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Circadian Misalignment, Reward-Related Brain Function, and Adolescent Alcohol Involvement

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Abstract

Background—Developmental changes in sleep and circadian rhythms that occur during adolescence may contribute to reward-related brain dysfunction, and consequently increase the risk of alcohol use disorders (AUDs).

Methods—This review (a) describes marked changes in circadian rhythms, reward-related behavior and brain function, and alcohol involvement that occur during adolescence, (b) offers evidence that these parallel developmental changes are associated, and (c) posits a conceptual model by which misalignment between sleep-wake timing and endogenous circadian timing may increase the risk of adolescent AUDs by altering reward-related brain function.

Results—The timing of sleep shifts later throughout adolescence, in part due to developmental changes in endogenous circadian rhythms, which tend to become more delayed. This tendency for delayed sleep and circadian rhythms is at odds with early school start times during secondary education, leading to misalignment between many adolescents' sleep-wake schedules and their internal circadian timing. Circadian misalignment is associated with increased alcohol use and other risk-taking behaviors, as well as sleep loss and sleep disturbance. Growing evidence indicates that circadian rhythms modulate the reward system, suggesting that circadian misalignment may impact adolescent alcohol involvement by altering reward-related brain function. Neurocognitive function is also subject to sleep and circadian influence, and thus circadian misalignment may also impair inhibitory control and other cognitive processes relevant to alcohol use. Specifically, circadian misalignment may further exacerbate the cortical-subcortical imbalance within the reward circuit, an imbalance thought to explain increased risk-taking and sensation-seeking during adolescence. Adolescent alcohol use is highly contexualized, however, and thus studies testing this model will also need to consider factors that may influence both circadian misalignment and alcohol use.

Conclusions—This review highlights growing evidence supporting a path by which circadian misalignment may disrupt reward mechanisms, which may in turn accelerate the transition from alcohol use to AUDs in vulnerable adolescents.

Keywords

circadian rhythms; sleep; reward function; adolescence; alcohol use disorders

In this review, we hypothesize that developmental changes in sleep and circadian rhythms that occur during adolescence may contribute to impaired reward-related brain function, and

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consequently increase the risk of alcohol use disorders (AUDs). Sleep-wake timing tends to shift later during adolescence, driven in part by changes in the endogenous circadian clock. This biologically-driven tendency for later sleep-wake timing conflicts with the earlier sleep-wake schedules demanded by school start times, thus resulting in *circadian misalignment*. Emerging evidence indicates that circadian misalignment disrupts reward mechanisms. We propose that this disruption of reward mechanisms accelerates the transition from alcohol use to AUDs in vulnerable adolescents. We recognize that adolescent alcohol use is highly contextualized, and thus psychosocial factors that may influence both sleep patterns and alcohol use need to be considered as additional influences or alternative explanations. Furthermore, alcohol use has marked effects on sleep and circadian rhythms (Hasler et al., 2012b, Brower, 2001), adding to the challenge of determining directionality between sleep/circadian disturbance and adolescent alcohol use. We assert here that taking on this challenge is warranted. While psychosocial influences and the effects of alcohol use on sleep and circadian function are also pertinent, we contend that circadian misalignment may be an underappreciated risk factor for adolescent AUDs.

Sleep and circadian rhythms

Many physiological and behavioral processes show periodicity, oscillating in a 24-hour cycle. Daily oscillations with a demonstrably endogenous basis are known as *circadian* (from the Latin, “about a day”) rhythms; oscillations with an ambiguous or a demonstrably exogenous basis (e.g., sociocultural factors) are referred to more generally as *diurnal* rhythms. The principal endogenous contributor to circadian rhythmicity is the central pacemaker, the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The SCN is influenced by exogenous stimuli known as *zeitgebers* (“time givers”) in order to match internal rhythmicity to the 24-hour day. This process of synchronization of internal-to-external time is known as *entrainment*. Entrainment is a necessarily ongoing process because the circadian period of most individuals is somewhat longer than 24 hours, requiring a daily re-setting of the internal clock. The most powerful zeitgeber in humans is light, with other zeitgebers including feeding, exercise, and social interaction (Czeisler and Buxton, 2011).

The SCN synchronizes behavioral and physiological rhythms through internal messengers, including melatonin (Arendt, 2005). Melatonin secretion by the pineal gland occurs during biological night, which coincides with actual night in normally entrained individuals. Melatonin is the most reliable marker of internal circadian timing (Arendt, 2005), although it must be assessed under carefully controlled conditions. Typically, melatonin levels are assessed in serial samples of plasma or saliva, which are collected beginning 5–6 hours before bedtime and continuing at least past bedtime in order to capture the onset of melatonin production (Benloucif et al., 2008). This onset is termed the Dim Light Melatonin Onset because melatonin secretion is suppressed by light and thus must be collected under dim light conditions.

Human sleep and wake phases are largely matched to the dark and light periods, respectively. Sleep/wake timing is influenced by circadian rhythms, the homeostatic sleep drive, and scheduling influences. Homeostatic sleep drive increases with time spent awake and dissipates during sleep. During the biological day, a rising circadian alerting signal counteracts the increasing sleep drive to maintain wakefulness in the evening hours. The circadian alerting signal steeply declines at the start of the biological night, allowing the accumulated sleep drive to induce sleep. The circadian alerting signal then continues to decline, reaching its nadir a few hours before wake-up time, maintaining sleep as the sleep drive dissipates. This circadian-homeostatic interplay is described in the Two-Process Model of Sleep Regulation (Borbely, 1982, Dijk and von Schantz, 2005). Sleep/wake timing is also

influenced by sociocultural scheduling pressures from academic activities, employment, and peers (Carskadon, 2002).

Circadian misalignment

Circadian misalignment, defined as a mismatch between the sleep/wake schedule and internal circadian timing, is typically associated with night shift work and jet lag (Sack et al., 2007). Circadian misalignment also occurs when work or school schedules are mismatched with individual circadian tendencies, a scenario sometimes referred to as “social jetlag” (Wittmann et al., 2006). Individuals vary in their chronotype—their preferred sleep-wake timing—along a continuum from extreme morning-types (larks) to extreme evening-types (owls) (Roenneberg et al., 2003). Evening-types can struggle with the early wake-up times required by conventional work or school schedules, leading to pronounced circadian misalignment on weekdays. Furthermore, evening-types often resume their preferred sleep-wake timing on the weekend, which experimental studies show leads to further delays in their internal timing (Crowley and Carskadon, 2010). Their internal circadian timing cannot shift earlier in time for the start of the school week (Gallo and Eastman, 1993), thus maintaining circadian misalignment (i.e., “social jet lag”) on subsequent weekdays (Wittmann et al., 2006). The extent of difference between weekday and weekend sleep-wake timing thus serves as a proxy for the degree of circadian misalignment (Wittmann et al., 2006), albeit an imperfect one. Longitudinal studies in adolescents are needed to fully elucidate to what extent circadian misalignment is present in conjunction with weekday-weekend swings in sleep patterns.

Circadian misalignment leads to decrements in sleep duration and sleep continuity (Sack et al., 2007, Carskadon et al., 2004), as well as impaired attention, performance, and learning, mood dysregulation, school absenteeism, diminished job safety, gastrointestinal disturbance, and adverse cardiovascular and metabolic effects (Carskadon et al., 2004, Boivin et al., 2007). Conditions that induce misalignment, such as shift work and chronic jet lag, are associated with increased alcohol consumption and smoking (Trinkoff and Storr, 1998, Rogers and Reilly, 2002). Circadian timing and homeostatic sleep drive interact to influence sleep propensity, and to modulate mood, neurobehavioral performance and reward motivation (Murray et al., 2009, Dijk and von Schantz, 2005), all processes that influence adolescent alcohol involvement (Clark et al., 2008, Hittner and Swickert, 2006).

Adolescence, sleep and alcohol use disorders

Adolescent sleep patterns—eveningness, delayed circadian timing, and weekday-weekend differences

Weekday bedtimes shift almost an hour later from middle school to high school, and weekend bedtimes shift even more than an hour in the same timeframe (Crowley et al., 2007). Cross-cultural studies of adolescent chronotype (i.e., morningness-eveningness) consistently report that *preferred* sleep times shift later throughout adolescence (i.e., towards greater eveningness) (Randler, 2008, Carskadon et al., 2004, Roenneberg et al., 2004). The progression to later sleep onsets and shorter total sleep times precedes overt signs of pubertal maturation (Sadeh et al., 2009), and the timing of sleep continues to delay until around the age of 20, when it sharply stops delaying and begins to advance (Roenneberg et al., 2004). Later sleep schedules result, in part, from the timing of the circadian clock becoming relatively delayed (shifting later), and also because adolescents appear to become resistant to the homeostatic sleep drive that accumulates with time spent awake (Hagenauer et al., 2009). While normative, these developmental changes are potentially problematic, particularly for adolescents with more delayed circadian timing (i.e., greater eveningness). Early school start times conflict with adolescents’ increasing night owl tendencies, leading

to circadian misalignment, sleep disturbance, and sleep loss on weekdays. Consequently, on the weekends, adolescents often attempt to "catch-up" on lost sleep by getting up later. Adolescents also tend to retire later on the weekends, at times more consonant with the delayed timing of their circadian clock. These weekend delays are generally greater in older adolescents (Crowley et al., 2007).

Circadian misalignment contributes to sleep decrements and other problems during adolescence. Sleep *duration* decreases during adolescence (Sadeh et al., 2009) while sleep *need* is unchanged (Carskadon et al., 2004). Sleep *disturbance* is also highly prevalent among adolescents (Johnson et al., 2006). Together, insufficient or disturbed nighttime sleep leads to increased daytime sleepiness, increased substance use, poor academic performance, more frequent absenteeism, more frequent drowsy-driving accidents, emotional dysregulation, and completed suicides (e.g., (Moore and Meltzer, 2008).

Circadian misalignment during adolescence has consequences beyond sleep disturbance. On weekdays, evening-type adolescents must rise abnormally early relative to their internal clock. These adolescents begin their academic day near their circadian trough in alertness, which ideally occurs in the hours before rising (Dijk and von Schantz, 2005). On weeknights, adolescents often attempt to fall asleep while their circadian clock is still promoting wakefulness. Attempting to sleep or to be active at times incompatible with the circadian clock may have direct effects on adolescents' physical and mental health. Notably, these effects are reversible--even modest delays of school start times can result in demonstrable improvements in daytime sleepiness, mood, and motivation (Owens et al., 2010).

It is important to note that sleep/wake timing reflects the combined influence of social, behavioral, and biological factors. To the extent that these influences predict both sleep/wake timing and alcohol use, these factors may exacerbate the effects of circadian misalignment or constitute an alternative explanation. For example, in some adolescents, later sleep time may be due to a preference for engaging in sanctioned activities, including alcohol use, when parents are asleep and the adolescent is unsupervised. Parents who allow adolescents to be away from the home late in the evening may generally provide less supervision, an environmental risk for alcohol use (Clark et al., 2005). A recent paper reported that both sleep behavior and drug use "spread" through adolescent social networks, and that the spread in sleep behavior (i.e., sleep duration) partially mediated the spread in drug use (Mednick et al., 2010). Sleep difficulties are associated with psychological dysregulation and related mental disorders that predict accelerated alcohol use trajectories in adolescence (Vanyukov et al., 2003, Johnson and Breslau, 2001). In addition, insufficient sleep and consequent sleepiness may impair executive functioning (Anderson et al., 2009), thereby increasing risk for alcohol use. These factors will need to be considered in research testing the proposed model.

Eveningness linked to alcohol use and other reward-related outcomes

Evening-types' preference for later sleep-wake timing is partly a consequence of the later timing of their internal clock (e.g., (Duffy et al., 2001). Extreme eveningness may manifest as Delayed Sleep Phase Disorder, a circadian rhythm sleep disorder that is most common during adolescence (Saxvig et al., 2012). Evening-types are often challenged by schedules that force them to rise at too early relative to their internal clock, resulting in circadian misalignment and sleep loss. The resulting "social jet lag" may explain the association between eveningness and increased substance use (Witmann et al., 2006), however, social motivations for later sleep timing are also important to consider.

Adult evening-types, compared to morning-types, report greater alcohol consumption, greater nicotine use and dependence, and larger weekday-weekend differences in wake-up times indicating circadian misalignment (Adan, 1994, Broms et al., 2011). Adolescent evening-types similarly show indicators of circadian misalignment, more psychological dysregulation and greater alcohol and other substance involvement (e.g., (Gau et al., 2007, Pieters et al., 2010, Saxvig et al., 2012). In these studies, the association between eveningness and greater substance use was independent of age, pubertal development, race, socioeconomic status, educational level, and psychopathology.

Eveningness is associated with indicators of reward-related brain dysfunction, including greater depression, reduced reward responsiveness, and greater sensation seeking (Hasler et al., 2010, Tonetti et al., 2010). Evening-types also show altered brain activity in areas involved in reward processing (Hasler et al., 2012a). Consonant with the hypothesis that adolescents' relative insensitivity to reward may drive reward-seeking through alcohol (Spear, 2000), we speculate that evening-type adolescents may be insensitive to typical rewards, and thus have a propensity to pursue the more intense reward experiences of alcohol and other drug use.

Two adolescent studies have reported that larger weekday-weekend sleep differences–ostensibly indicating circadian misalignment–are linked to increased risk-taking behaviors, substance use, and depressed mood (Pasch et al., 2010, O'Brien and Mindell, 2005). The weekday-weekend differences in sleep timing remained associated with substance use and risk-taking after controlling for sleep duration and daytime sleepiness. This suggests that circadian misalignment contributes to increased alcohol use and risk-taking independent of the effects of sleep loss. Although the cross-sectional nature of these studies precludes determining the direction of these effects, the results suggest that chronotype interacts with scheduling pressures to influence alcohol and other substance use.

Circadian misalignment and reward mechanisms

Circadian regulation of reward-related behavior and physiology

Reward-related behaviors and physiology exhibit circadian rhythms. Positive affect, an experiential manifestation of the reward system, and psychophysiologically-assessed reward motivation show 24-hour rhythms that are modulated by circadian timing and the homeostatic sleep drive (Murray et al., 2009). With levels that are lowest close to wake-up time and a rise to a peak in the late afternoon or evening, these reward-related rhythms parallel the core body temperature rhythm, as well as the diurnal patterns of reward-related behaviors (e.g., socializing) (Hasler et al., 2008b) and of activity in reward-related brain regions (Hasler et al., 2012a). This temporal pattern is also observed in alcohol consumption among adults, which troughs in the early morning and peaks in the early evening (Arfken, 1988). Given the tendency for later circadian phase among adolescents, we would expect that their peak in drinking would preferentially occur somewhat later in the evening, although this timing is clearly impacted by contextual factors influencing drinking opportunities (e.g., parents going to bed, being out at a party).

Complementing the human findings, rodent studies show circadian modulation of reward-related behavior and physiology. Drug-seeking behavior and responsiveness to drugs of abuse show diurnal rhythms (e.g., (Webb et al., 2009). These rhythms in reward-related behavior are paralleled by rhythms in the expression of the dopamine transporter and of tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis), as well as in the expression of several circadian genes in the medial prefrontal cortex and the mesolimbic dopamine system, the neural circuit most closely linked to reward (Webb et al., 2009, Sleipness et al., 2007). The circadian modulation of these reward-related processes and

behaviors may be signaled through melatonin, one of the primary output signals of the central clock. Melatonin appears critical to the rhythmicity within striatal areas and to concomitant diurnal rhythms in locomotor and reward measures of cocaine sensitization (Uz et al., 2003). Melatonin may regulate striatal dopamine production (Alexiuk and Vriend, 2007). Transgenic mouse models suggest that circadian genes (e.g., *Clock, Per1*, and *Per2*) in reward-related brain areas are involved in the regulation of appetitive behavior, and both animal and human studies link circadian genes to reward functioning and response to alcohol, cocaine, and heroin (Forbes et al., 2012, McClung, 2007, Li et al., 2009). As a caveat, making analogies to humans based on animal models must be done with caution. For example, the cited studies used nocturnal rodents.

If circadian rhythms modulate reward-related physiology and behavior, it follows that circadian misalignment may lead to reward-related dysregulation. Indeed, emerging evidence suggests that circadian misalignment in adolescents may be related to substance use disorder (SUD) severity. In adolescents with SUD history and current sleep disturbance (Hasler et al., 2008a), circadian alignment was quantified as the interval between the dim light melatonin onset (DLMO) and their wake-up time, as based on wrist actigraphy. Greater circadian misalignment (shorter DLMO-wake-up intervals) was associated with more severe SUD symptoms over the previous 30 days. Circadian misalignment was unrelated to measures of sleep continuity, suggesting that sleep disturbance was not responsible for this association. Subsequent studies testing this assertion should also assess sleep architecture, as decreased slow-wave sleep and rapid eye movement (REM) sleep have been documented during chronic drug and alcohol use among adults (Schierenbeck et al., 2008, Brower, 2001).

In animal studies, some (e.g., (Gauvin et al., 1997), but not all (e.g., (Rosenwasser et al., 2010), studies found that experimentally-induced circadian misalignment induced increased alcohol consumption. However, most animal studies have used rest/activity rhythms as their sole measure of circadian functioning and thus have not examined the relative alignment between the rest/activity cycle and circadian clock markers. A recent mouse study of chronic circadian misalignment examined core body temperature as a circadian marker. Circadian misalignment disrupted temperature rhythms, led to reduced neuronal complexity in prelimbic prefrontal brain areas, and diminished behavioral inhibition (Karatsoreos et al., 2011). Diminished behavioral inhibition could lead to increased alcohol use.

Sleep loss, substance use, risk-taking, and response to reward

Because circadian misalignment is usually accompanied by sleep decrements, it is important to consider the effects of sleep disturbance and sleep loss (i.e., elevated homeostatic drive) on risk-taking, reward responsiveness, and substance use. Survey studies of adolescents and college students generally report links between self-reported sleep problems and increased use of alcohol and other substances (Pieters et al., 2010, Lund et al., 2010). Experimental and neuroimaging studies mostly report increases in risk-taking and reward responsiveness following sleep loss. In a fMRI study of healthy adolescents using a monetary reward-based task, less sleep and lower sleep quality were associated with less reward-related striatal activation (Holm et al., 2009). Sleep *timing* effects on reward-related striatal activation were less clear-cut; later sleep onset times were associated with *less* reward reactivity while later wake times were associated with *greater* reward reactivity. These results, which may speak to circadian timing effects, illustrate the complexity of studying phenomena that may vary across the 24-hour day. While we did not find experimental studies of the effect of sleep deprivation on adolescent risk-taking or reward function, acute sleep deprivation in adults has been found to lead to greater risk-taking and reduced concern for negative consequences in gambling tasks (Killgore et al., 2006).

Neuroimaging findings in young adults indicate that acute sleep deprivation increases the neural response to reward (broadly-defined), while attenuating the response to loss (Venkatraman et al., 2011, Gujar et al., 2011). Across different methodologies—whether winning money or observing pleasant images—these studies report that sleep deprivation amplified mesolimbic reactivity. The observed neural changes paralleled behavioral changes indicating increased reward motivation, such as a shift towards decision-making seeking gains rather than avoiding losses (gambling task), or a tendency toward rating images as more pleasurable (picture stimuli).

No published studies have experimentally probed the effect of sleep loss on alcohol use. A human study of cigarette smoking (Hamidovic and de Wit, 2009) and a rodent study of cocaine use (Puhl et al., 2009) both reported that sleep loss increased drug consumption. Survey and longitudinal studies of sleep in adults with AUDs indicate that sleep disturbance can lead to increased alcohol involvement: alcoholics with insomnia will self-medicate using alcohol (Brower et al., 2001), and persistent sleep disturbance during abstinence predicts relapse (Drummond et al., 1998).

Taken together, the evidence indicates that the reward system is modulated by both circadian timing and homeostatic sleep drive. In cross-sectional studies, circadian misalignment and sleep disturbances show consistent associations with alterations in mood, substance use, reward-related behaviors, and reward-related brain activation. Experimental studies of chronic circadian misalignment in mice and acute sleep deprivation in young adult humans suggest that the increases in substance involvement may be due to changes in reward-related neural responses. The reward-related changes manifest as increased reactivity to rewarding stimuli, reduced concern about losses, and diminished behavioral inhibition. However, no studies have experimentally probed misalignment-induced changes in reward processing as a mechanism for increased adolescent alcohol use.

Cognitive aspects of reward processing are influenced by circadian timing and sleep drive

Circadian timing and homeostatic sleep drive modulate basic reward processes and also influence neurocognitive performance relevant to reward processing (Dijk and von Schantz, 2005). Sleep loss leads to decrements in neurocognitive performance, particularly for executive functioning (Durmer and Dinges, 2005). Likewise, circadian timing influences alertness, vigilance, selective attention, working memory, declarative memory, procedural memory, and inhibition (Schmidt et al., 2009). The evidence to date suggests that circadian misalignment impairs executive functioning and inhibitory control, plausibly influencing reward-related decision-making and alcohol involvement.

Reward-related brain function and the development of AUDs

Adolescence is characterized by developmentally specific changes in positive affect, approach motivation, and reward processing (Forbes and Dahl, 2005), as well ras changes in reward-related behavior, such as risk-taking and novelty- and sensation-seeking (Spear, 2000). Adolescents show differences from both children and adults in the cortical areas (e.g., medial prefrontal cortext [mPFC]) that provide top-down modulation, and the subcortical areas (e.g., ventral striatum) that underlie approach motivation and reward processing (Ernst and Fudge, 2009). These reward-related developmental differences are thought to be due to lagging maturation of the frontal cortical areas relative to that of the subcortical components of the mesocorticolimbic circuit (Ernst and Fudge, 2009, Forbes and Dahl, 2005, Spear, 2000). Although there is some consensus that this cortical-subcortical imbalance is a contributor to elevated sensation-seeking and risk-taking during adolescence, details of the

mechanisms underlying these functional consequences remain a matter of some debate (Forbes et al., 2010, Galvan, 2010). On the one hand, it has been hypothesized that hyper-responsive striatal regions during adolescence drive greater reward-seeking and risk-taking behavior (Ernst and Fudge, 2009, Galvan, 2010). On the other hand, an alternative hypothesis is that a hypo-responsive striatum during adolescence leads to seeking high-intensity rewards (Bjork et al., 2008, Forbes et al., 2010). Variations in findings may be influenced by sample characteristics, such as variations in age range, influential covariates, such as pubertal stage, or differences in experimental methods (Galvan, 2010). Another plausible, but relatively unexplored, explanation for the disparity of findings is that there may be a threshold effect; specifically, adolescents may be less responsive to low-intensity rewards, but more responsive to high-intensity rewards (Forbes et al., 2010).

The initiation and advancement of alcohol involvement during adolescence may be influenced by changes in reward related brain functioning (Spear, 2000). Relative deficits in executive functioning, behavioral inhibition, and affect regulation—related features of a broader construct termed *psychological dysregulation*— may characterize those adolescents most like to develop AUDs (Clark et al., 2008). Psychological dysregulation may, in part, be due to reward processing impairments. For example, behavioral genetic studies suggest that a trait-like low level of response to alcohol predicts the development of AUDs (Schuckit et al., 2004), indicating that alcohol-related reward hyposensitivity may enhance AUD vulnerability. Delayed discounting studies suggest that adolescents at higher risk for AUDs demonstrate “incentive dependence”; that is, they are more dependent on immediate and tangible rewards to optimize their responses to challenging behavioral tasks (Clark et al., 2008). Evidence of decreased anticipatory reward motivation in adolescents (Geier and Luna, 2009) parallels diminished PFC reactivity to reward anticipation in adults with SUDs (Goldstein et al., 2007). Hypo-responsitivity of the ventral striatum to the anticipation of low-intensity rewards may lead adolescents to compensate by seeking out more extreme incentives (Bjork et al., 2008, Forbes et al., 2010). When paired with relative hyper-responsivity of striatal areas to received rewards (Ernst and Fudge, 2009, Galvan, 2010), these reward-related response tendencies may partially explain the acceleration of alcohol involvement to AUDs in some adolescents. In summary, disruption of circadian rhythms and related alterations in reward function may be a previously unrecognized factor influencing individual variations in risk for AUDs.

Proposed conceptual model of a circadian-reward pathway to AUDs

We propose that circadian misalignment leads to altered functioning in the reward circuit, thereby increasing risk for the development of AUDs. As a result of a mismatch between their increasing tendency for delayed circadian phase and early school start times, many adolescents may experience chronic circadian misalignment. Circadian misalignment disturbs sleep and waking function, including apparent changes to reward-related neural circuitry, and appears to lead to greater risk-taking and increased alcohol use. Experimental sleep deprivation studies suggest these behavioral changes are caused by increased neural reactivity to rewards with decreased sensitivity to losses. We hypothesize that these changes in reward-related brain function result in a prioritization of immediate rewards over long-term consequences, a marker of risk for adolescent AUDs.

We contend that circadian misalignment leads to accelerated alcohol involvement and increased risk for AUDs via an interaction between altered circadian timing and an elevated homeostatic sleep drive. The model presumes that circadian misalignment will impact reward processing differentially at different circadian phases, and at different levels of sleep debt. Because the typical circadian rhythm in reward motivation peaks in the late afternoon and early evening, adolescents with delayed circadian rhythms should experience peaks in

reward motivation that occur later in the evening. Under rested conditions, this peak would be in the normal range. However, circadian misalignment during the school week leads to accumulating sleep deprivation, which builds throughout each day to maximally impair neurocognitive functioning in the late evening. The cortical-subcortical imbalance may be particularly exacerbated in the evening hours, leading to elevated behavioral and neural reactivity to reward, with diminished behavioral inhibition and concern about losses, at the same time that contextual factors include diminished parental supervision and increased opportunities for alcohol use. We hypothesize that enhanced reward motivation, increased propensity toward risk-taking, and facilitative contextual factors increase the likelihood of problematic alcohol use. These circumstances, along with alcohol use, are likely to further delay bedtimes on weekend nights, compounding the circadian misalignment.

Alcohol impacts sleep and circadian rhythms

While we have focused on sleep and circadian pathways as risks for alcohol involvement, the early stages of alcohol use may also contribute to sleep and circadian alignment disturbances. All-too-limited data suggests that adolescents with sleep complaints may turn to alcohol as a hypnotic (Bootzin and Stevens, 2005), compounding their sleep disturbance and increasing the risk of AUDs. Acute and chronic alcohol use, as well as withdrawal, lead to disturbances to sleep continuity and changes in sleep architecture (Brower, 2001, Hasler et al., 2012b). Some of these changes (e.g., disturbances to rapid eye movement, or REM, sleep) can persist into abstinence. Besides its effects on sleep *per se*, alcohol also disrupts the circadian system according to both human and animal studies, with the latter suggesting that alcohol directly impairs the ability of the circadian system to shift in response to changing schedules (e.g., (Ruby et al., 2009)—an impairment that would increase the likelihood of circadian misalignment.

Research implications

This model relies on an imperfect extant literature, composed in large part by cross-sectional evidence and findings for adulthood that have not been definitively established in adolescence. Future studies should investigate time-of-day differences in reward-related brain activation across age groups, including experimental designs (i.e., forced desynchrony) capable of parsing circadian versus homeostatic modulation of the reward circuit. Understanding the relative contributions of circadian misalignment and sleep loss to reward function will be critical to optimizing sleep- and circadian-based prevention and intervention approaches to AUDs. Likewise, experimental studies are needed to probe the effect of circadian misalignment on reward-related brain activation, and its subsequent impact on alcohol involvement.

Although we contend that the relationship between circadian misalignment and alcohol involvement is worthy of further study, mechanisms in addition to altered reward-related brain function should be considered. For example, greater eveningness may impact drinking primarily through contextual influences. Evening-type adolescents may drink more because they are up later on weekend nights, leading to affiliation with older peers or less parental supervision. Ecological momentary assessment designs that measure the timing of adolescent alcohol use along with other contextual variables would be useful in evaluating these other potential factors. Such studies should assess the use of electronic media—increasingly pervasive among teens—which has been consistently shown to delay bedtimes and shorten total sleep time (Cain and Gradisar, 2010), and late-night use of electronic devices, including texting via cell phones, can occur covertly without parental knowledge. Cross-sectional designs preclude adequate consideration of characteristics that may antedate and influence both sleep and alcohol use, including childhood phenotypes (i.e., psychological dysregulation) or endophenotypes (i.e., neuromaturational delays or deficits).

Longitudinal studies are needed for determining the temporal relationships among sleep, circadian rhythms, reward function, alcohol use, and other relevant factors as a means to clarifying mechanisms.

In conclusion, although much work remains to be done to definitively characterize the links among circadian rhythms, sleep, reward-related brain function, and adolescent AUDs, this line of inquiry holds promise for providing novel insights into pathways to risk for adolescent AUDs.

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