

Impact of Sleep Quality on Amygdala Reactivity, Negative Affect, and Perceived Stress

ARIC A. PRATHER, PhD, RYAN BOGDAN, PhD, AND AHMAD R. HARIRI, PhD

Objective: Research demonstrates a negative impact of sleep disturbance on mood and affect; however, the biological mechanisms mediating these links are poorly understood. Amygdala reactivity to negative stimuli has emerged as one potential pathway. Here, we investigate the influence of self-reported sleep quality on associations between threat-related amygdala reactivity and measures of negative affect and perceived stress. **Methods:** Analyses on data from 299 participants (125 men, 50.5% white, mean [standard deviation] age = 19.6 [1.3] years) who completed the Duke Neurogenetics Study were conducted. Participants completed several self-report measures of negative affect and perceived stress. Threat-related (i.e., angry and fearful facial expressions) amygdala reactivity was assayed using blood oxygen level-dependent functional magnetic resonance imaging. Global sleep quality was assessed using the Pittsburgh Sleep Quality Index. **Results:** Amygdala reactivity to fearful facial expressions predicted greater depressive symptoms and higher perceived stress in poor (β values = 0.18–1.86, p values < .05) but not good sleepers (β values = -0.13 to -0.01, p values > .05). In sex-specific analyses, men reporting poorer global sleep quality showed a significant association between amygdala reactivity and levels of depression and perceived stress (β values = 0.29–0.44, p values < .05). In contrast, no significant associations were observed in men reporting good global sleep quality or in women, irrespective of sleep quality. **Conclusions:** This study provides novel evidence that self-reported sleep quality moderates the relationships between amygdala reactivity, negative affect, and perceived stress, particularly among men. **Key words:** sleep, amygdala, stress, depression, negative affect.

DNS = Duke Neurogenetics Study; **BOLD fMRI** = blood oxygen level-dependent functional magnetic resonance imaging; **DSM-IV** = Diagnostic and Statistical Manual for Mental Disorders; Fourth Edition; **SCID** = Structured Clinical Interview for DSM Disorders; **PSQI** = Pittsburgh Sleep Quality Index; **PSS** = Perceived Stress Scale; **CES-D** = Center for Epidemiologic Depression Scale; **MASQ** = Mood and Anxiety Symptom Questionnaire.

INTRODUCTION

Sleep disturbance is a key behavioral risk factor for several medical illnesses including cardiovascular disease (1–4) and diabetes (5,6) and is implicated in the pathogenesis of psychopathology, most prominently mood (7–11) and anxiety disorders (12–15). For instance, prospective studies find poor sleep to be a significant and independent contributor to major depressive disorder (8,10) and a common residual symptom upon remission (16). How sleep affects health and, in particular, psychopathology risk remains unclear; however, recent experimental evidence points to enhanced sensitivity to stressful or negative emotional stimuli.

Laboratory-based studies demonstrate that inadequate sleep and daytime sleepiness are associated with increased stress sensitivity and self-reported negative emotions (17), dampened positive affect (18), and greater physiological reactivity to negative or stressful stimuli (19–21). Moreover, early indications

suggest that these associations extend beyond the laboratory setting. For example, in a study of police officers, those who screened positive for sleep disorders were more likely to endorse uncontrolled anger toward a suspect than officers free of sleep disorders (22).

Despite the demonstrated relationships between sleep, stress, and negative affect, little is known about the biological mechanisms underlying these associations. In a seminal study, Yoo and colleagues (21) demonstrated that compared with healthy, normal sleepers, those experiencing a single night of sleep deprivation exhibited exaggerated amygdala reactivity to negative emotional stimuli. This finding is particularly striking given the critical importance of the amygdala in mediating both physiological and behavioral responsiveness to threat and stress. However, such extreme forms of sleep deprivation are rare, and most individuals experience milder disturbances in sleep quality. Thus, the relevance of potentiated amygdala reactivity to more commonly observed links between poor sleep quality, mood, affect, and stress sensitivity remains unclear.

The links between sleep, negative affect, and amygdala reactivity may be further complicated by sex differences. Indeed, there are well-characterized sex disparities in psychopathology risk (23–25), which may, in part, be mediated by differences in emotional processing and related neural mechanisms including amygdala reactivity (reviewed in Stevens and Hamann (26)). Furthermore, men and women differ on sleep measures, with women generally reporting poorer subjective sleep quality (27,28) and men exhibiting shorter sleep duration and poor sleep continuity measured objectively (29,30). The extent to which sex moderates the complex associations between amygdala reactivity, sleep, and negative affect has not been investigated.

The aims of the present study were as follows: a) to examine whether threat-related amygdala reactivity covaries with symptoms of perceived psychological stress, depression, and anxiety in a sample of young, healthy volunteers and b) to test whether sleep quality moderates these associations. On the

From the Department of Psychiatry (A.A.P.) and The Robert Wood Johnson Foundation Health and Society Scholars Program (A.A.P.), University of California, San Francisco, and University of California, Berkeley, California; BRAIN Lab, Department of Psychology (R.B.), Washington University in St. Louis, St. Louis, Missouri; and Laboratory of NeuroGenetics, Department of Psychology and Neuroscience, Institute for Genome Sciences and Policy (R.B., A.R.H.), Duke University, Durham, North Carolina.

Address correspondence and reprint requests to Aric A. Prather, PhD, Center for Health and Community, University of California, San Francisco, 3333 California St., Suite 465, San Francisco, CA 94118. E-mail: prathera@chc.ucsf.edu

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basis of the existing evidence, we hypothesized that greater threat-related amygdala reactivity would positively associate with measures of negative affect and perceived stress. Moreover, we hypothesized that these associations would be stronger among individuals reporting poorer sleep quality. Finally, given the emergent evidence for sex differences, particularly with regard to amygdala reactivity (26), we also examined the potential moderating role of sex in these associations as part of exploratory analyses.

METHODS

Participants

Three hundred fifty participants (141 men, 48% white, mean [M; standard deviation {SD}] age = 19.6 [1.3] years) were recruited for the Duke Neurogenetics Study (DNS), an ongoing protocol investigating the neurogenetic pathways of variation in human behavior among 18- to 22-year-old college students. The focus of the DNS on this population reflects our primary interests in mapping biological pathways that interact with experiential factors to predict psychopathology typically emerging in young adulthood such as substance use and abuse (31). However, as is clear in our current report, many other aspects of behavior and physiology vary significantly in this population, allowing the DNS to usefully inform questions that may be of greater clinical relevance in other populations.

The data contained in this article were collected between January 2010 and November 2011; the study is currently ongoing. Participants qualified for the DNS if they were free of the following study exclusions: a) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; b) use of psychotropic, glucocorticoid, or hypolipidemic medication; and c) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Diagnosis of any current Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) Axis I disorder (32) was not an exclusion criterion because the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology (e.g., impulsivity, aggression, and anxiety)¹. All participants provided informed consent in accord with Duke University Medical Center guidelines and were in good general health and free of study exclusions.

Participants enrolled in the DNS complete 3 separate sessions, most occurred within a 1-month period (M [SD] number of days to complete all 3 sessions = 17.96 [17.43]). In the first session, a doctorate-level clinician or trained and supervised research assistant administers the Mini-International Neuropsychiatric Interview to assess the presence of Axis I psychopathology, the structured clinical interview for DSM-IV-II to assess whether borderline personality disorder or antisocial personality disorder are present, and a neuropsychological assessment battery. In the second session, participants complete a host of computerized self-report measures assessing mood, anxiety, substance use, and a host of personality characteristics. In the third session, neuroimaging data including structural and functional magnetic resonance imaging (MRI) are collected. All participants were instructed to refrain from drinking caffeinated drinks at least 2 hours before their scheduled scan, and all scans were randomly collected between the hours of 8 AM and 7 PM Eastern Standard Time.

Of the 350 participants completing the DNS, data from 299 were available for our analyses (Table 1). Participants were excluded from analyses because of the following: a) incidental structural brain abnormalities ($n = 3$), b) significant movement outliers in functional MRI (fMRI) data ($n = 5$; see the Artifact detection Tool [ART] description below), c) inadequate signal in regions of interest ($n = 4$; see description of procedure below), d) scanner artifacts in fMRI data ($n = 2$), e) technical difficulties during fMRI data collection ($n = 1$), and f) poor behavioral performance (i.e., <75% accuracy:

TABLE 1. Sociodemographic and Psychosocial Characteristics of the Study Sample ($n = 299$)

Variable	M (SD) or Percentage
Age, y	19.6 (1.3)
Sex (% female)	58.0
Race (% European)	50.3
Perceived psychological stress score	14.8 (6.0)
Depressive symptoms	
CES-D score	10.4 (8.2)
MASQ _{depression}	21.3 (8.2)
MASQ _{anhedonia}	52.6 (12.9)
Anxiety symptoms	
MASQ _{anxiety}	17.4 (5.1)
MASQ _{anxious arousal}	21.2 (5.5)
PSQI global sleep quality	4.8 (2.3)

M = mean; SD = standard deviation; CES-D = Center for Epidemiologic Depression Scale; MASQ = Mood and Anxiety Symptom Questionnaire; PSQI = Pittsburgh Sleep Quality Index.

$n = 35$). In addition, inspection of the data revealed inclusion of an extreme outlier (>5 standard deviations above the mean on our measures of negative affect); as such, this participant ($n = 1$) was excluded from analyses. Excluding this extreme outlier, no significant group differences (p values > .10) were observed on any sociodemographic characteristic or psychosocial measure between participants included and excluded in the present study.

Amygdala Reactivity Paradigm

Our fMRI challenge paradigm has been used extensively to elicit a robust and replicable amygdala response across an array of experimental protocols and sample populations (33–39). The experimental fMRI paradigm consisted of four blocks of a perceptual face-matching task interleaved with five blocks of a sensorimotor control task. The DNS version of this paradigm consists of one block each of fearful, angry, surprised, and neutral facial expressions presented in a pseudorandom order across participants. Here we focus our analyses on amygdala reactivity to anger and fear because each represents a canonical threat stimulus (40). Anger represents an explicit threat to the viewer, whereas fear represents an implicit threat somewhere in the environment. Moreover, both anger and fear represent conditioned stimuli, which have predicted measures of negative affect in prior research (41).

During face-matching blocks, participants view a trio of faces and select one of two faces (on the bottom) identical to a target face (on the top). Each face processing block consists of six images, balanced for sex, all of which were derived from a standard set of pictures of facial affect (42). During the sensorimotor control blocks, participants view a trio of simple geometric shapes (circles and vertical and horizontal ellipses) and select one of two shapes (bottom) that are identical to a target shape (top). Each sensorimotor control block consists of six different shape trios. All blocks are preceded by a brief instruction (“Match Faces” or “Match Shapes”) that lasts 2 seconds.

In the task blocks, each of the six face trios is presented for 4 seconds with a variable interstimulus interval (ISI) of 2 to 6 seconds (M = 4 seconds), for a total block length of 48 seconds. A variable ISI is used to minimize expectancy effects and resulting habituation and maximize amygdala reactivity throughout the paradigm. In the control blocks, each of the six shape trios is presented for 4 seconds with a fixed ISI of 2 seconds, for a total block length of 36 seconds. Total task time is 390 seconds.

Blood Oxygen Level-Dependent Functional fMRI Data Acquisition

Each participant was scanned using a research-dedicated GE MR750 3T scanner at the Duke-UNC Brain Imaging and Analysis Center. This scanner is equipped with high-power, high-duty-cycle 50-mT/m gradients at a slew rate

¹Fifty-six (18.7%) of the 299 participants included in this study met the diagnostic criteria for a DSM Axis I or Axis II diagnosis. Findings reported in this study remain unchanged when diagnostic status (present versus absent) is included as a covariate in statistical models.

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of 200 T m⁻¹ s⁻¹, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz. A semiautomated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure–posterior commissure were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact (repetition time/echo time/flip angle = 2000 ms/30 ms/60; Field of View = 240 mm; 3.75 × 3.75 × 4-mm voxels; interslice skip = 0). Four initial radio frequency excitations were performed (and discarded) to achieve steady-state equilibrium. High-resolution structural images coplanar to the functional slices were acquired to facilitate spatial registration of each participant's data to a standard coordinate system.

Blood Oxygen Level–Dependent Functional fMRI

Data Preprocessing

Preprocessing was conducted using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images for each participant were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotaxic space (Montreal Neurological Institute template) using a 12-parameter affine model (final resolution of functional images, 2-mm isotropic voxels), and smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter set at 6-mm full width at half maximum. Next, the ART (http://www.nitrc.org/projects/artifact_detect) (43) was used to generate regressors accounting for the possible confounding effects of volumes with large motion deflections. Specifically, individual whole-brain blood oxygen level–dependent functional (BOLD) fMRI volumes varying significantly from mean-volume signal intensity variation (i.e., within volume mean signal of ≥ 4 SDs of mean signal of all volumes in time series), or individual volumes where scan-to-scan movement exceeded 2-mm translation or 2° rotation in any direction were assigned a lower weight in analyses. Five participants who had more than 5% of their acquisition volumes flagged by ART were dropped from further analyses.

After preprocessing, linear contrasts using canonical hemodynamic response functions were used to estimate expression-specific (i.e., fear > shapes, angry > shapes) BOLD responses for each individual. These individual contrast images (i.e., weighted sum of the beta images) were then used in second-level random-effects models to determine mean expression-specific neural reactivity using one-sample *t* tests. A voxel-level statistical threshold of $p < .05$, Family Wise Error corrected for multiple comparisons across the entire search volume, and a cluster-level extent threshold of 10 contiguous voxels were applied within bilateral amygdala regions of interest (ROIs) defined using the Automated Anatomical Labeling atlas (44) through the WFU Pickatlas tool in SPM8. Because of the potential for signal loss and noise often observed in the amygdala and adjacent regions, single-subject BOLD fMRI data were included in subsequent analyses only if there was a minimum of 90% signal coverage in the amygdala ROIs. Four participants had less than 90% coverage and were dropped from analyses.

BOLD parameter estimates exhibiting a main effect of expression (e.g., fearful faces > shapes) were extracted from functional clusters within the left and right amygdala using the Volume of Interest tool in SPM8. In addition to producing the necessary values for our hypothesis testing, extracting parameter estimates from functional clusters activated by our fMRI paradigm rather than clusters specifically correlated with our independent variables of interest precludes the possibility of any correlation coefficient inflation that may result when an explanatory covariate is used to select a ROI (45). We have used this more conservative and rigorous analytic strategy in recent studies (46–49).

Self-Reported Sleep Quality

Self-reported global sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (50). The PSQI is a widely used and reliable measure of global sleep quality and sleep-related symptoms over the past 1 month. The 19 items yield 7 component scores that reflect the frequency of sleep problems in the following areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The components are summed to yield a global score that ranges from 0 to 21, with poorer sleep quality associated with a higher score.

A PSQI global score of above 5 has routinely been used to distinguish “poor” from “good” sleepers (50).

Perceived Psychological Stress

The Perceived Stress Scale (PSS) (51) instructs participants to appraise how unpredictable, uncontrollable, and stressful their daily life was in the preceding week. It was selected because it is a widely used and well-validated measure of stress perception; it is heritable and has been linked to stress hormones, illness, and physiological stress responsiveness (51–53).

Depressive and Anxiety Symptoms

The Mood and Anxiety Symptom Questionnaire (MASQ) (54) is a well-validated measure of anxiety and depressive symptoms; it yields four subscales assessing symptoms specific to anxiety (Anxious Arousal [MASQ_{AA}]) or depression (Anhedonic Depression [MASQ_{AD}]) as well as nonspecific depression and anxiety-related symptoms (General Distress Anxiety [MASQ_{GDA}] and General Distress Depression [MASQ_{GDD}]).

The 20-item Center for Epidemiologic Depression Scale (CES-D) (55) was used to assess depressive symptoms over the past week. The CES-D is widely used and well validated for assessing depressive symptoms in the general population (55).

Data Analysis

All analyses were performed using SPSS for Macintosh (Version 18.0). Independent *t* tests and Pearson product moment correlations were used to examine associations among amygdala reactivity to fear and anger, sleep quality, and measures of negative affect. Hierarchical linear regressions were performed to assess whether expression-specific amygdala reactivity predicted measures of negative affect. To test the modifying effects of sleep quality, interaction analyses were performed according to the guidelines of Hayes and Matthes (56). Here, main effects of expression-specific amygdala reactivity, sleep quality, and the interaction terms of amygdala reactivity–sleep quality were entered into regression models predicting PSS, CES-D, MASQ_{GDD}, MASQ_{GDA}, MASQ_{AA}, and MASQ_{AD}. Sex was included as a covariate in all analyses. Simple slopes were calculated and tested for all significant interaction models.

In exploratory analyses, three-way interactions (amygdala reactivity × sleep quality × sex) were computed. To this end, expression-specific amygdala reactivity, sleep quality, and sex were entered in the first step of a hierarchical linear regression, followed by all two-way interactions in the second step. The three-way interactions were entered in the third step. Simple slopes stratified by sex were calculated and tested for significant three-way interactions.

RESULTS

Threat-Related Amygdala Reactivity and Negative Affect

Sociodemographic and psychosocial characteristics for this sample are provided in Table 1. Consistent with prior reports (57), there was robust bilateral threat-related (i.e., fear and anger) amygdala reactivity within our anatomically defined ROIs (Fig. 1). Adjusting for sex, right amygdala reactivity to fear was modestly associated with depressive symptoms (CES-D: $r = 0.10$, $p = .09$; MASQ_{GDD}: $r = 0.10$, $p = .09$) but not perceived stress (PSS: $r = 0.08$, $p = .16$), measures of anhedonic depression ($r = 0.06$, $p = .31$) or anxiety (MASQ_{GAD}: $r = 0.06$, $p = .32$; MASQ_{AA}: $r = 0.02$, $p = .76$). Furthermore, there were no statistically significant associations between measures of negative affect and left amygdala reactivity to fear (r values ranged from 0.01 to 0.05, p values > .35) or right and left amygdala reactivity to anger (r values ranged from -0.03 to 0.07, p values > .20).

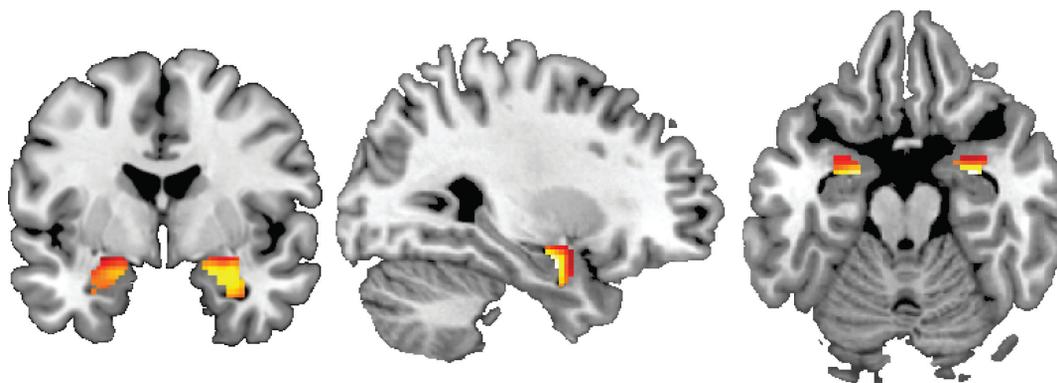


Figure 1. Mean bilateral amygdala reactivity to fearful facial expressions ($n = 299$). Statistical parametric map illustrating bilateral amygdala reactivity for the contrast “fearful facial expressions > shapes” overlaid onto a canonical structural brain images in the coronal ($y = -2$), sagittal ($x = 28$), and axial ($z = -20$) planes. Montreal Neurological Institute template coordinates and statistics for the max voxel are as follows: $x = 28, y = -4, z = -20$ [$p < .001$, cluster size = 200], and $x = -22, y = -6, z = -18$ ($p < .001$, cluster size = 168), for the right and left hemisphere, respectively.

Role of Sleep Quality

Overall poorer self-reported sleep quality, indexed by PSQI global sleep quality, was associated with higher levels of perceived stress ($r = 0.41, p < .001$), depressive symptoms (CES-D: $r = 0.45, p < .001$; MASQ_{GDD}: $r = 0.39, p < .001$; MASQ_{AD}: $r = 0.37, p < .001$), and anxiety (MASQ_{GDA}: $r = 0.33, p < .001$; MASQ_{AA}: $r = 0.29, p < .001$), but not amygdala reactivity to fear (right amygdala: $r = 0.003, p = .96$; left amygdala: $r = 0.02, p = .79$) or anger (right amygdala: $r = -0.01, p = .89$; left amygdala: $r = -0.01, p = .89$). Interaction analyses revealed that sleep quality predicted measures of depression, perceived stress, and anxiety as well as moderated associations between right and left amygdala reactivity to fear (but not anger) and measures of perceived stress and depression (Table 2).

To better understand the pattern of results, simple slopes were calculated (Table 3). As displayed in Figure 2 and Table 3, poor sleepers (i.e., those 1 SD above the mean PSQI global sleep quality score) had a significant positive relationship between amygdala reactivity and CES-D scores; no such relationship was present in good sleepers (i.e., those 1 SD below

the mean PSQI global sleep quality score). As reported in Table 3, this same pattern of results was observed in predicting MASQ_{GDD} and perceived stress scores.

Using the interaction methods described previously, we determined the approximate PSQI global sleep quality score at which associations between amygdala reactivity to fear and measures of negative affect became statistically significant. In the right amygdala, a statistically significant association with levels of perceived stress emerged at PSQI global sleep quality scores of 5.3 and higher. Significant associations with CES-D and MASQ_{GDD} emerged at scores of 4.7 and 4.8 and higher, respectively. In the left amygdala, statistically significant positive associations between reactivity and measures of perceived stress, CES-D, and MASQ_{GDD} emerged at PSQI global scores of 6.2, 6.4, and 5.4, respectively.

Sex Differences in the Moderating Effects of Sleep Quality

In secondary analyses, we investigated possible sex differences that may exist in the links mentioned previously between

TABLE 2. Interaction Analyses (Amygdala Reactivity-by-PSQI Global Sleep Quality Score) Predicting Self-Reported Measures of Negative Affect and Perceived Stress

Outcome	Fearful Facial Expressions				Angry Facial Expressions			
	Left		Right		Left		Right	
	β	p	β	p	β	p	β	p
Perceived stress	0.16	.004	0.10	.08	-0.03	.54	-0.03	.54
Depressive symptoms								
CES-D	0.14	.01	0.11	.03	-0.001	.98	-0.001	.98
MASQ _{GDD}	0.15	.007	0.13	.02	-0.07	.18	-0.07	.18
MASQ _{AD}	0.08	.14	0.05	.41	-0.04	.51	-0.04	.51
Anxiety symptoms								
MASQ _{GDA}	0.09	.13	0.02	.69	-0.05	.42	-0.05	.42
MASQ _{AA}	0.08	.17	0.04	.44	-0.02	.70	-0.38	.70

PSQI = Pittsburgh Sleep Quality Index; CES-D = Center for Epidemiologic Depression Scale; MASQ = Mood and Anxiety Symptom Questionnaire; GDD = General Distress Depression; AD = Anhedonic Depression; GDA = General Distress Anxiety; AA = Anxious Arousal. All analyses adjusted for sex.

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TABLE 3. Simple Slope Analyses Predicting the Association of Right and Left Amygdala Reactivity to Fearful Facial Expressions With Self-Reported Measures of Negative Affect and Perceived Stress at 1 SD Above (i.e., Poor Sleepers) and 1 SD Below the Mean (i.e., Good Sleepers) on PSQI Global Sleep Quality Score

Outcome	Left Amygdala				Right Amygdala			
	+1 SD PSQI		-1 SD PSQI		+1 SD PSQI		-1 SD PSQI	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Perceived stress	0.193	.02	-0.127	.07	0.184	.02	-0.012	.87
Depressive symptoms								
CES-D	0.179	.03	-0.101	.14	0.220	.004	-0.011	.88
MASQ _{GDD}	1.800	.007	-0.075	.28	1.855	.003	-0.026	.73
MASQ _{AD}	1.209	.28	-0.076	.29	1.39	.19	0.015	.85
Anxiety symptoms								
MASQ _{GDA}	0.742	.10	-0.031	.67	0.415	.32	0.036	.64
MASQ _{AA}	0.652	.19	-0.043	.56	0.363	.44	-0.026	.74

SD = standard deviation; PSQI = Pittsburgh Sleep Quality Index; CES-D = Center for Epidemiologic Depression Scale; MASQ = Mood and Anxiety Symptom Questionnaire; GDD = General Distress Depression; AD = Anhedonic Depression; GDA = General Distress Anxiety; AA = Anxious Arousal. All analyses adjusted for sex.

amygdala reactivity to fear, sleep quality, and negative affect. There were no significant sex differences in the PSQI global sleep quality score or study outcomes with two exceptions: women scored higher on the PSS (women: M [SD] = 15.3 [6.0]; men: M [SD] = 13.9 [5.7]; $t(297) = 1.97, p = .05$) and MASQ_{GDD} (women: M [SD] = 22.1 [8.3]; men: M [SD] = 20.2 [8.1]; $t(297) = 2.29, p = .01$). In addition, there were no sex differences in associations between amygdala reactivity to fear and levels of depression, anxiety, or perceived stress ($\beta_{\text{right amygdala} \times \text{sex}}$ ranged from -0.15 to 0.16, p values > .40; $\beta_{\text{left amygdala} \times \text{sex}}$ ranged from -0.20 to 1.39, p values > .40).

These secondary analyses revealed several significant three-way interactions. Specifically, there was a significant interaction (right amygdala reactivity \times sleep quality \times sex) in the prediction of CES-D scores ($\beta = -0.49, p = .004$), MASQ_{AD} ($\beta = -0.54, p = .003$), and perceived stress ($\beta = -0.48,$

$p = .006$). In the left amygdala, a three-way interaction emerged in predicting MASQ_{AD} only ($\beta = -0.40, p = .02$). Calculated simple slopes for these associations in the left and right amygdala, stratified by sex, are reported in Table 4. As illustrated in Figure 3, in men 1 SD above but not below the mean PSQI global sleep quality scores, greater right amygdala reactivity was significantly associated with higher CES-D scores.

Closer examination of the specific PSQI global sleep quality scores at which associations between amygdala reactivity and measures of negative affect become statistically significant in men revealed interesting differential effects. First, consistent with the findings reported earlier, greater right amygdala reactivity to fear was associated with higher levels of perceived stress and depressive symptoms (CES-D and MASQ_{AD}) at PSQI global sleep quality scores of 4.5, 4.8, and 6.0 or higher, respectively. However, significant inverse associations between amygdala reactivity and these measures of negative affect were also observed at low levels of PSQI global sleep quality scores (for PSS: 0.90; for CES-D: 2.5; for MASQ_{AD}: 1.8). Notably, only 16 (12.8%) of the 125 male participants had a PSQI global sleep quality score of 2 or lower. In women, there were no associations between amygdala reactivity and measures of perceived stress and depressive symptoms, irrespective of sleep quality.

Specificity Analyses: Right Visual Cortex

In an effort to test whether the reported associations between reactivity to fearful facial expressions and measures of negative affect and perceived stress were specific to the amygdala, we extracted BOLD parameter estimates from the maximally activated voxel across the entire brain volume, which was located in the right visual cortex (Montreal Neurologic Institute coordinates $x = 18, y = -86, z = -8; t = 25.38, p < .001$), and evaluated whether this interacted with PSQI global sleep quality scores to predict our outcome measures. In this regard, none of our measures of negative affect or perceived stress were predicted by an interaction between sleep quality

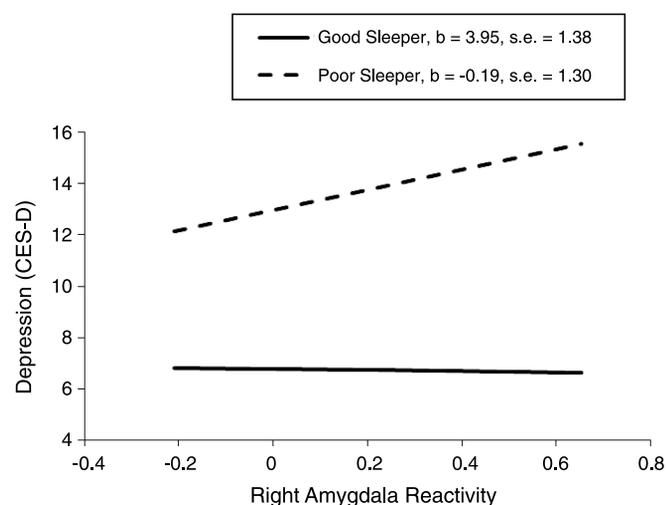


Figure 2. Self-reported sleep quality moderates the association between threat-related amygdala reactivity to fearful facial expression and CES-D depression scores. CES-D = Center for Epidemiologic Depression Scale.

TABLE 4. Simple Slope Analyses Predicting Associations of Bilateral Amygdala Reactivity to Fearful Facial Expressions With Measures of Negative Affect and Perceived Stress at 1 SD Above (i.e., Poor Sleepers) and 1 SD Below the Mean (i.e., Good Sleepers) on PSQI Global Sleep Quality Score Stratified by Sex

	Men (<i>n</i> = 125)				Women (<i>n</i> = 174)			
	+1 SD PSQI		-1 SD PSQI		+1 SD PSQI		-1 SD PSQI	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Left amygdala								
MASQ _{AD}	0.332	.03	-0.152	.15	-0.093	.34	0.011	.91
Right amygdala								
Perceived stress	0.468	.0001	-0.096	.40	-0.037	.71	0.022	.81
CES-D	0.469	.0001	-0.199	.07	0.067	.51	0.099	.29
MASQ _{AD}	0.296	.02	-0.196	.11	-0.049	.63	0.145	.12

SD = standard deviation; PSQI = Pittsburgh Sleep Quality Index; MASQ = Mood and Anxiety Symptom Questionnaire; AD = Anhedonic Depression; CES-D = Center for Epidemiologic Depression Scale.

and right visual cortex activation (PSS, $p = .62$; CES-D, $p = .65$; MASQ_{GDD}, $p = .62$; MASQ_{AD}, $p = .99$; MASQ_{GDA}, $p = .30$; MASQ_{AA}, $p = .22$).

DISCUSSION

The aim of the present study was to investigate whether normative variability in self-reported sleep quality, indexed by PSQI global sleep quality scores, moderated associations between threat-related amygdala reactivity and measures of negative affect and perceived stress. Consistent with our hypothesis, bilateral amygdala reactivity positively covaried with measures of depressive symptoms and perceived psychological stress in participants reporting poor overall sleep. In contrast, there was an absence of association between amygdala reactivity and our outcome measures among better sleepers,

suggesting that sleep quality serves as an important behavioral modulator of the neural correlates of mood, affect, and stress sensitivity. Moreover, these relationships were specific to amygdala reactivity and did not generalize to the task-elicited response of other brain regions (i.e., visual cortex).

The present findings extend prior laboratory studies demonstrating the consequence of sleep restriction on neural emotion processing (21) and stress sensitivity (17,19). Indeed after a night of total sleep deprivation, participants report increased negative mood and have heightened pupillary dilation in response to negative emotional stimuli compared with non-sleep-deprived controls (18). Unlike prior laboratory research, this is the first study to show that natural variation in a global measure of sleep quality modulates similar brain-behavior relationships. As noted, a score above 5 on the PSQI is indicative of a poor sleeper (50). Intriguingly, our analyses demonstrated that significant associations between amygdala reactivity and our measures of negative affect emerged at PSQI scores ranging from 4.7 to 6.4 and higher, suggesting that sleep quality may serve as a tipping point in linking neural threat responsiveness and corresponding affective experience.

Although our primary analyses revealed that the modulatory effects of sleep were independent of sex, sex-specific analyses found that the influence of sleep on associations between amygdala reactivity and affective measures emerged in men but not in women. Such a sex disparity is in line with an emerging set of neuroimaging studies on emotion processing (26); however, explanations for these differences are lacking. Prior research posits sex differences in emotion regulation processes (58), neural lateralization and temporal processing characteristics in emotional responsiveness (59), and sex-specific subjective reporting as potential pathways. Our findings raise the possibility that sleep, a health behavior rarely measured in neuroimaging research, may also help elucidate sex differences in future work.

How sleep influences the impact of amygdala reactivity on self-reported negative affect and perceived stress remains unclear. Zohar and colleagues (60) propose a cognitive-energy

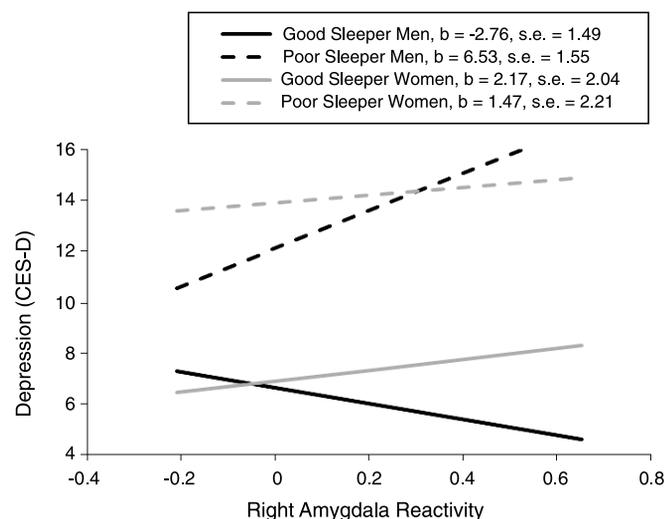


Figure 3. Amygdala reactivity to fearful facial expressions is associated with higher CES-D depression scores among men with poor self-reported sleep quality. There is no significant association between amygdala reactivity and CES-D scores among men who report good sleep quality or in women, irrespective of their self-reported sleep quality. CES-D = Center for Epidemiologic Depression Scale.

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model wherein disruptive or challenging circumstances require effortful self-regulation, leaving less energy available for behavioral regulation of emotional experience. This notion is supported by neuroimaging data showing that compared with nondeprived sleepers, participants under sleep deprivation conditions show a loss of functional connectivity between the amygdala and the medial prefrontal cortex (mPFC), which is critical for the effective regulation of amygdala reactivity and the translation of this reactivity into adaptive behavioral responses (61). Interestingly, our analyses revealed that in men who are better sleepers, there is an inverse association between amygdala reactivity and negative affect. This further suggests that poor sleep may, in fact, gate the expression of amygdala reactivity to threat as greater or lesser negative affect. A recent study reported that greater rapid eye movement sleep, which is higher in better sleepers, predicted decreased subjective emotional responsiveness to negative stimuli and a decrease in amygdala reactivity as well as an increase in amygdala-mPFC connectivity over consecutive scans (62). These authors speculate that the impact of rapid eye movement sleep on neural and behavioral responsiveness to negative emotion reflects the down-regulation of noradrenergic signaling, which is one modulator of corticolimbic circuit function, during this sleep stage. It will be interesting to explore the relationship between normative sleep quality and such amygdala habituation and amygdala-mPFC connectivity in shaping the expression of negative affect in future studies.

In addition to these potential biological and psychological mechanisms, unmeasured behavioral and social pathways may also clarify these findings. For instance, poorer sleep efficiency has been related to lower levels of perceived social support (63). Recent evidence suggests that perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety (64). In addition, poor sleep may likely cluster with other negative health behaviors (e.g., physical inactivity and poor diet) that may potentiate the amygdala-negative affect relationship.

Two unique characteristics of our observations deserve specific consideration. First, the moderating role of sleep quality was unique to the relationship between amygdala reactivity to fear and measures of negative affect and perceived stress and did not extend to amygdala reactivity to anger. This likely reflects the implicit nature of threat conveyed by fearful facial expressions, which triggers a broad increase in behavioral and physiological arousal to facilitate exploration of the local environment for the source of the threat (40). Such general changes in broad measures of arousal and negative affect are characteristic of poor sleep (65,66). In contrast, amygdala reactivity to anger results in a more focused and directed response to the immediate threat present (i.e., the person displaying the angry expression) and has been mapped onto variability in aggression and not more general negative affect (46,57,67,68).

Second, the moderating role of sleep quality was specific to the relationship between amygdala reactivity to fear and measures of depressive but not anxiety symptoms. It is unclear why we did not observe an association between amygdala reactiv-

ity and anxiety symptoms because prior studies have generally reported positive correlations (41,69–71). In this sample, sleep quality was more strongly related to measures of depressive symptoms than anxiety. This pattern may reflect the relative variability reported across measures of state negative affect in our sample. Participants reported a larger range of scores related to depressive compared with anxiety symptoms, yielding greater variance to be possibly explained in depressive symptoms by the interaction between amygdala reactivity and sleep quality. Many prior studies reporting positive correlations between amygdala reactivity and anxiety assessed variability in trait and not state anxiety, as was done with the current measures. Thus, it is possible that amygdala reactivity is more strongly linked with measures of trait anxiety but state depression. Additional work, ideally with multiple measures of state and trait negative affect, may help resolve this unexpected finding.

In summary, our study provides novel evidence that normative variability in self-reported sleep quality moderates the link between neural threat processes, negative affect, and perceived stress, particularly among men. Although the implications of this work remain to be elucidated, these findings contribute to a growing literature linking sleep disturbance with poor mental and physical health, particularly in response to stress. For instance, a recent laboratory study demonstrated that poor sleep potentiated blood pressure reactivity to a social evaluative stressor (20), which complements research linking blood pressure reactivity to heightened stress-induced activation of corticolimbic circuitry including the amygdala (72,73). Poor sleep also predicts later stress-related psychopathology, particularly depression (11), which is associated with exaggerated amygdala reactivity (74,75). Thus, further research investigating the links between sleep quality, threat-related amygdala reactivity, negative affect, and perceived stress promises to advance opportunities for intervention to prevent the progression and/or incidence of physical and mental health disability associated with poor sleep.

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