Rhythms and reward: Do circadian factors contribute to risk for adolescent substance use?

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Johns Hopkins Bloomberg School of Public Health
Department of Mental Health Noon Seminar Series
February 27, 2019

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Circadian rhythms – (very brief) intro

Organize physiological and behavioral processes for optimal interaction with the environment

“Temporal order is essential for health” - Arne Wingfield (2003)

Clocks everywhere

Timing is everything: U.S. trio earns Nobel for work on the body's biological clock

Reward and circadian modulation (briefly)

Wanting  Liking

Pursuing rewards  Consuming rewards

Circadian control of reward circuitry (e.g., Logan et al. 2014, 2017; McChesney, 2007; Webb et al. 2015)

Mechanisms?

Sleep and/or circadian disturbance  Mood and substance use disorders

• Appetitive motivation and reward processes are modulated by the circadian system
• Circadian disturbance can dysregulate appetitive motivation and reward function

A good overview...

Review

Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents

Ryan W. Logan, Brant P. Hasler, Erika E. Fruehan, Peter L. Franzon, Mary M. Tommazzoli, Yanhua H. Huang, Daniel J. Buysse, Duncan B. Clark, and Colleen A. McClung

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

ABSTRACT

Several factors contribute to adolescence being a particularly vulnerable time for the development of substance use and substance use disorders. We review the roles of sleep and circadian rhythms changes on addiction vulnerability during adolescence and how these may impact reward function and substance use. We highlight key additional research.

Vulnerability for Substance Use and Affective Behaviors. Early initiation of use and factors such as peer influence) and school start times are often earlier in adolescence and the use of stimulants, creating further diurnal misalignment (e.g., Logan et al, 2014, 2017; McChesney, 2007; Webb et al. 2015). We focus on factors typically receiving far less attention) and school start times are often earlier in adolescence and the use of stimulants, creating further diurnal misalignment (e.g., Logan et al, 2014, 2017; McChesney, 2007; Webb et al. 2015). We focus on factors typically receiving far less attention.)

Additional research. Despite variability in the age of onset and the pattern of use of substances, there is a striking epidemiological pattern pointing to adolescence as a vulnerable period for the development of substance use during adolescence occurs in the context of decreased cognitive control and increased sensitivity to the rewarding effects of drugs. Our review focuses on factors typically receiving far less attention.)

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Research Strategies

1. Documenting circadian rhythmicity in affect, behavior, and brain function
2. Examining associations between circadian alignment (or proxies thereof), affect/motivation, and symptoms
3. Examining associations between circadian alignment and brain function (observational and experimental)

Diurnal rhythms in reward-related processes

Time of day changes in neural response to monetary reward

For a deeper dive...
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Circadian misalignment (working definition)

A mismatch between the timing of the behavioral sleep-wake schedule and that of the internal circadian clock

Circadian alignment and adolescent substance abuse

- Sample of 21 sleep-disturbed adolescents with history of substance abuse
- Shorter phase angles associated with greater substance abuse and dependence
  \[ r^2 = .38, p < .01 \]

Haller, Bootzin, et al. 2008
Adolescents are subject to chronic circadian misalignment (aka social jet lag)

- Chronic and prefered sleep timing shift later (delay) post-puberty
- Shift towards evening chronotype
- Mismatch with early school start times

Evening-types exhibit delayed and blunted rhythms in positive effect

- Healthy young adults
- Adults with primary insomnia
- Healthy middle-aged adults

Proxies for circadian misalignment: Evening chronotype

- Chronotype (sleep timing preference) on a continuum
  - Morning-types (larks) and evening-types (owls)
- Chronotype correlates with (physiological) circadian phase
  - Morning- and evening-types have different phase alignment
- Evening types exhibit more disrupted sleep, depression, and substance involvement
- Evening types tend to report more impulsivity, risk-taking, and sensation and/or novelty seeking

Proxies for circadian misalignment: Social jet lag

- $\Delta$T = difference in sleep timing on school/work days and free days
- Tends to be worse for evening-types/late chronotypes

Childhood and adolescent sleep characteristics predict later substance involvement

- Insomnia
- Poor sleep quality
- Restless sleep
- Daytime sleepiness
- Short sleep duration
- Evening chronotype
- Weekend delays (SJs)
- Variable sleep timing
- Alcohol use
- Binge drinking
- Alkohol intoxication
- Alkohol-related problems
- AUD diagnoses or symptoms
- Onset of alcohol involvement
- Marijuana use
- Marijuana-related problems
- Other illicit drug use
- SUD diagnoses or symptoms
- Onset of marijuana involvement
- Nicotine/tobacco use

Eveningness, late sleep timing, and short sleep, but not social jet lag, predict heavy alcohol use @ 1-year

729 adolescents 12-21 y/o's from NCANDA study baseline and 1-year follow-up

- Binge alcohol use @ 1-year
- Including demographic Covariates
- Including demographic covariates and social jet lag

<table>
<thead>
<tr>
<th>Binge alcohol use @ 1-year</th>
<th>Including demographic Covariates</th>
<th>Including demographic covariates and social jet lag</th>
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Hasler et al (2017) ACER
Eveningness, late sleep timing, and short sleep, but not social jet lag, predict marijuana use @ 1-year follow-up

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<th>Marijuana use @ 1 year</th>
<th>Morning</th>
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Covariates: age, sex, race, ethnicity, SES, and baseline substance use.

Hasler et al (2017) ACER

Naturalistic study of circadian alignment in late adolescent drinkers (R21)

- 36 18-22 y/o drinkers (light, moderate, heavy) over 14 days
- Weekday-weekend transition as “natural experiment”

Smaller weekday DLMO-midsleep phase angles predicts greater weekend alcohol use

Findings hold when accounting for weekday alcohol use, sex, and/or TST

Hasler et al (in press) Chrono Int

Questions about social jet lag

- Mixed results
- Timing vs duration
- Importance of context
  - e.g., atypical social jet lag in mostly-undergrad sample

Late sleep timing and stimulation response to alcohol

144 young adult social drinkers; 10 days sleep diary; Alcohol and Control lab sessions
Self-reported stimulation based on Biphasic Alcohol Effects Scale (Alcohol-Control)

Later midsleep in Whites predicts greater stimulation ratings after alcohol consumption

Later midsleep in Males predicts greater stimulation ratings throughout the Alcohol session

Research Strategies

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Impaired reward processing may mediate link between circadian misalignment and substance use

Internal factors
- Delayed sleep phase
External factors
- Early school start times

Reward dysfunction
- Impulsivity, reward sensitivity
  - mPFC, striatum

Substance involvement

“Social jet lag” and eveningness associated with altered reward function in adolescents

Internal factors
- 56 teens (aged 11-13)
- MRI monetary reward task
- Weekday-weekend shifts in midsleep (actigraphy)

External factors
- All 20 y/o males
- MRI monetary reward task
- 21 E-types vs 13 M-types

Medial PFC
Ventral striatum

Hasler et al. Biol Psychol. 2012
Hasler et al. (2013) Psychiatry Res Neuroimag

Chronotype and “dual systems” models

INCREASING EVENINGNESS

Cognitive control

Casey, 2015; Roenneberg, 2003; Steinberg, 2010; Hasler (in preparation)

Causal direction?

Does circadian misalignment lead to altered reward function (or vice versa)?

K01 - Circadian misalignment and reward function in adolescents

Experimental study in healthy adolescents
Primary aim: To probe the effects of circadian misalignment on reward-related brain functioning.
Within-person experimental design, comparing:
**Delayed Sleep Phase Study:** 150 high schoolers (100 "delayed" phase, 50 "normal" phase)

**Social Jet Lag Study:** 150 high school drinkers (stratified across sleep timing)

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**Circadian misalignment reduces neural response during response inhibition**

- **18 healthy teens**
- Go/NoGo task: NoGo vs Rest
- Included DLMO covariate

Aligned > Misaligned - AM

- No difference on behavioral measure of accuracy during NoGo trials; no differences on Delay Discounting Task
- No regions showed greater activation during Misaligned condition (AM or PM)

249 voxel cluster peaking in left inferior frontal gyrus (t=7.25, cluster p<0.001)

Logan, Barlow, and Hasler (in preparation)

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**Ongoing adolescent studies**

**Social Jet Lag Study:** 150 high school drinkers (stratified across sleep timing)

**Delayed Sleep Phase Study:** 150 high schoolers (100 "delayed" phase, 50 "normal" phase)

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**Conclusions; what’s next**

- **Strong evidence of circadian-reward links in animal lit**
- **Growing evidence of circadian-reward links in humans**
- **Next steps**
  - More experimental designs and use of physiological measures
  - Advance sleep timing & extend sleep duration to reduce risk
  - More focus on circadian phenotype
  - Unpacking of “eveningness”—addiction association using objective sleep and circadian measures—is it all about circadian misalignment?
  - Drilling down into social jet lag construct—timing vs duration context
  - Research on caffeine’s role in teen circadian misalignment and addiction

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Don’t forget about caffeine!

- Common among adolescents
  - ~75% consume caffeine daily (Branum et al., 2014 Pediatrics)
  - 30% of 12th graders report past-month energy drink use (Terry-McElrath et al., 2014)
- Disturbs sleep and circadian rhythms
  - Double shot 3 h before habitual bedtime → 40 m phase delay in DLMO (Burke et al., 2015)
  - Caffeine enhanced light-induced phase delays in mice (Ruby et al., 2018)
- May increase substance use risk
  - High school students who mix alcohol and energy drinks also report more alcohol use and problems (Tucker et al., 2016)
  - In adolescent rats, caffeine use enhanced dopaminergic responses to cocaine (O'Neil et al., 2015)

Start with the sleep/circadian phenotype:
Circadian misalignment increases prevalence of depression in DSPD

Circadian vs Non-circadian

- Circadian
- Non-circadian
- Circadian
- Non-circadian

Murray et al. (2017) Science