 7, 10, 11} even after insomnia remission.⁵ Though exposure to stress and insomnia disorder are posited to increase susceptibility to future disease onset,^{8, 9} the manner in which premorbid vulnerabilities evolve as a consequence of exposure to insomnia and major life stress has not yet been characterized. This investigation sought to test for sensitization of the sleep system—evidenced by significant increases in sleep reactivity—in response to insomnia development and stress exposure. Specifically, we examined whether self-reported sleep reactivity significantly increased with the development of insomnia and evaluated the impact of major life stress on changes in sleep reactivity. Finally, we investigated the influence of sleep system sensitization on depression and anxiety symptoms during and following the onset of insomnia.

The conditions under which the initial onset of insomnia develops may differ from those that perpetuate its course or give rise to recurrent episodes. Borrowing from the depression literature, life stress models propose that premorbid vulnerabilities to depression evolve in response to development of the disorder such that each episode of depression increases risk for recurrence and chronicity by sensitizing or kindling the stress-response system.^{12, 13} Importantly, studies have demonstrated kindling and sensitization effects of the stress system to be most pronounced in individuals at low genetic risk for depression, whereas individuals with high genetic risk have been described as *pre-kindled*.¹³ Owing to shared phenotypic^{2, 7, 14} and genotypic^{8, 15} vulnerabilities between the two disorders, it is important to determine whether etiological factors of insomnia similarly evolve in response to initial disease onset. In a recent report, Palagini and colleagues⁸ proposed that exposure to stress and insomnia disrupt neurobiologic systems that modulate sleep-wake regulation and stress-response, thereby perimorbidly increasing risk for chronic and recurrent insomnia. Though high premorbid sleep reactivity augurs insomnia development^{1, 2} and insomniacs report exaggerated sleep-related stress reactivity,⁸ the degree to which exposure to life stress and insomnia may sensitize stress-response and the sleep system has not yet been investigated. Characterization of phenotypic changes in sleep system sensitivity in response to stress

exposure and insomnia would offer valuable insight into the evolving roles of etiological factors in recurrent and chronic insomnia.

Sleep reactivity is a vulnerability to insomnia that manifests as a sleep system that is sensitive or reactive to stress and other sleep challenges.^{2, 16, 17} Prior investigations have shown that highly reactive sleepers experience greater sleep disturbance in response to caffeine intake,^{16, 18} circadian misalignment,^{16, 19} and interpersonal stressors²⁰ than do non-reactive sleepers. Importantly, sleep reactivity has shown to be a more robust predictor of insomnia incidence than premorbid sleep disturbance and proband-reported parental insomnia history.²¹ Though heritability studies suggest a genetic basis for sleep reactivity, evidence indicates that environmental factors exert influence on the sensitivity of the sleep system.^{22, 23} Thus, it is important to evaluate whether the sleep system becomes more sensitive in response to stress and insomnia, the latter of which has been conceptualized as a stressor in and of itself.⁸ As the experience of stress and insomnia may alter pathways to subsequent and chronic episodes,^{8, 9, 24, 25} it is thus critical to test for perimorbid changes in sleep reactivity associated with insomnia development.

Critically, the effects of evolving insomnia vulnerability may not be limited to insomnia chronicity and recurrence. A growing body of research on the comorbidity between mood and sleep pathology indicates that shared trait phenotypic characteristics may represent common vulnerabilities to sleep and affective disorders,^{2, 14, 19, 26, 27} and likely give rise to high comorbidity rates. Recent research has shown that sleep reactivity is related to indices of cognitive-emotional hyperarousal, including arousability, pre-sleep cognitive arousal, and maladaptive emotional coping.¹⁴ Therefore, any perimorbid changes in insomnia-risk may be accompanied by changes in depressed or anxious mood. As sleep reactivity has been shown to be associated with mood symptoms in insomniacs,^{2, 28} it is critical to investigate whether sensitization of the sleep system is associated with severity of depression or anxiety symptoms during insomnia.

The goals of this study were to test for changes in sleep system sensitivity that occur with the development of insomnia, identify factors associated with sensitization of the sleep system, and to describe any associations between sleep system sensitization and affective symptoms during and following insomnia onset. To accomplish these goals, we analyzed data from a large community-based adult sample recruited in the Evolutions of Pathways to Insomnia Cohort (EPIC)²⁰ study. Using a prospective design, we collected three waves of annual web-based epidemiological survey data from a sample with no current or lifetime history of insomnia or depression at baseline who developed insomnia at 1-y follow-up. We hypothesized that the sleep system would show evidence of sensitization as indicated by significant increases in sleep reactivity from premorbid baseline assessment to disease onset. Consistent with life stress models of major depression,¹³ we predicted that sensitization would be most pronounced in individuals with low premorbid sleep reactivity, and that exposure to major life stress would be associated with greater increases in sleep reactivity. Importantly, we hypothesized that sleep system sensitization would be state independent as supported by data showing that sleep reactivity would not return to baseline following insomnia remission. Finally, we predicted that sleep system sensitization would be associated with greater severity of depression and anxiety at 1-y and 2-y follow-ups.

2. Methods

2.1 Participants

Data were collected from a large community sample in Southeastern Michigan as part of a 3-year NIMH-funded investigation. Detailed recruitment, eligibility, and demographic information has been reported in detail elsewhere (see Drake, Pillai, & Roth, 2013²). For baseline assessment (Year 0), study invitations were mailed to a randomly generated list of adults (N=36,002) from a major HMO database. Of these individuals, 7,608 completed the online eligibility survey, which screened for current/lifetime history of DSM-IV²⁹ based insomnia and major depression, as well as inconsistent and indiscriminate responding. A total of 2,590 screened positive for current/lifetime insomnia and/or depression, whereas 149 individuals were identified as inconsistent or indiscriminate responders, resulting in the exclusion of 2,739 individuals. A total of 4,869 individuals were eligible to participate as they screened negative for current/lifetime history of insomnia or depression and did not engage in inconsistent or indiscriminate responding, though 1,339 of these individuals declined to participate in the study. In total, 3,530 eligible individuals elected to participate in the study at Year 0 assessment. One year later, 2,892 completed Year 1 follow-up (attrition rate = 18.1%), and 262 of these participants were classified as meeting criteria for insomnia (9.1% incidence rate). As such, the present study's sample consisted of 262 adults with no lifetime history of insomnia or depression who developed insomnia at 1-y follow-up.

2.2 Procedure

All study protocols were approved by the Henry Ford Hospital institutional review board. Individuals were required to provide informed consent prior to participating. The setting of this study was a web-based epidemiological survey. Data were collected in three annual waves. Year 0 data were collected after participants met eligibility requirements using web-delivered questionnaires. One month prior to each annual follow-up (at Years 1 and 2), participants received email reminders. Each assessment took approximately 30 minutes to complete.

2.3 Measures

Insomnia—Individuals were classified with insomnia at Years 0, 1, and 2. At Year 0, those who met criteria for insomnia were excluded from the study. DSM-IV based insomnia classifications were established using the following questions: “In the past year (since your last survey), have you experienced difficulty falling asleep for at least one month?” “In the past year (since your last survey), have you experienced difficulty staying asleep for at least one month?” and “In the past year (since your last survey), have you experienced difficulty with non-refreshing sleep for at least one month?” Responses ranged from 0 (“not at all”) to 4 (“very much”), and participants who reported a score of 2 (“somewhat”) or higher met that nocturnal symptom criterion. In addition, participants were asked to estimate the number of days per week they reported these nocturnal insomnia symptoms, and estimate the duration, in months, these symptoms lasted. Further, participants had to endorse daytime impairment secondary to sleep difficulties in response to the following question: “To what extent do you consider your sleep problems to interfere with your daily functioning?” Responses again

ranged from 0 to 4, and participants who reported a score of 2 (“somewhat”) or higher met the daytime impairment criterion. To meet criteria, participants had to report experiencing one or more of these nocturnal insomnia symptoms three or more nights per week for at least a 1-month period, and meet the daytime impairment criterion for a duration of one month or longer.

Sleep reactivity—The present study assessed sleep reactivity at Years 0, 1, and 2 using the Ford Insomnia Response to Stress Test (FIRST).¹⁸ The FIRST is a self-report measure of sleep reactivity that asks respondents to rate the likelihood (not, somewhat, moderately, and very likely) that they would experience sleep difficulties in reaction to nine hypothetical stressful situations (e.g., ‘after a stressful experience during the day,’ ‘before an important meeting the next day’). Higher FIRST scores indicate a more highly sensitive sleep system. Individuals who score 16 or higher on the FIRST are nearly three times as likely to develop incident insomnia compared to low reactive sleepers, and the 16 cutoff value boasts a 77% sensitivity and 50% specificity in identifying future insomniacs.²¹ In the present study, participants with FIRST scores of 15 or below were characterized as having low sleep reactivity, whereas those who scored 16 or higher were characterized as having high sleep reactivity. Further, we operationally defined changes in FIRST scores as indicative of changes in sensitivity of the sleep system, with significant increases in FIRST scores representing sensitization of the sleep system.

Maternal history of insomnia—To assess maternal history of insomnia, participants were asked to respond ‘yes’ or ‘no’ to the following question: ‘Has your biological mother had difficulty falling asleep, staying asleep, or non-refreshing sleep 3 or more times per week for at least 1 month?’ Paternal insomnia history was not analyzed as prior analysis of these data have shown paternal insomnia history to not be associated with insomnia-risk in this sample.²¹

Stress exposure

Number of events—Exposure to major life stress was based on the Social Readjustment Rating Scale (SRRS-R),^{30, 31} an inventory of 52 stressful life events commonly reported by US adults (e.g., divorce, change in residence, loss of employment). In the present study, we examined the total number of endorsed events for each participant reported at Year 1.

Depression—Participants also completed the 16-item version of the Quick Inventory of Depressive Symptomatology (QIDS)³², which quantifies depressive symptoms on a 4-point (0-3) Likert-type scale with higher scores indicating greater depression severity. To reduce collinearity with insomnia, the sleep disturbance items of the QIDS were excluded. Total scores representing depression severity were used for hypothesis testing.

Anxiety—Participants self-reported anxiety levels using the Beck Anxiety Inventory (BAI)³³, a 21-item questionnaire which measures the severity of common anxiety symptoms. Responses are rated on a 4-point (0-3) Likert-type scale with higher scores

indicating greater anxiety severity. Total scores representing anxiety severity were used for hypothesis testing.

2.4 Analysis plan

Paired t-tests were used to characterize changes in sleep reactivity coinciding with insomnia development ($FIRST_{Y1}-FIRST_{Y0}$), disease remission and chronicity ($FIRST_{Y2}-FIRST_{Y1}$), and overall trends irrespective of insomnia course ($FIRST_{Y2}-FIRST_{Y0}$). Cohen's d effect sizes were calculated accounting for dependence between pre and post means based on recommendations for paired t-tests.³⁴ In effort to provide a nuanced depiction, sleep reactivity changes were first investigated in the total sample, then in subgroups of high and low sleep reactive subjects. Additionally, linear regression was used to identify factors associated with increases in sleep reactivity. Finally, we used linear regression to test for significant associations among sleep system sensitization and depression and anxiety severity at 1-y and 2-y follow-ups.

3. Results

3.1 Sample characteristics

See Table 1 for full baseline sample characteristics. The insomnia sample (N=262) was largely middle-aged ($44.0 \pm 13.4y$), female (67.6%), and white (63.7%). As expected for an insomnia sample, mean FIRST scores (18.9 ± 4.3) at Year 0 reflected high disease vulnerability.²¹ Approximately half of insomniacs reported a maternal history of insomnia, though 37.3% of the sample was unable to indicate any known positive or negative maternal insomnia history. Lastly, we evaluated rates of known maternal insomnia for insomniacs with low vs high premorbid sleep reactivity per the FIRST 16 cut-point. Subjects with high premorbid sleep reactivity reported higher rates of maternal insomnia (76/129, 58.9% among responders) compared to those with low premorbid reactivity (11/38, 28.9%), $\chi^2=10.56$, $p<.01$.

3.2 Sleep System Sensitization

We began by investigating the manner in which FIRST scores changed in correspondence to the development of insomnia between baseline assessment and 1-y follow-up (see Table 2 for full results). In the full sample, a paired t-test revealed an increase in FIRST scores of 0.97 points reflecting a modest degree of sensitization for the full sample (Cohen's $d = .22$). Using the FIRST 16 cut-point, we next split the sample into two groups: low premorbid reactivity sleepers ($n=60$) and high premorbid reactivity sleepers ($n=202$). Among insomniacs with low premorbid sleep reactivity, FIRST scores increased on average from 13.35 (mean below threshold) to 17.17 (mean above threshold). This increase of 3.82 points represented a nearly 1 SD increase in FIRST scores from Year 0 to Year 1, and corresponded to a large effect (Cohen's $d=1.05$).¹ Consistent with sensitization of the sleep system, 41 out

¹Though our focus is to characterize changes in sleep reactivity in response to insomnia development, it is important to demonstrate here that similar increases do not occur in individuals who do *not* develop insomnia. Therefore, changes in sleep reactivity were evaluated in a control group of 60 randomly selected unaffected subjects with low baseline sleep reactivity ($48.5y \pm 13.1$, 61.7% female). No significant change in sleep reactivity was observed between baseline and 1-y follow-up ($t=.27$, $p=.47$) or 2-y follow-up ($t=.15$, $p=.68$).

of 60 insomniacs with low baseline sleep reactivity developed high reactivity at the time of insomnia onset at Year 1 (68.3% re-classification rate). Contrary to hypotheses, no significant change in FIRST scores was observed for individuals with high baseline sleep reactivity ($p=.68$).

After finding evidence in support of sleep system sensitization among insomniacs with low premorbid vulnerability, we sought to identify factors associated with increases in sleep reactivity. We first estimated changes in FIRST scores ($FIRST_{Y1-Y0}$) as predicted by age, gender, maternal insomnia history, baseline FIRST scores, and major life stressors. The overall regression model was significant ($F=10.93$, $p<.001$) and predictors accounted for 23% of the variance in $FIRST_{Y1-Y0}$ (adjusted $R^2 = .23$). Consistent with the paired t-test results, insomniacs with lower baseline sleep reactivity reported greater increases in sleep reactivity from Year 0 to Year 1 ($b=-.50$, $t=-6.58$, $p<.001$). Also consistent with predictions, stress exposure was associated with greater increases in sleep reactivity ($b=.33$, $t=2.42$, $p=.02$). Age ($p=.49$), gender ($p=.10$), and maternal history ($p=.75$) were non-significant predictors.

3.3 Changes in sleep reactivity associated with insomnia chronicity and remission

We then examined changes in sleep reactivity from Year 1 to Year 2 separately for chronic insomniacs and remitted insomniacs (see Table 3 for full results). In chronic insomniacs, a paired t-test showed that FIRST scores did not significantly change from Year 1 ($M=20.89$) to Year 2 ($M=20.52$), indicating that sleep reactivity remains stable after insomnia onset in this subgroup. However, contrary to those with chronic insomnia, individuals whose insomnia went into remission reported a slight decrease in sleep reactivity from Year 1 ($M=19.20$) to Year 2 ($M=18.07$), which corresponded to a small effect (Cohen's $d=.25$).

3.4 Overall changes in sleep reactivity from Year 0 to Year 2

After determining that changes in sleep reactivity serve as a function of both insomnia course (i.e., acute versus chronic) and premorbid sleep reactivity (i.e., high versus low), we examined changes in sleep reactivity among four subgroups: (1) chronic insomniacs with low baseline sleep reactivity ($n=10$); (2) chronic insomniacs with high baseline sleep reactivity ($n=54$); (3) acute insomniacs with low baseline reactivity ($n=29$); and (4) acute insomniacs with high baseline reactivity ($n=79$). As these groups resulted in modestly sized subsamples (as low as $n=10$) which are at risk for being under-powered, one-tailed paired t-tests consistent with *a priori* hypotheses were used. Analyses revealed that both acute and chronic insomniacs with low baseline reactivity reported significant increases in sleep reactivity from Year 0 to Year 2, which corresponded to medium-large to large effects (see Table 4 for full results). In contrast, neither high baseline sleep reactivity groups reported increases in sleep reactivity from baseline to 2-y follow-up.

3.5 Impact of sleep system sensitization on depression and anxiety at Years 1 and 2

Finally, using linear regression, we tested whether severity of depression and anxiety at 1-y and 2-y follow-ups were associated with changes in sleep reactivity. First, we estimated depression symptoms at Year 1 as predicted by age, gender, baseline depression, premorbid sleep reactivity, and changes in FIRST scores from baseline to Year 1 ($FIRST_{Y1-Y0}$; see

Table 5 for full results). The overall model was significant ($p < .001$) and the aggregated effects of the predictors accounted for 30% of the variance in self-reported depression at 1-y follow-up. Results revealed that increases in FIRST scores were independently related to depression ($b = .20$, $p < .001$), such that greater sensitization of the sleep system was associated with more severe depression at the onset of insomnia in Year 1. Notably, premorbid sleep reactivity total scores did not predict follow-up depression in this sample. Baseline depression ($b = .53$, $p < .001$) was shown to be a significant covariate in the model, whereas gender ($p = .82$) and age ($p = .92$) were not. To test the stability of the effect of sleep sensitization on depressive symptoms, we predicted depression severity at Year 2 using the above predictors. Results supported stability of the effect such that increases in FIRST scores predicted greater depression symptoms at 2-y follow-up ($b = .15$, $p = .01$). Baseline ratings of depression ($b = .49$, $p < .001$) and sleep reactivity ($b = .23$, $p < .01$) were significant covariates, whereas age and gender remained non-significant.

Lastly, we estimated anxiety symptoms at Year 1 as predicted by age, gender, baseline anxiety, premorbid sleep reactivity, and changes in FIRST scores from baseline to Year 1 (see Table 5 for full results). The overall model was significant ($p < .001$) and the aggregated effects of the predictors accounted for 33% of the variance in self-reported anxiety at 1-y follow-up. Changes in FIRST scores were independently related to anxiety ($b = .45$, $p < .001$), such that increased sensitivity of the sleep system was associated with greater anxiety at insomnia onset at Year 1. Consistent with the depression model, premorbid sleep reactivity did not predict anxiety at 1-y follow-up. Baseline anxiety ($b = .56$, $p < .001$) was shown to be a significant covariate in the model, whereas gender ($p = .17$) and age ($p = .20$) were not. To test the stability of this effect, we predicted anxiety severity at Year 2 using the above predictors. Unlike the depression model, results did not support an enduring effect of sleep sensitization on anxiety as changes in FIRST scores were not associated with anxiety at 2-y follow-up ($p = .29$). Baseline anxiety ($b = .52$, $p < .001$) and sleep reactivity ($b = .29$, $p = .03$) were significant covariates, whereas age and gender remained non-significant.

4. Discussion

This investigation sought to describe changes in sensitivity of the sleep system that accompany insomnia onset. Findings showed that sleep reactivity substantially increases with the development of insomnia in individuals with low levels of this premorbid vulnerability. Importantly, exposure to major life stress served to kindle this sensitization process. Sleep system sensitization was also shown to be associated with greater severity of depression and anxiety during insomnia. Notably, these heightened levels of sleep reactivity persisted to 2-y follow-up among individuals with low premorbid reactivity, irrespective of remission status. Together, these findings offer strong empirical support for sleep system sensitization in response to insomnia development and major life stress in individuals without this premorbid vulnerability.

Results revealed a large sensitization effect on the sleep system in individuals with low premorbid sleep reactivity. Moreover, stress exposure leading up to insomnia development was associated with amplification of the sensitization process. Among subjects with low premorbid sleep reactivity, over two-thirds developed high sleep reactivity after insomnia

onset. These findings mirror stress sensitization models of depression recurrence and chronicity^{12, 13, 35} showing increases in cognitive and neurobiologic vulnerability to depression as a function of disease exposure, and that this sensitization process is most profound in individuals with low premorbid susceptibility. Borrowing terminology from the depression literature, individuals with high premorbid insomnia-risk may be considered *pre-kindled*. In comparison, individuals without these premorbid, typically inherited, vulnerabilities appear to undergo a sensitization or kindling process in response to the development of insomnia and exposure to stress. Consistent with this interpretation, maternal history of insomnia has been shown to be a robust risk factor for insomnia.^{7, 21} In the present study, we found that insomniacs with low premorbid sleep reactivity reported lower rates of known maternal insomnia than subjects with high premorbid sleep reactivity (28.9% vs 58.9%). This difference in maternal history may reflect individuals with low premorbid sleep reactivity carrying less inherited risk or genetic load for insomnia, thus highlighting the etiological heterogeneity of insomnia.

In a recent review of insomnia, stress exposure, and gene expression, Palagini and colleagues⁸ highlighted the impact of stress on epigenetics and stress-related brain plasticity. They posited that insomnia itself serves as a stressor, and that the disorder may perpetuate its course through neurobiologic changes in systems that modulate stress-response and sleep regulation. Should major life stress and insomnia profoundly impact gene expression and neurobiologic circuitry, it would behoove future investigators to characterize the genetic and neurobiologic bases of sleep reactivity and investigate whether alterations in these systems correspond to phenotypic changes in sleep reactivity.

Interpreting our study results in the context of prior investigations of premorbid vulnerabilities for chronic insomnia,^{7, 21} the data support the existence of two pathways to chronic or recurrent insomnia. First, certain individuals carry endogenous premorbid vulnerabilities to insomnia and are thus at risk for chronic or recurrent insomnia prior to ever developing the disorder, i.e., *pre-kindled* individuals.^{7, 21} Second, other individuals may not have these risk factors prior to insomnia onset, but rather begin to develop these phenotypic susceptibilities peri, or even post, morbidly. These alternate pathways to insomnia chronicity/recurrence highlight the importance of not only identifying premorbid vulnerabilities, but also capturing the evolving roles of etiological factors. Furthermore, the separate pathways open alternative explanations for insomnia biomarkers. For instance, functional neuroimaging has shown insufficient abatement of arousal mechanisms when transitioning from wakefulness to sleep in insomniacs.³⁶ However, the degree to which this deficient down-regulation of wake promoting areas of the brain exist premorbidly versus develop as a consequence of insomnia disorder is unclear.

Demonstrating a sensitization process necessitates ruling out a purely state-dependent effect. That is, changes in sleep reactivity that are entirely reliant on insomnia status would merely represent insomnia-related fluctuations in sleep reactivity, rather than a sensitization process. Overall, findings supported sleep system sensitization, though results also indicated that ratings of sleep reactivity were modestly influenced by insomnia status/remission. Importantly, subjects with low premorbid risk reported medium-large to large increases in sleep reactivity at 2-y follow-up compared to initial assessment, and these increases in sleep

reactivity were found in both chronic insomniacs and individuals whose insomnia remitted. As sleep reactivity ratings did not return to premorbid levels after insomnia remission, these findings demonstrate a scarring effect on the sleep system as a consequence of exposure to insomnia.

We lastly observed that sleep system sensitization was associated with greater severity of depression and anxiety. These findings are perhaps most intriguing as this study failed to demonstrate a direct relationship between premorbid sleep reactivity and depression or anxiety. Indeed, past studies on sleep reactivity and psychopathology have shown that the effects of sleep reactivity on depression and anxiety are largely mediated by the development of sleep disorders such as insomnia² and shift work disorder.¹⁹ Prior research has shown that ratings of cognitive-emotional hyperarousal—including arousability, pre-sleep cognitive arousal, ruminative and emotion-focused coping styles—are strongly related to sleep reactivity.^{14, 20} Given the close relationship between cognitive-emotional hyperarousal and sleep reactivity, coupled with evidence supporting heritability between these separate disease risk factors,²³ these phenotypic traits represent overlapping vulnerabilities to insomnia, anxiety, and depression. By extension, insomnia-related sensitization effects may not be specific to the sleep system. That is, heightened cognitive-emotional hyperarousal may accompany sensitization of the sleep system, which is consistent with the observed impact of sleep system sensitization on depression and anxiety in our study. Though individuals with low sleep reactivity may not be at elevated premorbid risk for developing depression and anxiety, their vulnerability to these disorders appears to increase substantially when the sleep system becomes sensitized.

We believe the present study adds to the literature on insomnia risk, recurrence, and chronicity, but must be interpreted in the context of some methodological limitations. Though higher sleep reactivity corresponds to elevated risk for future insomnia, we were unable to directly test the relationship between sleep system sensitization and subsequent insomnia episodes. Future prospective studies with longer duration and more waves of data collection are needed to test this risk relationship. Second, regression to the mean was considered among low reactive sleepers. Notably, we observed that unaffected subjects did not demonstrate a significant increase in sleep reactivity across the study (footnote 1 in Results). Further, low reactive sleepers who were insomnia-free at Years 0 and 1 reported increased sleep reactivity with insomnia development at Year 2.² Though we cannot entirely rule out regression to the mean having any impact on our data, we believe our findings are more consistent with a meaningful increase in sleep reactivity coinciding with insomnia onset. Similarly, though at no time point was any insomnia group mean within 2 SDs of the maximum possible score on the FIRST, we cannot rule out a ceiling effect of sleep reactivity scores in the high sleep reactivity group. Future investigators may consider augmenting self-reported sleep reactivity with measurements of elicited sleep disturbance, e.g., in response to controlled caffeine administration, circadian misalignment, or some other manipulated sleep challenge, as pre and post indicators of sleep system sensitivity for a more rigorous test of the sensitization process.

²($t=2.71$, $p=.01$)

4.1 Conclusions

The present study provides evidence for changing roles of etiological factors in insomnia. Specifically, we found that exposure to major life stress and insomnia development lead to increases in the sensitivity of the sleep system in individuals without this premorbid vulnerability. Harmful effects of sleep system sensitization may extend beyond risk for future insomnia, and may result in increased vulnerability to insomnia-related depression and anxiety.

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Highlights

- We studied 262 good sleepers who developed insomnia at 1-y follow-up.
- For low risk individuals, developing insomnia *sensitizes* the sleep system.
- Exposure to major life stress amplifies this sensitization process.
- Sleep system sensitivity does not return to baseline after remission.

Table 1

Sample characteristics at baseline for the full sample, acute insomniacs, and chronic insomniacs.

	Full Sample n=262	Acute Insomnia at Y1 only n=108	Chronic Insomnia at Y1 and Y2 n=64
Age M±SD, range	44.0±13.4, 18-65	44.5±13.7, 18-65	42.7±12.8, 18-64
Female (n, %)	177, 67.6%	75 female; 69.4%	64 female; 68.8%
Ethnicity (n, %)*			
White	167, 63.7%	74; 68.5%	37; 57.8%
Black	74, 28.2%	27; 25.0%	23; 35.9%
Asian or Pacific Islander	7, 2.7%	1; 0.9%	1; 1.6%
Hispanic or Latino	4, 1.5%	2; 1.9%	1; 1.6%
Middle Eastern or Indian	5, 1.9%	2; 1.9%	1; 1.6%
Other	4, 1.5%	2; 1.9%	1; 1.6%
Stress exposure M±SD	2.6±2.2	2.3±2.0	2.8±2.3
FIRST scores M±SD	18.9±4.3	18.4±4.1	20.2±4.4
Highly reactive (FIRST 16; n, %)	202, 77.1%	79, 73.1%	54, 84.4%
Maternal history of insomnia (n, %)	70/133, 52.6%; 79 missing	39/72 (54.2%); 36 missing	23/44 (52.3%); 20 missing

Notes: 'No insomnia' = never met criteria for insomnia. 'Acute insomnia' = met criteria for insomnia at Year 1 *or* 2. 'Chronic insomnia' = met criteria for insomnia at Years 1 *and* 2.

FIRST = Ford Insomnia Response to Stress Test.

* Due to rounding, percentages do not equal 100.0% for the 'Acute Insomnia' or 'Chronic Insomnia' groups. Stress exposure measured using a count of the number of events endorsed on the Social Readjustment Rating Scale-Revised between Years 0 and 1.

Table 2

Sleep system sensitization from Y0 to Y1.

	FIRST scores at Year 0 (M±SD)	FIRST scores at Year 1 (M±SD)	FIRST
Full sample (n=262)	18.88±4.31	19.85±4.55	+0.97±4.48; t=3.50, p<.01, Cohen's d=0.22
Low baseline reactivity (n=60)	13.35±1.60	17.17±4.01	+3.82±4.07; t=7.26, p<.001, Cohen's d=1.05
High baseline reactivity (n=202)	20.52±3.43	20.65±4.40	+0.12±4.25; t=0.41, p=.68

Notes: FIRST = Ford Insomnia Response to Stress Test. FIRST 16 indicates high sleep reactivity.

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Table 3

Changes in sleep system sensitivity from Y1 to Y2.

	FIRST scores at Year 1 (M±SD)	FIRST scores at Year 2 (M±SD)	FIRST
Chronic insomniacs (n=64)	20.89±5.10	20.52±5.34	-0.38±4.92; t=-0.61, p=.54
Acute/Remitting insomniacs (n=108)	19.20±4.17	18.07±4.66	-1.13±4.51; t=-2.72, p<.01, Cohen's d=.25

Notes: FIRST = Ford Insomnia Response to Stress Test. FIRST 16 indicates high sleep reactivity.

Table 4

Overall sleep system sensitization trends from Y0 to Y2 based on insomnia course and premorbid sleep reactivity.

	FIRST scores at Year 0 (M±SD)	FIRST scores at Year 2 (M±SD)	FIRST
Chronic insomnia, low reactivity (n=10)	13.70±1.57	16.70±5.33	+3.00±5.23; t=1.81, p=.05, Cohen's d=.69
Chronic insomnia, high reactivity (n=54)	21.35±3.69	21.22±5.08	-0.13±4.91; t=-0.19, p=.85
Acute insomnia, low reactivity (n=29)	13.21±1.63	15.66±4.65	+2.45±4.25; t=3.10, p<.01, Cohen's d=.72
Acute insomnia, high reactivity (n=79)	20.27±2.90	19.00±4.30	-1.27±4.01; t=-2.77, p=NS

Notes: FIRST = Ford Insomnia Response to Stress Test. FIRST 16 indicates high sleep reactivity. p-values correspond to one-way significance threshold based on a *priori* hypotheses. NS = not significant.

Table 5

Changes in depression and anxiety associated with baseline sleep reactivity and sleep system sensitization.

Outcome	Model significance, effect size	Predictors	b	pr	t	p
Depression at Year 1	F=23.23, p<.001, adj R ² =.30					
		Age	.00	-.01	-.01	.92
		Gender	.10	--	.22	.82
		Depression at Y0	.53	.50	9.24	<.001
		FIRST at Y0	.08	.09	1.46	.15
		FIRST _{Y1-Y0}	.20	.24	3.88	<.001
Depression at Year 2	F=18.64, p<.001, adj R ² =.34					
		Age	-.04	-.15	-1.91	.06
		Gender	-.45	--	-.83	.41
		Depression at Y0	.49	.48	7.09	<.001
		FIRST at Y0	.23	.25	3.36	<.01
		FIRST _{Y1-Y0}	.15	.19	2.51	.01
Anxiety at Year 1	F=26.80, p<.001, adj R ² =.33					
		Age	-.04	-.08	-1.29	.20
		Gender	1.25	--	1.39	.17
		Anxiety at Y0	.56	.52	9.67	<.001
		FIRST at Y0	.18	.10	1.58	.12
		FIRST _{Y1-Y0}	.45	.26	4.31	<.001
Anxiety at Year 2	F=15.91, p<.001, adj R ² =.30					
		Age	-.05	-.09	-1.22	.22
		Gender	.82	--	.76	.45
		Anxiety at Y0	.52	.49	7.24	<.001
		FIRST at Y0	.29	.17	2.19	.03
		FIRST _{Y1-Y0}	.13	.08	1.07	.29

Note: F = F-ratio for overall regression model. p = significance value. adj R² = adjusted R². b = unstandardized beta coefficient. pr = partial correlation. t = t-value for the corresponding predictor. Depression measured using the Quick Inventory of Depressive Symptomatology. Anxiety measured using the Beck Anxiety Inventory. FIRST = Ford Insomnia Response to Stress Test. FIRST_{Y1-Y0} = Changes in FIRST scores from Year 0 to Year 1.