Review

Biological Psychiatry

Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents

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ABSTRACT

Sleep homeostasis and circadian function are important maintaining factors for optimal health and well-being. Conversely, sleep and circadian disruptions are implicated in a variety of adverse health outcomes, including substance use disorders. These risks are particularly salient during adolescence. Adolescents require 8 to 10 hours of sleep per night, although few consistently achieve these durations. A mismatch between developmental changes and social/environmental demands contributes to inadequate sleep. Homeostatic sleep drive takes longer to build, circadian rhythms naturally become delayed, and sensitivity to the phase-shifting effects of light increases, all of which lead to an evening preference (i.e., chronotype) during adolescence. In addition, school start times are often earlier in adolescence and the use of electronic devices at night increases, leading to disrupted sleep and circadian misalignment (i.e., social jet lag). Social factors (e.g., peer influence) and school demands further impact sleep and circadian rhythms. To cope with sleepiness, many teens regularly consume highly caffeinated energy drinks and other stimulants, creating further disruptions in sleep. Chronic sleep loss and circadian misalignment enhance developmental tendencies toward increased reward sensitivity and impulsivity, increasing the likelihood of engaging in risky behaviors and exacerbating the vulnerability to substance use and substance use disorders. We review the neurobiology of brain reward systems and the impact of sleep and circadian rhythms changes on addiction vulnerability in adolescence and suggest areas that warrant additional research.

Keywords: Addiction, Adolescence, Circadian, Circuitry, Reward, Sleep

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Adolescence is a particularly vulnerable time for initiating drug use and developing substance use disorders (SUDs). The early onset of drug abuse is strongly related to the development of lifelong addiction (1,2), and earlier use (11–17 years of age) predicts later dependence (i.e., within 2 years) for almost every drug of abuse (1). Identifying the risk factors for substance use and abuse in adolescence is therefore a high public health priority.

Several factors contribute to adolescence being a particularly vulnerable time for the development of substance abuse, including earlier maturation of neural reward systems relative to the development of cognitive control systems, increased sensation-seeking behavior, the combination of increased peer influence and reduced parental monitoring, and greater sensitivity to the rewarding effects of drugs. Our review focuses on factors typically receiving far less attention—sleep and circadian rhythms (Figure 1). We focus on developmental changes to sleep and circadian rhythms during adolescence and how these may impact reward function and substance use. We highlight key findings related to potential genetic and molecular mechanisms underlying sleep and circadian function in relation to reward. Finally, we present an integrative model with parallels between human and animal studies and discuss implications for intervention and treatments.

REWARD AND SUBSTANCE USE IN ADOLESCENCE

Vulnerability for Substance Use and Affective Disorders

Initiation of substance use (i.e., first use of alcohol, marijuana, or other drugs) typically occurs during mid- to late adolescence (~14–18 years of age), with frequency of use increasing during adolescence into early adulthood, and peaking during their 20s, then an eventual decline (3). Alcohol and tobacco use remains relatively steady from late adolescence to the mid-30s, while frequency of use of other substances, such as marijuana or other illicit drugs, declines into adulthood (3). Despite variability in the age of onset and pattern of use of substances, there is a striking epidemiological pattern pointing to adolescence as a vulnerable period for beginning substance use and other risky behaviors. Early initiation of use and factors such as peer influence and socioeconomic status increase the risk for later substance use problems. From a developmental perspective, substance use during adolescence occurs in the context of

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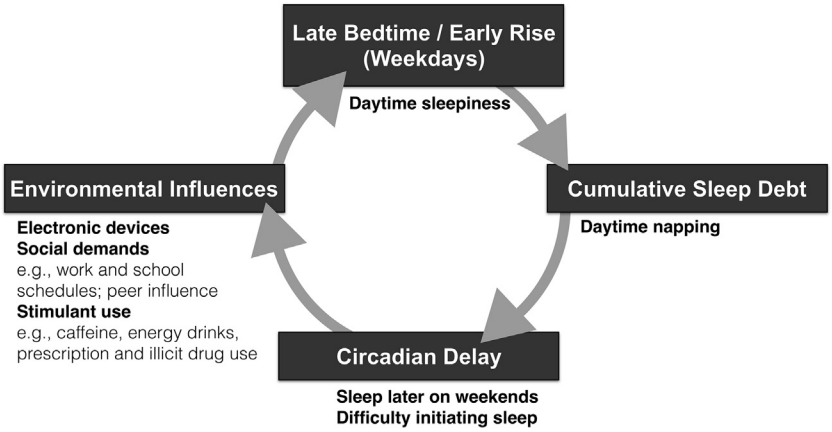

Figure 1. Factors contributing to sleep deprivation in adolescents are compounded by the consequences of sleep and circadian disruptions.

normative changes in reward circuitry and behavior, affect, and sleep and circadian function (Figure 2).

Affective problems, such as depression and anxiety, also often emerge during adolescence, both of which are associated with greater rates of substance use (4,5). Rates of comorbidity between affective disorders and SUDs during adolescence range from 9.0% to 47.9%, and although depression and anxiety typically precede substance problems (5), alcohol and substance use (rather than disorders) may also precede depression (6). The combination of affective disorders and SUDs involve more severe depressive episodes and a higher risk for suicidality (7,8), and the development of psychiatric comorbidity has substantial public health significance.

Changes in Reward Circuitry and Social Context

Adolescence is marked by dramatic development in frontostriatal reward circuitry, including the ventral striatum (VS), dorsal striatum, and medial prefrontal cortex (mPFC) (9,10). Dopamine availability increases during adolescence (11,12), potentially driving incentive motivation and sensation seeking, and likely underlying vulnerability for risky decisions and substance use. Conceptual models of brain development (13,14) postulate that the combination of altered reactivity of reward- and threat-related circuits, in conjunction with slowly maturing cognitive control, creates a developmental risk for heightened emotionality and reward-seeking behaviors. Although debate continues over specific aspects of these models (15,16), there is consensus that the plasticity associated with changes in

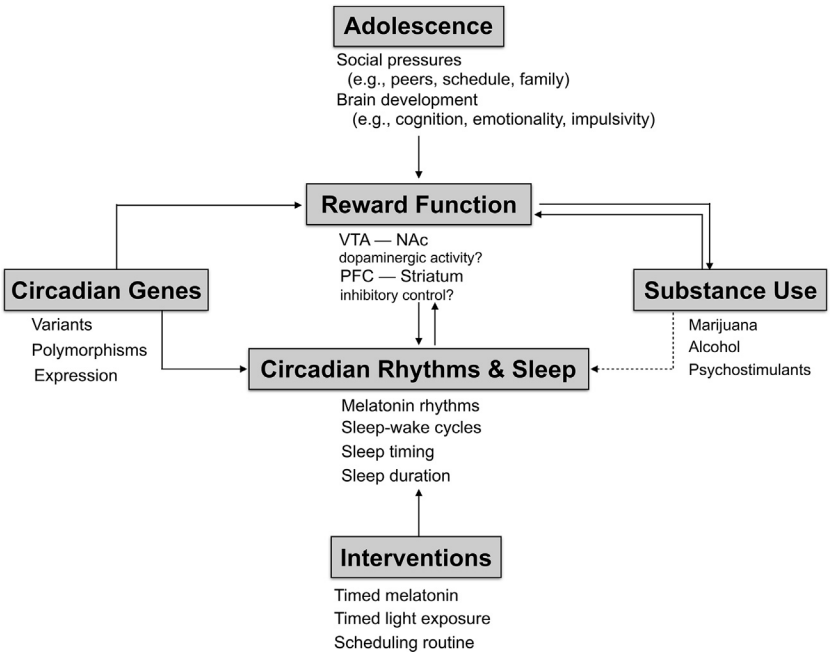

Figure 2. Working model of the interplay between circadian rhythms, sleep, "reward," and vulnerability to substance use during adolescence. Developmental changes in neural circuitry controlling reward function occurs during adolescence and seems to be altered by sleep deprivation and circadian misalignment, potentially leading to risk-taking, impulsivity, and poor decision making. These changes likely contribute to vulnerability to substance use, particularly in adolescents. Rodent studies have demonstrated associations between certain circadian variants, striatal dopamine, and brain response to reward stimuli. Interventions to phase shift, resynchronize, and/or improve sleep timing may be effective for treating mood and substance issues often experienced during adolescence. NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area.

structure and function of reward circuitry during adolescent development make this a vulnerable period for reward-driven behaviors and problems such as substance use.

Evidence From Animal Models

Animal studies support the clinical observations that biological changes during adolescence increase addiction vulnerability. Thus, certain aspects of brain development are conserved across species and may contribute to the propensity for adolescents to use drugs. Cortical dendritic spine and synapse numbers increase during early development and are gradually pruned during adolescence in humans, nonhuman primates, and rodents (17–22). Dopamine systems involved in salience and reward also undergo changes during adolescence. In adolescence, firing rates of dopamine neurons of the ventral tegmental area (VTA) increase, and dopamine receptor expression peaks (23). Thus, the development of brain reward system is, at least partially, evolutionarily conserved, suggesting that mechanisms mediating adolescent vulnerability to substance abuse can be investigated using animal models.

Adolescents may experience the effects of drugs as more positive and the negative effects as less negative relative to adults (24), a theory that is also supported by animal studies. Adolescent rats voluntarily ingest larger quantities of alcohol than adults using a variety of access paradigms (25–28). Adolescents also require higher doses of alcohol than adults to form a conditioned taste aversion, or to exhibit sedation and motor incoordination (29,30). Thus, adolescent rats appear more vulnerable to high levels of alcohol consumption than adults. Adolescent rats are also more likely to self-administer the cannabinoid receptor agonist WIN 55,212-2 (WIN) in higher quantities than adults, with a greater propensity to display relapse-like behavior to WIN-associated cues after adolescent relative to adult WIN self-administration (31). Adolescents also self-administer more cocaine than adults (23), but only when self-administration begins after (not before) the onset of puberty (23,32). While prepubertal cocaine use may not differ from use in adults, cocaine exposure occurring during this period does promote the development of habitual response strategies, potentially increasing an individual's vulnerability to substance abuse as an adult (33,34). In summary, adolescent rodents are willing to self-administer greater quantities of rewarding substances than adults, which may be mediated by an increased drive for rewards, largely supporting the clinical evidence for enhanced vulnerability to substance use during adolescence.

SLEEP AND CIRCADIAN FUNCTION IN ADOLESCENCE: A NOVEL RISK FACTOR FOR SUBSTANCE USE?

Normative Changes in Sleep and Circadian Rhythms

Delays in sleep, circadian preference (i.e., preferred sleep/wake times), and chronotype begin around puberty and reach their maximum around 20 years of age before beginning a long, slow shift toward earlier timing over the lifespan (35,36). Sleep timing shifts later, i.e., "delays," throughout adolescence, with greater delays on weekends, when sleep timing is unconstrained by school schedules (37). Parallel shifts occur in circadian preference, indicated by an increase in self-reported eveningness, and in chronotype (i.e., behavioral manifestations of underlying circadian timing), indicated by later sleep/wake times. Changes in sleep/circadian timing appear to result from both phase delays in the timing of the circadian clock (38) and a slower accumulation in homeostatic sleep drive (37). Some studies suggest that adolescents are more sensitive to light exposure during times of day when light causes delays (evening) and less sensitive when light causes advances (morning) (37,39). The increasingly pervasive use of electronic devices influences adolescent sleep timing, duration, continuity, and quality by inducing circadian phase delays (40). Behavioral and environmental factors also contribute to changes in adolescent sleep timing, such as social pressure from peers and/or decreasing parental involvement in bedtime routines, both of which may lead to later sleep timing and reduced sleep duration (41,42).

Coincident with these changes in sleep timing, adolescents tend to experience reduced sleep duration, increased daytime sleepiness, and increased sleep disturbances (37). Although sleep duration decreases, sleep need—i.e., the amount of sleep required to ensure maximal alertness and performance—appears to remain unchanged (37). Adolescents need 8 to 10 hours of sleep per night (43), but the vast majority (71%) of high school students sleep fewer than 8 hours per night, and 44% sleep fewer than 6 hours per night (44). Decreased sleep duration and increased sleep disturbance may be a consequence of delayed sleep timing, conflicting with school start times on weekdays (which is typically earlier in high school than in elementary or middle school), resulting in circadian misalignment and sleep loss (38,45). On weekends, adolescents tend to stay up later and sleep later the next day to make up for lost sleep. Weekend oversleep compounds the delay in the time of sleep initiation on weekend nights (46,47), making it even more difficult to get up on Monday morning. Weekday–weekend shifts in sleep are often referred to as "social jet lag" (45,48), a term that aptly captures the vicious cycle of circadian misalignment, sleep disturbance, and sleep loss.

Other endogenous and exogenous sleep changes during adolescence could plausibly contribute to sleep duration and continuity. For example, slow wave sleep decreases by approximately 60% across adolescence (49), possibly reflecting synaptic pruning and resulting efficiency of network connectivity (50,51). This "lightening" of sleep depth also contributes to impaired sleep continuity. Caffeine, alcohol, and other substances also impact sleep and circadian rhythms—caffeine later in the day disrupts sleep and delays circadian timing (52,53). Endogenous developmental changes together with social, educational, environmental, and other influences make adolescence a uniquely vulnerable period for circadian misalignment, sleep disturbance, and sleep loss.

Sleep/Circadian Vulnerability for Substance Use

Circadian misalignment, sleep disturbance, and sleep loss during adolescence are associated with increased substance use and related problems. Adolescents with short sleep duration are more likely to use substances—including caffeine, nicotine, alcohol, and illicit drugs (54–56)—and to engage in

other risky behaviors (54,57,58). Prospective studies in adolescents implicate short sleep (59,60) and weekend oversleep as a risk for future alcohol and illicit drug use. Certainly, not all adolescents are similarly vulnerable to these changes. Some adolescents have trait-like characteristics that predispose them to engage in (or enjoy) more late-night activities, feel sleepy later in the night, or put themselves in more reward-focused environments, all of which could expose them to experiences that contribute to substance use problems.

Sleep and circadian characteristics typical of circadian misalignment are associated with affective disorders and SUDs. The largest evidence base comes from studies of circadian preference, variously referred to as morningness–eveningness, or chronotype. Circadian preference is partly a consequence of endogenous circadian phase (61) and individual differences in homeostatic sleep drive (62). Cross-sectional studies in adolescents and adults report associations between greater eveningness and more frequent substance use and increased substance problems (63). Recent prospective evidence suggests that eveningness predicts increases in substance involvement, and not merely a consequence of staying up late because the subjects are engaging in substance use (64,65).

Some, but not all, studies support a link between social jet lag or circadian misalignment and adolescent substance involvement. Weekday–weekend sleep differences have been associated with increased risk-taking behaviors, substance use, and depressed mood (66,67). Several longitudinal studies have linked markers of social jet lag, including larger weekend delays and more variable sleep timing, with greater likelihood of alcohol use 2 years later (59), greater alcohol use disorder symptoms at both 3 and 5 years later (68), and an earlier onset of alcohol use disorder (69). However, two other longitudinal studies reported that later sleep timing (i.e., eveningness), rather than weekend changes in sleep timing, predicted increases in substance use (64,65).

Effects of Sleep and Circadian Changes on Reward Function

Multiple lines of evidence support sleep and circadian modulation of reward function, suggesting a mechanistic pathway to substance abuse (Figure 2). Diurnal rhythms have been observed in self-reported positive affect and behavior, and an objective measure of reward activation (70–72). Moreover, eveningness is associated with depression, reduced reward responsiveness, blunted positive affect rhythms, sensation seeking, poor self-regulation, and impulsivity (70,71,73–79). Later bedtimes, more variable bedtimes, and shorter sleep may also contribute to these behaviors (67,78). These changes in sleep timing and chronotype are associated with altered reward-related brain function in adolescents (80–82).

Reward-related brain circuitry may thus underlie the link between adolescent sleep/circadian function and substance and affective disorders. Striatal response to monetary reward and relative glucose metabolism in the striatum and mPFC show diurnal variation—increasing in the afternoon/evening relative to the morning (70,83,84). Furthermore, reactivity in key nodes of reward circuitry is sensitive to circadian disturbance and sleep loss. In early adolescence, larger weekday–weekend differences in sleep timing (i.e., social jet lag) are associated with lower mPFC reactivity to anticipation and receipt of monetary reward, even after adjusting for puberty, gender, and total sleep time (82). Later sleep timing is also associated with reduced mPFC (81) and VS responses to monetary reward (85). Later adolescents (20-year-old men) who were evening types exhibited lower mPFC responses to reward anticipation and higher VS response to reward outcome relative to morning types, controlling for time of scan (65). In turn, these eveningness-associated patterns of neural response to reward predicted greater concurrent alcohol dependence and alcohol consumption.

Sleep deprivation also disrupts reward neural circuitry, usually enhancing brain reactivity to positive experiences. In response to reward, VS response increases and mPFC decreases in young adults (18–25 years of age) after one night of total sleep deprivation (86). In decision- making and reward-processing contexts, sleep deprivation shifts adults from protecting against loss and toward increasing pursuit of gains, increases VS activity during risky decision making, and decreases insula and orbitofrontal cortical activity to loss (87). Pleasant pictures elicit a similar response (88), with greater mesolimbic network response (putamen and VTA) in sleep-deprived adults. Thus, sleep deprivation enhances mesolimbic reward brain activity and reduces prefrontal cortical response to perform executive functions (88–90). Sleep deprivation may affect brain reactivity differently in adolescents than adults, perhaps related to the shift toward greater neural and behavioral sensitivity to reward during adolescence (9). For instance, sleep restriction is associated with a blunted striatal reactivity to reward outcome in adolescents (91) but a heightened response in young adults (92).

Naturalistic differences in sleep quality and duration are also associated with function in adolescents' reward circuitry, which may help explain the consistent associations of sleep with affective psychopathology and substance use (63). Typically developing adolescents with shorter sleep duration and lower sleep quality exhibit lower caudate response to reward anticipation (85), greater insula response to risk taking, and lower functional connectivity between dorsolateral PFC and both insula and VS during risk taking (89) (Figure 3). Less effective frontostriatal regulation during rewarding contexts and behavioral compensation for blunted motivation could thus serve as a mechanism for the higher level of risky behaviors in adolescents with short sleep duration (93). Alterations in reward circuitry may also be a mechanism underlying the increased risk of depression associated with insomnia (94). This association appears to be mediated by higher dorsolateral PFC response to reward, a pattern that is consistently associated with adolescent depression (95).

Changes in sleep and circadian rhythms, in combination with normative changes in reward circuitry, may constitute vulnerability factors for developing affective or substance use problems during adolescence. However, while the effects of circadian misalignment and sleep loss on neural circuits have been described, their cellular and molecular underpinnings remain poorly understood. Initial findings suggest that sleep deprivation reduces dopamine D_2/D_3 receptors in the VS without affecting basal dopamine release (96); D_2 receptors in the VS are closely associated with risk-taking behaviors and compulsive drug consumption (97,98). While decreased striatal

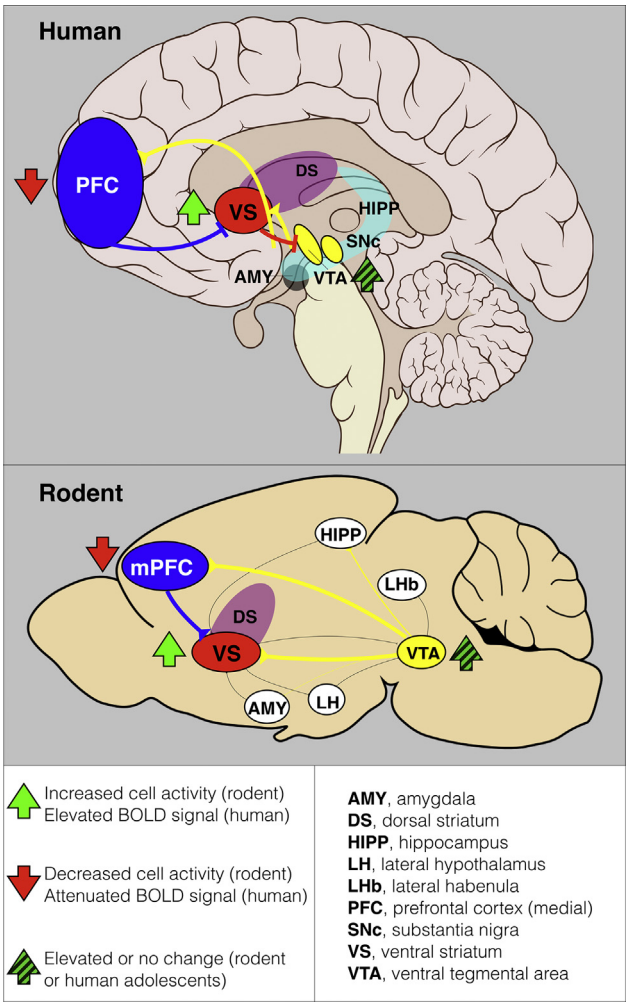

Figure 3. Sagittal sections of a representative **(A)** human and **(B)** rodent brain illustrating major pathways of "reward" neural circuitry. Sleep deprivation and/or circadian misalignment leads to reduced activity of the prefrontal cortex (PFC) (in humans, both dorsolateral and medial PFC [mPFC]) and increased activity of the ventral striatum (VS) or nucleus accumbens in response to reward anticipation in adolescents. The imbalance of excitatory and inhibitory signaling is hypothesized to lead to poor executive function, academic performance, and decision making, while increasing impulsivity and risk-taking behavior, all of which likely contribute to a vulnerability to substance use and abuse. In rodents, sleep deprivation and/or circadian disruptions, whether environmental or genetic, usually lead to poor cognitive performance, working memory, and increased impulsivity, risk-taking behavior, and drug self-administration. Yellow pathways represent ascending dopaminergic pathways from the ventral tegmental area (VTA), and blue pathways represent descending glutamatergic pathways from the PFC. AMY, amygdala; BOLD, blood oxygen level–dependent; DS, dorsal striatum; HIPP, hippocampus; LHb, lateral habenula; LH, lateral hypothalamus; SNc, substantia nigra.

expression of D_2/D_3 receptors is a potential mechanism by which sleep deprivation enhances risk and reward seeking, additional experimental studies in humans and animals are needed to better define the mechanisms underlying relationships between sleep, circadian rhythms, and reward. Furthermore, such experimental studies will be necessary to clarify the directionality of processes linking sleep/circadian characteristics, reward function, and substance use. Although we hypothesize that sleep/circadian disturbances influence reward function and, in turn, substance use, other models are plausible. For instance, a more sensation-seeking personality may drive some adolescents to stay up later, to engage in rewarding, risky activities, and to thereby sacrifice sleep.

Evidence From Animal Models

Animal studies have begun to determine the impact of sleep restriction and circadian misalignment on the behavioral responses to drugs of abuse. Acute sleep deprivation or chronic partial sleep restrictions in animals often leads to enhanced risk taking and reward seeking, including cocaine and alcohol intake, sucrose self-administration, and intracranial self-stimulations (99–103). In various aspects, animal studies have recapitulated the phenomenon of sleep loss–enhanced reward seeking observed in humans. The similarities between the two suggest that there may be hardwired molecular, cellular, and circuit-based mechanisms across species.

Sleep deprivation may alter synaptic transmission onto the principal neurons of the VS. As in humans, function in frontostriatal reward circuitry—in particular, the balance between mPFC and VS—plays a central role in sleep deprivation effects. Glutamate release probability is reduced selectively at the mPFC to nucleus accumbens (NAc) synapses after acute sleep deprivation in mice. Reversing this projection-specific synaptic alteration by optogenetically boosting the release probability at mPFC-to-NAc synapses reverses the sleep deprivation–induced enhanced sucrose self-administration (100). These results suggest that a weakening of the mPFC-to-NAc connection may facilitate reward seeking by reducing "top-down" inhibitory control (104–106). It remains to be determined whether such weakening at the mPFC-to-NAc pathway alone is sufficient for enhanced reward seeking after acute sleep deprivation (Figure 3). Finally, given the extensive evidence on the importance of this pathway in regulating various drug seeking and relapse behaviors (107–111), it is likely that similar mechanisms may underlie enhanced drug and alcohol intake after sleep loss.

Much of the evidence from human imaging studies supports dysfunction in the VTA-PFC-NAc circuit after sleep disturbances and/or circadian misalignment. Each of these regions expresses circadian genes and maintains rhythms of activity and responses. In humans, rats, and mice, striatal and midbrain activity show diurnal variation (83,84,112–115). In the NAc, rhythms of dopamine, glutamate, and gamma-aminobutyric acid are independent of light input (116,117) and may be controlled by diurnal variations of dopamine transporter activity (118). Sleep loss and/or circadian disruptions also affect these circuits, impacting reward-seeking and relapse behaviors (119). For example, acute sleep deprivation leads to relapse of cocaine self-administration in rats via reduced excitatory transmission from the mPFC to the NAc (100), suggesting that excitatory and inhibitory imbalances to the NAc may promote drug self-administration (120,121). Reduced inhibition of the NAc after sleep deprivation is usually associated with reduced PFC activity and offers a plausible mechanism for elevated VS and reduced

frontocortical responses in adolescents with circadian misalignment (80,112,122).

As described above, circadian misalignment can heighten the risk for substance use and abuse (123). Changes in photoperiod and day length are often used to model environmental sleep/circadian disruptions in animals. Repeated shifts of the light/dark cycle can decrease and increase alcohol drinking in male and female rats, respectively (124). However, these effects vary by strain and species, and similar paradigms produce little to no effect on alcohol intake in mice. Shorter days (6 hours light/18 hours dark) attenuate reinstatement of cocaine-seeking behavior in rats. The effect of short days persists even after returning to a standard 12-hour light/dark cycle and correlates with photoperiodic modulation of tyrosine hydroxylase and dopamine transporter expression in the mPFC and dorsal striatum (125).

The impact of these environmentally induced circadian changes likely involves direct and indirect projections from the circadian pacemaker of the suprachiasmatic nucleus to reward-related circuitry, including the VTA (126), medial preoptic area, and dorsomedial hypothalamus (127). However, other brain regions receiving direct light input from the eye may also contribute to regulation of reward circuitry through noncanonical circadian pathways. For example, the lateral habenula receives direct inputs from both the suprachiasmatic nucleus and the eyes (128) and modulates the activity of dopamine neurons in the VTA (Figure 3), suggesting another potential pathway for light to affect mood and reward-related behaviors (129).

Timing of light exposure (e.g., light at night) also impacts mood and reward circuits and behavior. Even brief exposure to light suppresses melatonin secretion at night. Light exposure at night, whether acute or chronic, alters melatonin release, which affects both sleep and circadian systems. In animals, exposure to aberrant light during early life or adolescence suppresses melatonin rhythms and leads to anxiety and depressive-like behaviors in adulthood (130). Whether aberrant light impacts reward or motivation behaviors is unknown, but changes in melatonin signaling can affect dopamine neurotransmission (131) and behavioral responses to drugs of abuse (132).

Animal studies also support findings in humans associating circadian gene variants with addiction. Variants of *PER2* are associated with dopamine D_2 receptor availability and cocaine addiction vulnerability (133,134), risky alcohol drinking under high psychosocial stress (135), and disrupted sleep (136). Interestingly, in healthy adolescents, specific *PER2* alleles are associated with VS and mPFC responses to reward outcomes (81). In alcohol-dependent adults, a *PER1* variant predicts heavy drinking (137). *CLOCK* variants, particularly the *CLOCK* 3111T/C polymorphism, are associated with alcohol dependence (138) and an increased risk for comorbid depression and alcohol use disorders (139). Located within the 3′ untranslated region, this polymorphism affects the expression, function, and stability of *CLOCK* (140). Mice with mutations of any of the core circadian genes, such as *Per1, Per2,* or *Clock*, among others, display altered behavioral responses to many drugs of abuse. For example, *Clock* mutant mice have reduced sleep and disrupted rhythms with increased risk-taking behavior and preference for alcohol and cocaine. *Per1* and *Per2* mutant mice voluntarily consume more alcohol than wild-type mice (141,142), which is further elevated after stress in *Per1* mutant mice (137). *Per1* and *Per2* within the NAc also regulate anxiety-like behaviors (143), further suggesting that *Per* genes may be important for mood and addiction comorbidity. Other circadian genes, such as *Npas2*, regulate cocaine reward behaviors, likely via a cell type–specific mechanism within the NAc (144). Circadian genes impact these behaviors through their regulation of neuronal function in reward-related circuitry, including circadian regulation of VTA-mediated dopamine release and responsivity of downstream targets (114,145,146). Additional studies are necessary to fully understand the impact of specific variants identified in human studies on endogenous gene and protein expression (140) and their potential effects during adolescence because most, if not all, of these studies were completed in adulthood.

Treatment Implications

Chronotherapies, such as bright light therapy and social rhythm therapy, are efficacious treatments for certain mood disorders in adults and have favorable side effect profiles (147,148). Few studies have evaluated these interventions on mood, sleep problems, and circadian alignment in adolescents. Studies have only focused on teens with depression or delayed phase sleep disorder (149). One randomized crossover trial of 28 adolescents with depression found that bright light therapy (2500 lux vs. 50 lux placebo) induced an antidepressant response and a phase advance of cortisol and melatonin rhythms, with no adverse treatment effects (150). Given the promise of these initial findings, further studies are needed to examine the effects of sleep and circadian interventions on a range of outcomes, including reward function and the vulnerability for substance use and SUDs.

Public policy offers another avenue for intervention. In 2014, the American Academy of Pediatrics stated that "Although a number of factors, including biological changes in sleep associated with puberty, lifestyle choices, and academic demands, negatively affect middle and high school students' ability to obtain sufficient sleep, the evidence strongly implicates earlier school start times (i.e., before 8:30 AM) as a key modifiable contributor to insufficient sleep, as well as circadian rhythm disruption, in this population. Furthermore, a substantial body of research has now demonstrated that delaying school start times is an effective countermeasure to chronic sleep loss and has a wide range of potential benefits to students regarding physical and mental health, safety, and academic achievement." A combination of later school start times at the population level and sleep and circadian interventions at the individual level could help align adolescent's biological rhythms with the environment and perhaps mitigate future psychiatric and substance abuse problems.

SUMMARY

Sleep and circadian rhythms undergo developmental changes from childhood through adolescence and into adulthood. During adolescence, an evening preference combined with social demands and other environmental factors contributes to circadian misalignment and further exacerbates sleep

disturbances, impacting neural circuits underlying mood and reward. Adolescent development is associated with enhanced reward sensitivity relative to cognitive control, phase delay in endogenous circadian rhythms, and reduced homeostatic sleep drive. Genetic, environmental, and social factors interact with these developmental processes, often resulting in late sleep timing, short sleep duration, and circadian misalignment. These observations lead to a testable hypothesis: that late sleep timing, short sleep duration, and circadian misalignment adversely impact corticolimbic function in adolescents, further enhancing reward function, impairing cognitive control, and increasing substance use risk. Future studies should examine naturally occurring sleep and circadian phenotypes, both cross-sectionally and longitudinally, to investigate the neural, molecular, and genetic mechanisms by which sleep/circadian rhythms affect reward function and substance use risk. Furthermore, experimental manipulations of sleep and circadian rhythms can be investigated to examine their effects on reward function and substance use behavior. Such studies could lead to novel strategies for identifying vulnerability and mitigating the risk of developing SUDs in adolescence.

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