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Endogenous circadian rhythms in mood and well-being

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ABSTRACT

Objectives: We examined whether the endogenous circadian timing system modulates proxies of mood vulnerability and well-being.
Methods: Nineteen healthy participants (mean age: 26.6 years [23.0-30.2], seven females, body-mass index: 22.8 kg/m^2 [21.1-25]) completed a laboratory protocol with a 32-hour Constant Routine, a stringently controlled protocol designed to isolate assessment of endogenous circadian rhythms. We assessed hourly anxiety- and depression-like mood (i.e., those typically observed in depression and anxiety) and well-being (i.e., associated with mental fatigue and physical comfort).
Results: Significant endogenous circadian rhythms were observed in anxiety-like and depression-like mood, as well as well-being (p values from the mixed-model analysis using false discovery rates < .001). Post-hoc comparisons revealed more anxiety-like and depression-like mood during the circadian phase 60°-75° (~8–9 a.m.), and more mental fatigue and less physical comfort during the circadian phase 30°-60° (~6–8 a.m.).
Conclusions: Our data indicate endogenous circadian rhythms in anxiety-like and depression-like mood and well-being in healthy young adults. Future studies will help establish circadian-based therapeutics for individuals experiencing mood and anxiety disorders.

Introduction

Mental health conditions are increasing worldwide, such that ~20% of the global population experiences mood and/or anxiety disorders at some point in their lives.[1] Depression and anxiety are now among the 10 leading health causes of heightened mortality, disability, and morbidity, particularly among adolescents and young adults.[2] Importantly, sleep and circadian rhythm disturbances are bidirectionally intertwined with almost every category of psychiatric disorder.[3] Sleep and circadian rhythm disturbances are associated with the onset of psychiatric disorders and are among the earliest signs of relapse.[4] Hence, there is a growing interest in identifying circadian rhythms and sleep as modifiable factors associated with the onset and persistence of psychiatric disorders.

Human clinical data indicate day/night (diurnal) rhythms in symptoms of depression, with a morning worsening in positive affect levels in young adults experiencing major depressive disorder (MDD).[5] Albeit far less established, there is limited evidence for a diurnal profile in anxiety symptoms (i.e., fear and perceived threat), with a peak during the morning hours in patients with generalized anxiety disorder.[6] However, such findings collected during regular sleep/wake cycles cannot determine whether the temporal pattern is caused by the endogenous circadian system or by daily behavioral and environmental factors. Stringently controlled laboratory studies show endogenous circadian rhythms in mood constructs often associated with depression, such as positive and/or negative affect[7–10] and sadness/happiness levels,[11,12] with most studies yielding lower mood levels in the circadian morning hours. Such findings suggest that a circadian influence on mood may be contributing to the well-described diurnal mood rhythms. However, far less is known whether the circadian system modulates anxiety-like mood and well-being.[13]

Approximately 301 million people live with an anxiety disorder (~4% of the global population), including 58 million children and adolescents.[1] Hence, it is essential to unearth a potential contribution of the endogenous circadian system to these mood constructs. Here, we hypothesized that (1) anxiety-like mood, depression-like mood, and well-being have endogenous circadian rhythms independent of sleep/wake, dark/light, and fasting/eating cycles, and (2) the acrophase (time

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of the maximum) of anxiety-like mood, depression-like mood, and the nadir (time of the minimum) of well-being levels occur in the circadian morning. This study assessed anxiety- and depression-like mood (i.e., an amalgam of mood states often observed in depression and anxiety), as well as well-being (i.e., mental fatigue and physical comfort, which are negatively affected in depression and anxiety) during a stringently controlled circadian laboratory protocol.

Methods

Participants and study design

The protocol was approved by the Mass General Brigham's Institutional Review Board, performed in accordance with the principles of the Declaration of Helsinki, and participants provided written informed consent. Participants did not experience medical and psychological conditions, as assessed by clinical history, biochemical and toxicology blood and urine screenings, Minnesota Multiphasic Personality Inventory (MMPI-2), Beck Depression Inventory II (BDI-II), State-Trait Anxiety Inventory (STAI), and physical and psychological exams. Participants were nonsmokers and not taking drugs or any medications (excepting oral contraceptives), and from screening until study completion refrained from caffeine or alcohol, as assessed by urine toxicological screening. Twenty participants completed the study, and data from one participant were excluded due to their inability to fully consume all meals (for study-related characteristics, see Table 1).

Before the laboratory protocol, participants maintained a fixed, self-selected habitual bedtime with 8 hours time in bed for ∼2 weeks. We verified compliance by using actigraphy (Actiwatch, Respironics), sleep logs, and time-stamped voicemails. During the laboratory protocol, participants remained in individual laboratory suites in an environment free of time cues. Days 1-2 were laboratory adaptation days. Days 3-4 consisted of a constant routine (CR) protocol, during which participants spent 32 hours continuously awake in a constant semirecumbent body posture, at rest, in dim light (∼3 lux), and consuming hourly isocaloric snacks (Fig. S1). This allowed for the assessment of endogenous circadian rhythms of mood and well-being levels. We were, therefore, able to disentangle the relative contribution of endogenous circadian rhythms from the acute influences of sleep/wake, fasting/eating, rest/activity, and dark/light cycles. Other aspects of this study, which was designed to test separate, independent hypotheses, have previously been published.[14–16]

Table 1
Demographics and research participant characteristics assessed during screening

n	19
Age (years)	26.6 (23.0-30.2)
Sex	7 females; 12 males
Body-mass index (kg/m^2)	22.8 (21.1-25.0)
Race	2 Black; 1 Asian American; 16 White
Ethnicity	2 Hispanics; 17 non-Hispanics
Pittsburgh sleep quality index	2.1 (1.4-2.9)
Epworth sleepiness scale	4.6 (1.2-7.8)
Chronotype (Horne-Osberg)	57.8 (50.2-64.2)
Beck depression inventory	1.2 (0.1-6.1)
State-Trait Anxiety Inventory	25.2 (21.3-29.4)
Sleep onset time (hours:minutes)	23:20 ± 0:10
Wake-up time (hours:minutes)	07:20 ± 0:11
Sleep duration (hours:minutes)	07:55 ± 0:10
MMPI-2 subscales	
Hypochondriasis	47.7 (41.8-52.6)
Depression	46.2 (42.3-50.9)
Hysteria	50.5 (45.1-53.9)
Psychopathic deviate	48.0 (41.8-52.7)
Paranoia	48.4 (43.8-54.1)
Psychasthenia	48.8 (43.1-53.4)
Schizophrenia	50.1 (47.6-52.9)
Hypomania	48.6 (42.2-54.5)
Social introversion	45.1 (37.7-53.6)

MMPI, Minnesota Multiphasic Personality Inventory.
Data correspond to mean and 95% confidence intervals, except for sleep variables, which correspond to mean and standard deviation. Sleep variables, that is, sleep onset time, wake-up time, and sleep duration, were derived from actigraphy (prelaboratory study).
Race and ethnicity were self-identified.
Values were within an average score (i.e., 30-54; see MMPI-2 interpretive tables).[25]

Measures

We assessed mood perception hourly during the CR using computerized visual analog scales (VASs; for details, see Ref. 15). The VAS is a 100-mm horizontal line presented during computerized test sessions with a word at each end that represents the extremes of mood perception. Anxiety-like mood corresponds to a composite score averaged over 4 items: "Excited/Calm," "Troubled/Tranquil," "Discontented/Contented," and "Tense/Relaxed." Depression-like mood corresponds to a composite score averaged over "Happy/Sad," "Hostile/Friendly," "Irritable/Cheerful," and "Withdrawn/Sociable." Well-being was indexed by mental fatigue and physical comfort. The former corresponds to a composite score averaged over "Groggy/Clearheaded," "Mentally Slow/Quick-witted," "Dreamy/Attentive," and "Incompetent/Competent." The latter corresponds to a composite score averaged over "Weak/Strong," "Clumsy/Well coordinated," "Sluggish/Energetic," and "Cold/Warm." VAS measurements have been extensively validated in previous laboratory studies.[11–13,17] The anxiety-like and depression-like mood and the mental fatigue constructs are based on individual VAS items, where most (except for the "Happy-Sad" item) reflect negative mood-associated words on the left (0) and positive mood-associated words on the right (100). For consistency's sake, the "Happy-Sad" item was inverted to fit the aforementioned logic of the individual VAS questions. As such, anxiety-like, depression-like, and mental fatigue constructs are constructed such that lower values represent more "negative" mood, and higher values correspond to less "negative" mood (for details, see Ref. 15).

Statistical analyses

We performed statistical analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive characteristics were computed for all variables. Data were normalized using an average of each participant's levels measured throughout the CR to minimize inter-individual differences. The first 5 hours after starting the CRs were excluded from analysis, as is standard, to allow for the adjustment of outcome measures to the CR conditions. We determined endogenous circadian rhythmicity using cosinor mixed-model analyses of variance. Cosinor analyses were used to identify a "circadian effect" (a fundamental circadian component of ∼24 hours). The individual circadian period was based on the core body temperature circadian period estimate (range: 23.4-24.7 hours[18]). A "linear effect" was included in the model to account for any gradual changes across time in the CR (a proxy for sleep homeostatic effects).[12,13] Moreover, we did not test for sex differences nor for differences in menstrual phase because of the limited sample size. Participant was included as a random factor. We used post-hoc comparisons with the Tukey-Kramer test. To control the overall type I error in null hypothesis testing when conducting multiple comparisons, we adjusted p values from the cosinor mixed-model analysis using false discovery rates (pFDR). Unless specified, data are the mean and standard error of the mean. The significance for all statistical tests was set as $p < .05$.

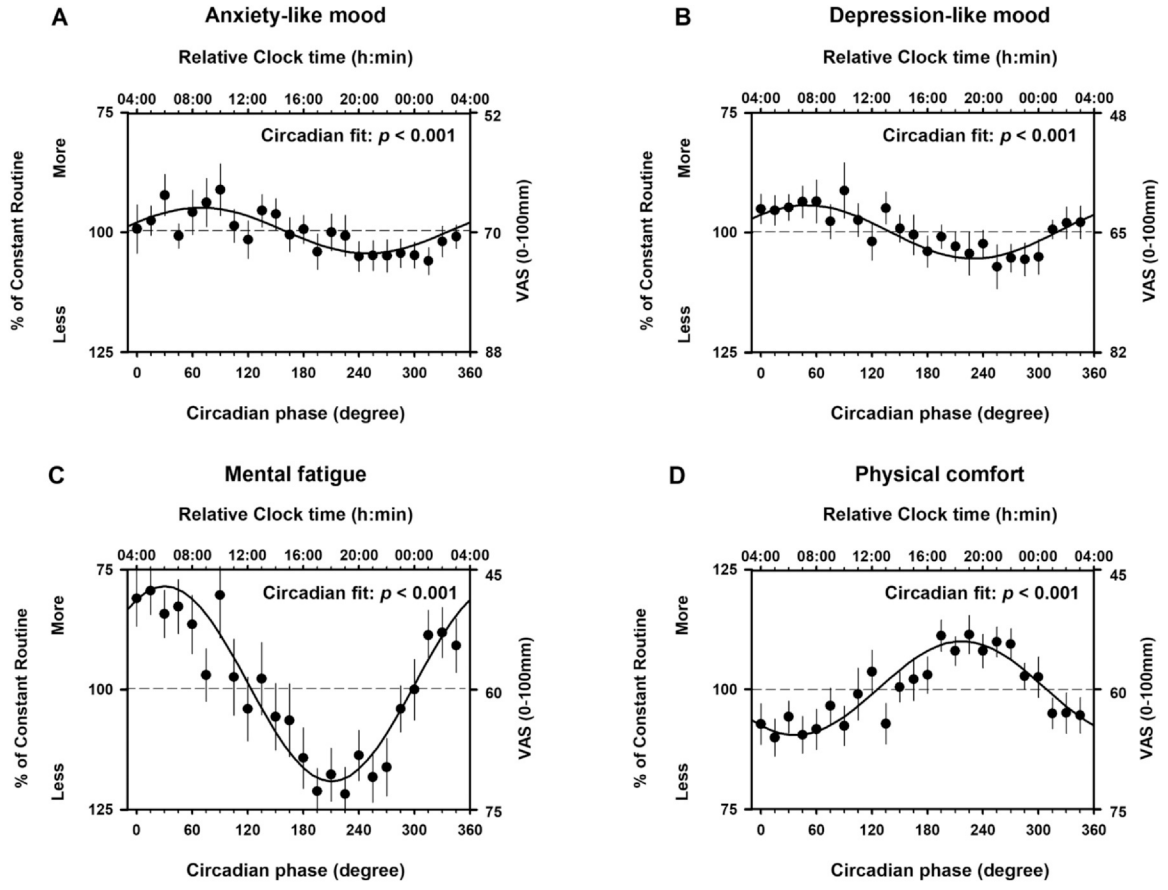

Fig. 1. Endogenous circadian rhythms in mood and well-being levels. (A) Anxiety-like- and (B) depression-like mood had significant endogenous circadian rhythms revealed during the CR. Likewise, well-being, as indexed by (C) mental fatigue and (D) physical comfort showed significant endogenous circadian rhythms during the CR protocol. In panel A, 0 means high anxiety-like mood levels and 100 means low anxiety-like mood levels. In panel B, 0 means high depression-like mood levels and 100 means low depression-like mood levels. In panel C, 0 means high mental fatigue levels and 100 means low mental fatigue. In panel D, 0 means low physical comfort and 100 means high physical comfort. The cosinor models use precise circadian phase data. To show that these models adequately fit the actual data, we also plot average data grouped into 15-circadian degree windows (~1-h resolution) with standard error of the mean error bars. Black circles correspond to detrended raw data (i.e., data presented following the removal of a linear—sleep homeostatic—component). Bottom x-axes correspond to the circadian phase with 0° indicating the timing of the fitted endogenous circadian core body temperature minimum (average ~4 a.m. in these participants). Top x-axes indicate the corresponding average clock time in these participants. Left y-axes correspond to the percentage of each individual's mean levels during the CR (i.e., we normalized the mood and well-being data using the average of each participant's levels measured throughout CR to minimize potential interindividual differences). Right y-axes indicate the VAS scores (from 0 to 100 mm). *P* values: significance of "circadian effect" derived from the cosinor mixed-model analyses.

Results

Table 1 includes the demographics and study-related characteristics of the nineteen participants (mean age: 26.6 years [95% confidence intervals, 23.0-30.2], 7 women, body-mass index, BMI: 22.8 kg/m^2 [95% confidence intervals, 21.1-25.0], 2 Black, 1 Asian American, 16 White, 2 Hispanics, and 17 non-Hispanics). Participants had Minnesota Multiphasic Personality Inventory subscale values within typical scores (ie, expected for individuals without a psychiatric disorder), and had typical scores for the BDI-II and STAI (Table 1). Based on these and an assessment by a study psychologist, participants were deemed as not having current and/or a history of mood and/or anxiety disorders.

Significant endogenous circadian rhythms occurred for anxiety-like and depression-like mood and well-being (Fig. 1). Anxiety-like mood levels showed a significant circadian rhythmicity ("circadian effect": F = 21.6; *p*FDR < .001). Post-hoc comparisons yielded significantly higher anxiety-like mood levels during the morning hours (ie, circadian phase 60^0-75^0; ~8-9 a.m.; Fig. 1A). Likewise, depression-like mood levels exhibited a significant circadian rhythmicity ("circadian effect": F = 22.1; *p*FDR < .001). Post-hoc comparisons yielded significantly higher depression-like mood levels during the morning hours (i.e., circadian phase 60^0-75^0; ~8-9 a.m.; Fig. 1B). Well-being levels showed a significant circadian rhythmicity ("circadian effect": respectively, F = 65.1, *p*FDR < .001; F = 41.0, *p*FDR < .001). Post-hoc comparisons indicated lower well-being levels during the early circadian morning hours (i.e., more mental fatigue and less physical comfort during circadian phase 30^0-60^0; ~6-8 a.m.; Fig. 1C-D; see Fig. S2A-D).

Discussion

We confirmed our primary hypothesis of endogenous circadian rhythms in different mood and well-being constructs. Likewise, we confirmed our secondary hypothesis that the acrophases of anxiety-like and depression-like mood, and the nadir of well-being levels, happen in the circadian morning hours. Because participants underwent a stringently controlled CR protocol, these effects were unlikely due to confounding factors, such as physical activity, social interaction, diet, posture, sleep duration, and/or light conditions. Likewise, because sleep strongly affects mood regulation,[17,19] we modeled linear effects to (partly) account for sleep homeostasis effects in our cosinor mixed-model analyses. Accordingly, we observed linear effects on all mood constructs (F > 30, *p*FDR < .001; Fig. S2), thus confirming the well-established sleep-related effects on mood and well-being.[3,20] Here, we confirm endogenous circadian rhythms

in depression-like mood akin to what has been observed in individuals experiencing MDD.[12] Importantly, we identified endogenous circadian rhythms in mood constructs often associated with anxiety. Anxiety disorders, including panic disorder (with or without agoraphobia), generalized anxiety disorder, social anxiety disorder, specific phobias, and separation anxiety disorder, are prevalent psychiatric disorders and are associated with increased health care costs and decreased quality of life.[2] According to large population-based surveys, up to ~30% of the population are affected by an anxiety disorder during their lifetime.[21] Hence, understanding the mechanisms underlying excessive anxiety is important for researchers and clinicians. There is increasing recognition that disruptions in the amount and timing of sleep are associated with anxiety symptoms and characteristics. While anxiety is often associated with sleep disruption,[19] comparatively little was known regarding circadian system-driven changes in anxiety-like mood. Our current findings, therefore, highlight the importance of addressing circadian factors in depression and anxiety. Of note, the amplitudes of variability in mental fatigue and physical comfort were higher than for anxiety-like and depression-like mood levels. These were likely due to the study sample characteristics, that is, healthy young participants with no previous or current psychiatric disorders.

All mood constructs herein exhibited an endogenous time-of-day effect with a circadian morning worsening that improved across the circadian day. Such findings (i.e., endogenous circadian rhythms) mirror diurnal rhythms (i.e., with mixed effects of circadian rhythms and of daily behavioral/environmental cycles) observed in patient populations.[5,6,22] Moreover, mood and well-being levels were maximal during the circadian evening, consistent with previous laboratory studies.[12,13,23] This time window coincides with the maximal circadian drive for wakefulness in the evening, which may also associate with mood and well-being improvements. Collectively, these results suggest that the circadian rhythms observed in our protocol have real-life relevance for contributing to these diurnal rhythms and highlight the morning hours as a potential window for circadian interventions. Treatments that directly target the circadian system are used as therapies for mood disorders, including MDD and seasonal affective disorder (e.g., light and dark therapies, agomelatine, social rhythm therapy, and sleep phase advances[24]), but are as of yet seldomly implemented for anxiety/anxiety-related disorders.

A limitation of our study is that we assessed the VAS mood constructs in healthy individuals and not in patients experiencing mood and anxiety disorders. Our current findings, therefore, required future studies to determine whether such endogenous circadian effects translate to mood and anxiety/anxiety-related disorders. Additional study limitations include participants who were lean (BMI < 25 kg/m^2; most of the American population has a BMI > 25 kg/m^2), did not experience current (or previous) psychiatric disorders, and were mostly White (84%) and young. The results, therefore, may not be generalizable to populations with higher BMI, of different ethnicities, with current psychiatric disorders, and/or who are older.

In conclusion, our findings demonstrate endogenous circadian rhythms in anxiety-like and depressive-like mood, and well-being in healthy young adults, with worst levels in the circadian morning *independent* of influences of sleep, activity, eating, and light. Future studies will help in the development of circadian-based therapeutics that could benefit individuals experiencing mood and anxiety/anxiety-related disorders in real-life settings.

Dr. Charles Czeisler's contributions to this work

Previous work by Dr. Czeisler and colleagues has shown that self-reported mood (i.e., sad-happy mood, which is adversely affected in individuals experiencing depression) is influenced by a complex and nonadditive interaction of the circadian phase and duration of prior wakefulness.[11] The nature of this interaction is such that moderate changes in the timing of the sleep-wake cycle may have profound effects on subsequent mood levels. This seminal work sets the framework on which our current study builds upon.

Public health relevance of this work

Mental health conditions are increasing worldwide, and disturbances in sleep and circadian rhythms are bidirectionally intertwined with almost every category of psychiatric disorder. Hence, it is essential to unearth a potential contribution of the endogenous circadian system to mood constructs. Here, we show endogenous circadian rhythms in anxiety-like and depression-like mood and well-being in healthy young adults. Future studies will help establish circadian-based therapeutics for clinical populations and accelerate translation to real-life settings.

Author contributions

Conceptualization: F.A.J.L.S. Funding acquisition: F.A.J.L.S. Investigation: S.L.C. Visualization: S.L.C. and F.A.J.L.S. Data curation: S.L.C. and F.A.J.L.S. Formal analysis: S.L.C. Validation: F.A.J.L.S. Writing—review and editing: S.L.C. and F.A.J.L.S.

Declaration of conflict of interest

F.A.J.L.S. served on the Board of Directors for the Sleep Research Society and has received consulting fees from the University of Alabama at Birmingham and Morehouse University. F.A.J.L.S.'s interests were reviewed and managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. F.A.J.L.S. consultancies are not related to the current work. The other author declares that she has no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.sleh.2023.07.012.

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