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Long-lasting effects of disturbing the circadian rhythm or sleep in adolescence

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Abstract

Circadian rhythms are endogenous, near 24-hour rhythms that regulate a multitude of biological and behavioral processes across the diurnal cycle in most organisms. Over the lifespan, a bell curve pattern emerges in circadian phase preference (i.e. chronotype), with children and adults generally preferring to wake earlier and fall asleep earlier, and adolescents and young adults preferring to wake later and fall asleep later than their adult counterparts. This well-defined shift speaks to the variability of circadian rhythmicity over the lifespan and the changing needs and demands of the brain as an organism develops, particularly in the adolescent period. Indeed, adolescence is known to be a critical period of development during which dramatic neuroanatomical changes are occurring to allow for improved decision-making. Due to the large amount of re-structuring occurring in the adolescent brain, circadian disruptions during this period could have adverse consequences that persist across the lifespan. While the detrimental effects of circadian disruptions in adults have been characterized in depth, few studies have longitudinally assessed the potential long-term impacts of circadian disruptions during adolescence. Here, we will review the evidence that disruptions in circadian rhythmicity during adolescence have effects that persist into adulthood. As biological and social time often conflict in modern society, with school start times misaligned with adolescents' endogenous rhythms, it is critical to understand the long-term impacts of disrupted circadian rhythmicity in adolescence.

Key Words: circadian, sleep, adolescence, development

Introduction

Having a steady sleep/wake cycle is important for an organism's survival and well-being across the lifespan. This is particularly true in adolescence, in which the brain undergoes considerable neuroanatomical changes into adulthood (Konrad et al., 2013; Larsen & Luna, 2018; Schneider, 2013). However, this sleep/wake cycle is transiently shifted during adolescence relative to other age periods, posing potential hurdles to brain and behavioral development when disrupted. We believe that sleep and circadian disruptions during adolescence may have long reaching impacts into adulthood, but to our knowledge, few studies have attempted to understand how adolescent circadian or sleep disruptions might persistently impact brain function and behavior as the organism matures and continues aging. In this review, we will begin by discussing how circadian rhythmicity and sleep behavior change across the developmental lifespan. Next, we will describe both the short- and long-term impacts of circadian disruptions in adults and review some of the well-characterized circadian and sleep disorders (CRSDs) that are experienced by up to 3% of the adult population (Kim et al., 2013) and describe their homologs in rodents. Finally, we will discuss the acute effects of circadian disruptions in adolescence and the evidence from multiple model organisms suggesting that perturbations to circadian rhythmicity in adolescence can have longitudinal impacts that continue into adulthood. Overall, this work highlights the importance of ensuring a steady circadian rhythm across the lifespan and developing interventions to prevent the potential long-term negative impacts of disrupted circadian rhythmicity in adolescence.

The Suprachiasmatic Nucleus (SCN): the central clock of the brain and body

Most organisms have a coordinated circadian rhythm, an intrinsic oscillation of biological function that cycles approximately every 24 hours. Circadian rhythms control several physiological and behavioral outputs in organisms, such as sleep, memory, vasodilation, feeding behavior, and a multitude of other homeostatic processes (Baron et al., 2014). The seat of circadian rhythmicity in mammals is the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is a collection of neurons located within the anterior hypothalamus that is widely considered to be the "central pacemaker" of the circadian system, due to its ability to synchronize with the environment and coordinate satellite clocks across peripheral brain regions and throughout the body. One well-studied satellite circadian clock, for example, is the liver, which shows diurnal patterns in several activities that align its various functions (e.g. nutrient uptake and liver detoxification) with the expected availability of food and estimated energetic demand across the 24h day (Mukherji et al., 2019).

One major role of the SCN is to "set" the body-wide circadian system to match environmental demands, such as the 24-hour day, using entrainment cues known as zeitgebers (ZTs). The most potent zeitgebers are photic cues, like light and dark or, in a naturalistic setting, sunrise and sunset. To enable SCN neurons to synchronize to these photic cues, there is a direct connection from the retina to the hypothalamus, known as the retinohypothalamic tract, that synchronizes the firing of SCN neurons to the light cycle (Ramkisoensing & Meijer, 2015; Hendrickson et al., 1972). While light is the major zeitgeber for mammals, there are many other signals that can similarly entrain or "reset" the circadian system, including feeding time, social interaction, and body temperature (Husse et al., 2015; Pickel & Sung, 2020; Mistlberger & Skene, 2004;

Refinetti, 2020). The myriad of factors that can serve as zeitgebers reflect the system's complexity and the importance of matching the circadian rhythm to the time of day. Any disruption to the system is likely to produce wide-ranging dysfunction, so it is critical to keep the circadian system synchronized with the diurnal cycle. Overall, the SCN is essential to maintaining circadian rhythmicity, which in turn affects nearly every aspect of our lives (Hastings et al., 2018).

The molecular machinery of the circadian rhythm and its modulatory role in local functions

Most cells in the brain and body, including cells within both the SCN and downstream satellite clocks, rely on a well-defined molecular feedback loop that provides some local time-of-day information even in the absence of direct SCN input. This autoregulatory transcription-translation loop (TTFL) begins when two proteins, Circadian locomotor output cycles protein kaput (CLOCK) and Basic Helix-Loop-Helix-ARNT Like 1 (BMAL1), form a heterodimer that binds to E-box motifs upstream of two gene families: *Period* (*Per1-3*) and *Cryptochrome* (*Cry1-2*), driving their transcription. The *Per* and *Cry* transcripts are translated in the cytoplasm, where they heterodimerize, ultimately moving back into the nucleus and inhibiting subsequent CLOCK/BMAL1 activity to reduce their own transcription. Eventually, the PER and CRY protein products are degraded, eliminating the inhibition of the CLOCK-BMAL1 heterodimer and enabling this loop to begin again (Figure 1). This whole transcription-translation negative feedback loop takes around 24 hours to complete, allowing individual cells to approximately maintain a 24-hour rhythm (Partch et al., 2014; Fagiani et al., 2022; Smies et al., 2022).

While many of the satellite clocks regulated by the SCN are related largely to homeostatic behaviors, there is also evidence for satellite clocks modulating more complex behaviors, such as memory consolidation. Previously, our lab has shown that a satellite clock in the dorsal hippocampus regulates spatial memory across the day-night cycle in adult mice, with the peak of memory occurring at ZT5/12pm (where ZT0=7am, lights-on), and the trough of memory occurring at ZT17/midnight. This oscillation in memory seems to be regulated by the clock gene *Per1*, suggesting that oscillations in the local molecular clock might be capable of regulating site-specific functions in the brain (Bellfy et al., 2023). Broadly, this speaks to the complex and varied nature of circadian rhythmicity, and the possibility for it to have a multitude of unexpected roles in the regulation of brain-body functioning.

Distinguishing between the effects of disrupting sleep versus the effects of disrupting circadian rhythmicity

It is important to note that although there is a great amount of overlap, homeostatic sleep drive and circadian rhythmicity are not synonymous with each other. These interconnected systems function in tandem to promote sleep-wake behavior, but circadian rhythms are responsible for regulating several other behaviors such as feeding behavior, metabolic processes, and vasodilation (Serin & Acar, 2019; Paschos & Fitzgerald, 2010; Bechtold & Loudon, 2013). Homeostatic sleep drive, on the other hand, has the sole function of acting as a sleep regulator –

as time awake increases, the more pressure there is to sleep (Deboer et al., 2018). When we look at sleep behavior, we can see a further separation between the two processes, especially when we look at Borbély's well-validated two-process model of sleep regulation (Figure 2). This model presents an S (homeostatic sleep pressure) process and a C (circadian rhythm) process. The S process states that the longer an organism is awake, the more its sleep pressure builds, something that can only be decreased by sleeping. The C process, on the other hand, stimulates the circadian rhythmicity of the organism. This includes processes that occur around the organism's regular bedtime, such as the increased melatonin released from the pineal gland (Zisapel, 2018). The greatest urge to sleep occurs when there is the most distance between the S process curve and the C process curve; which is when sleep pressure is high and circadian wakefulness is low, creating conditions ideal for sleep. Therefore, the circadian rhythm and sleep pressure interact to modulate sleep-wake behavior (Borbély, 1982).

There is a significant amount of evidence showing that homeostatic sleep drive and circadian rhythmicity work in parallel on sleep behavior, but there is a smaller collection of data showing that sleep drive may directly impact endogenous circadian rhythms, which in turn impacts sleep behavior (Deboer, 2018). The overlapping and interconnected nature of these systems makes it nearly impossible to parse them apart completely, as disrupting the circadian rhythm typically affects sleep and vice versa, but it is likely that each has a unique effect on an organism's behavior and development. Therefore, we will attempt to separate these processes when possible in this review, despite the extreme methodological challenges of separating them experimentally. When we refer to "homeostatic sleep drive", we are solely referring to the increasing pressure for sleep the longer an organism is awake. When we refer to "circadian rhythms", we are talking more broadly about the near 24-hour rhythms that govern a multitude of behaviors in addition to sleep-wake behaviors.

As it is nearly impossible to disrupt either sleep or the circadian rhythm without affecting both processes, most research on the subject has not attempted to separate these processes, but rather looks at them together. Currently, there are no validated experimental methods for disrupting one process without disrupting the other.

Acute and chronic effects of disruptions in sleep and circadian rhythms in adulthood

Most of what is known about the effects of disrupting the circadian rhythm and sleep comes from work that has been done in adults. One of the best examples of acute circadian rhythm disruption in adults is jetlag. This occurs when one travels across multiple different time zones in a short period of time, and is associated with fatigue, gastrointestinal distress, insomnia, irritability, and memory disruptions (Choy & Salbu, 2011; Horsey et al., 2020). Although acute disruptions of sleep and circadian rhythmicity have drastic short-term impacts, brief disruptions typically do not have lasting negative impacts. In contrast, chronic circadian disruption can persistently increase the risk of negative outcomes, both physiological and psychological, in individuals. One such example of chronic circadian disruption occurs in shift work, which puts individuals at a higher risk for cardiovascular disease, diabetes, affective disorders, obesity, fertility issues, cancer, and more (Costa, 2010). Rodents that underwent a paradigm mimicking human shift

work also showed many of these same negative and persistent effects (Marti et al., 2020; Banks et al., 2022).

There are several chronic sleep and circadian rhythm disorders that have been classified and well-characterized in adult humans and replicated within rodent models. Circadian rhythm sleep disorders (CRSDs) occur when there is a fundamental misalignment between an individual's endogenous circadian rhythm and their actual sleep-wake schedule. These fall into one of two categories: extrinsic or intrinsic. Extrinsic CRSDs, which have an exogenous cause, are most often caused by shift work and jet lag. Shift work sleep disorder is often seen in night shift workers and is characterized by excessive sleepiness and/or insomnia that occurs when a person's work schedule overlaps with their primary sleep period. Jet lag disorder occurs most prominently in individuals who frequently travel across multiple time zones and experience consistent rhythm disruptions. Many of the same negative symptoms are seen in jet lag disorder as shift work sleep disorder, but gastrointestinal distress is also a frequent outcome (Choy & Salbu, 2011; Bezrucha, 2017).

Intrinsic CRSDs, on the other hand, have endogenous causes, typically due to disruptions in the molecular clock needed to support healthy rhythmicity. There are four officially identified, genetically-based intrinsic CRSDs: delayed sleep phase disorder, advanced sleep phase disorder, non 24-hour sleep-wake disorder, and irregular circadian rhythm sleep disorder. In delayed and advanced sleep phase disorder, individuals have a 3-6 hour delay or advance, respectively, in their sleep wake cycle. Delayed sleep phase disorder is often characterized by difficulty falling asleep and difficulty waking, while advanced sleep phase disorder is associated with early evening sleepiness and early morning awakenings. Advanced sleep phase disorder is often much harder to identify due to its close match to many school and work schedules and is typically less disruptive to the individual. Non 24-hour sleep-wake disorder is a disorder in which individuals fail to entrain their circadian rhythms to a stable time, and therefore experience a continuous delay of circadian rhythms. This is most common within completely blind individuals who lack the ability to use visual zeitgebers to entrain to a circadian rhythm. Finally, irregular circadian rhythm sleep disorder is a rare condition in which no clear circadian rhythm is observed (Baron et al., 2014; International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual, 2005). Intrinsic CRSDs are prominently caused by mutations in specific clock genes, largely *Per* and *Cry* (Liu et al., 2022). Of the intrinsic CRSDs, the most common is delayed sleep phase disorder and therefore the negative outcomes of this disorder are the best studied. Delayed sleep phase disorder can result in impaired functioning during the daytime, a chronic lack of sleep, and an increased risk of affective disorders. One key domain of impaired functioning with loss of sleep is memory (Takaesu et al., 2022). In one relevant study, adolescents with delayed sleep phase disorder showed an improvement in memory-related cognition tasks after receiving 3 weeks of light therapy to help entrain them to regular circadian rhythm (Richardson et al., 2018).

Most of these CRSDs, especially those that are intrinsic and based on a genetic mutation, are replicable within rodent models. For example, researchers have been able to replicate advanced phase sleep disorder in a transgenic mouse model utilizing a forward genetics approach (Jiang et al., 2011). Several other dysregulations in circadian rhythmicity, translational to human CRSDs, have been produced using similar methodology in genetically modified mouse strains (Lowrey et

al., 2000; Xu et al., 2005). Ultimately, this work demonstrates that chronically disrupting sleep or the circadian rhythm, whether from internal or external causes, has severe consequences for a number of biological systems.

Additionally, non-pathological sleep disruptions can also have negative consequences. For example, sporadic disruptions to sleep in otherwise healthy adults, such as a bout of insomnia, can have both short-term and long-term deleterious consequences. The short-term consequences of sleep disruption include increased stress and negative emotional reactivity, as well as performance and cognitive difficulties. The long-term consequences of sleep disruption include cardiovascular disease, hypertension, and metabolic and weight-related issues (Medic et al., 2017). It has also been shown that short-term sleep deprivation can have long-term impacts in mice, specifically within the realm of memory. In fact, even a short period of sleep deprivation 1 hour after a learning event functionally impaired the formation of spatial memories within the dorsal hippocampus by decreasing neuronal connectivity (Havekes & Abel, 2017; Havekes et al., 2016).

Changing circadian rhythmicity across the lifespan

Perhaps the best-known descriptors of circadian rhythmicity and sleep patterns are the colloquial terms “lark” and “owl”, which refer to an individual’s general chronotype. The term “chronotype”, first presented by Ehret in the 1970s, refers to “the temporal phenotype of an organism” (Ehret 1974). Late chronotype “owls” are characterized by later bedtimes, and awakenings later in the day. Early chronotype “larks” are characterized by earlier bedtimes, and earlier awakenings. Although chronotypes were first defined in humans, rodents also show well-defined chronotypes when allowed to follow a free-running clock without external time-givers, like light, to establish their diurnal cycle. Due to the nocturnal nature of rodents, a slightly different equation known as the median of activity (MoA) is used to determine chronotype. MoA studies have revealed a difference in chronotypes within several common inbred strains of lab mice (Pfeffer et al., 2015; Wicht et al., 2014). C57Bl/6 mice, for example, display a “late” chronotype, with a longer latency to MoA, while C3H mice display an early chronotype, with a shorter latency and earlier ZT time to MoA (Pfeffer et al., 2015). Thus, it is important to consider that the peak and trough diurnal times may vary across both function and mouse strain.

Across the human lifespan, there is a stereotyped shifting of this chronotype. Although there is individual variability, chronotype tends to follow a bell curve shape, with an early chronotype preferred by children and adults and a later chronotype preferred by adolescents and young adults (Randler et al., 2017). Major changes in chronotype therefore occur in adolescence, with a sudden shift from an early to a late chronotype. Importantly, adolescence is a key developmental period and one in which an individual’s chronotypic preference is most at odds with social expectations. Therefore, adolescence emerges as an important time for studying the impact of circadian disruptions (Larsen & Luna, 2018).

Adolescence is a unique developmental period

Adolescence is a critical developmental period characterized by rapid neural and physical maturation (Larsen & Luna, 2018; Schneider, 2013). A basic reorganization of the brain occurs during adolescence, characterized by an overproduction of synapses and axons at the beginning of adolescence, followed by rapid dendritic pruning in late adolescence to fine-tune circuits, especially those involved with decision-making (Konrad et al., 2013). Importantly, adolescence is the first developmental period in which there emerges a fundamental mismatch between the individual's shifting chronotype and societal scheduling demands, like school hours. It is therefore critical to understand how circadian disruptions in adolescence may have a persistent impact on development and subsequent adult functioning.

Although the adolescent period does not have a precise and static definition, in humans, adolescence is typically defined via sociological and demographic parameters as the life phase spanning between 10 and 19 years old (WHO, 2023; Richter, 2006). In laboratory rodent models, although definitions also vary, adolescence is typically characterized as the period from postnatal day 21 (PN21) which is when weaning occurs, to approximately postnatal day 60 (PN60), when sexual maturation is achieved. This can be further broken down into the periods of early adolescence (PN21-PN36), periadolescence (PN37- PN48), and late adolescence (PN49- PN60) (Nelson et al., 2013). As a note, some researchers define adolescence in rodents as PN28-PN48, with PN21-PN27 being defined as the "juvenile" period (Schneider, 2013; Semple et al. 2013). Humans, which have an extended adolescence compared to other primates, map generally onto this same model. In the case of humans, early adolescence, periadolescence (typically referred to as middle adolescence), and late adolescence can be better understood as referring to the periods of pre-puberty, puberty, and post-puberty, respectively (Chini & Hanganu-Opatz, 2021; Christie & Viner, 2005).

Across model systems, adolescence is a critical period of development, when brain structures and circuitry associated with affective behaviors (such as anxiety, behavioral inhibition, decision-making, social behavior, and memory) are maturing. Key brain regions implicated in these behaviors include the medial prefrontal cortex (mPFC), nucleus accumbens (NA), and basolateral amygdala (BLA). These regions undergo rapid re-structuring that includes a host of postsynaptic changes across regions, such as dendritic spine and complexity increases during early adolescence (Casey et al., 2008; Koss et al., 2013). These morphological changes continue into periadolescence alongside pruning and increases in the capacity of PFC inputs to engage the amygdala into late adolescence (Cressman et al., 2010; Koss et al., 2013; Selleck et al., 2018). Similarly, NA neurons undergo a host of developmental changes from early adolescence into adulthood that are characterized by reduced excitability and excitatory postsynaptic currents that are postulated to contribute to the refinement of medium spiny neuronal and synaptic activity within the NA from adolescence into adulthood (Kasanetz & Manzoni, 2009). These maturational trajectories collectively identify several structural and functional changes throughout the adolescent time period that may regulate affective behavioral development and also coincide with and are impacted by puberty, a key period for sexual maturation and neuroendocrine system development (Romeo, 2005). Additionally, key structures involved in the circadian rhythm itself, notably the SCN, also undergo massive changes during adolescence. In addition to increased sensitivity to light during purberty and changes in circadian period length,

the structure itself increases in size, possibly due to gonadal hormone exposure during this period (Hagenauer et al., 2012). There is a dearth of research on whether the molecular clock itself is affected by these hormonal changes or whether molecular rhythm changes during adolescence, however, a critical gap in research that should be the focus of future work. This research is critical to develop a holistic understanding of how the brain matures during this period, and how these processes are governed by the circadian system, is therefore critical.

Disruptions in brain function that occur during adolescence can have long-lasting negative impacts that persist into adulthood. For example, individuals who experience early life stress (ELS) in adolescence are more susceptible to affective disorders in adulthood (Chapman et al., 2004). This finding has been replicated many times in rodent models, with higher levels of anxiety and depressive-like behavior in adulthood on a battery of behavioral tests if they experienced stress during the adolescent period (Ameen et al., 2022; Qin et al., 2021). This robust effect has also been shown in other model organisms, such as zebrafish. In one such study, zebrafish exposed to ELS exhibited immunodeficiency and increased anxiety-like behavior in adulthood (Graves et al., 2023). Additionally, stress in early life can also cause permanent gross anatomical and physiological changes in the brain, in addition to altered behavioral expression (Shin et al., 2023). In one particularly relevant study, mice exposed to early life circadian disruptions displayed increased anxiety-like behavior and impaired memory performance (Ameen et al., 2022). This was accompanied by a decrease in neuronal complexity, indexed with dendritic length, within the dorsal hippocampus (DH), BLA, and mPFC, stunting the typical dendritic maturational profile of these regions during adolescence (Ameen et al., 2022). Another study similarly showed that developmental sleep disruption in rodents also caused wide- ranging neuroanatomical changes, adding the ventral tegmental area (VTA) involved in social novelty to the list of impacted areas (Bian et al., 2022). Looking at circadian rhythmicity within adolescence is particularly important, as this is the first period during which a real mismatch between circadian rhythmicity and societal chronotype expectations is seen (Pfeffer et al., 2015; Randler et al., 2017). This suggests that perturbations occurring during adolescence can have severe and persistent consequences in the structure and function of the brain in adulthood. These morphological neural changes due to ELS can also be seen in humans, as several studies have shown reduced hippocampal volume in adulthood following ELS in adolescence (Hanson et al., 2015; Teicher et al., 2017).
Due to ongoing brain development, adolescent brain disruption could have long-term impacts on a number of modalities important to regular functioning, and it also makes adolescence an important period for intervention.

Baseline differences in circadian rhythmicity across the developmental lifespan

There is a well-defined shift in circadian rhythmicity across the lifespan of humans, in which general chronotypes follow a well-defined bell curve (Figure 3). In rodents, although this shift has not been as thoroughly characterized as in humans, phase advancement and circadian disruption occur with aging, due to alterations within the SCN and an overall lack of synchronization (Biello, 2009). Children and adults tend to have earlier chronotypes, whereas adolescents and young adults typically have later chronotypes (Pfeffer et al., 2015). Chronotypes exist in a number of species (including rodents, see below) and, in humans, have a genetic basis

(Kalmbach et al., 2017), suggesting that these diurnal preferences have a biological basis. Chronotypes are important and predictive, as it has been shown that having a late chronotype puts humans at a higher risk for several affective disorders and health conditions, possibly because late chronotypes are in conflict with societal demands. Fixed school and work schedules, for example, fit within an early chronotype pattern, conflicting with the late chronotype of some individuals, including adolescents. Therefore, late chronotype individuals are forced to comply with earlier wake up times despite their later bedtimes, causing sleep debt. This mismatch between natural chronotype and social chronotype is known as "social jetlag". Oftentimes, these individuals will compensate for this sleep debt on weekdays by sleeping for much longer periods on the weekends. However, this puts them at a disadvantage compared to early chronotype individuals who do not experience the same dissonance between natural chronotype and social chronotype. The constant game of catch-up played by late chronotype individuals puts them at a higher risk for mood disorders, such as depression and anxiety, as well as chronic diseases such as Type 2 diabetes and cardiovascular disease (Baldanzi et al., 2022; Zou et al., 2022).

Interestingly, although rodents do not experience the same social chronotype expectations as humans, they show many of the same markers of dysregulation seen in late chronotype humans. First, there is evidence for a pubertal shift in chronotype in mice towards a later chronotype, similar to that seen in adolescent humans (Weinert & Waterhouse, 1999). Perhaps the most interesting finding is that mice displaying an early chronotype showed more stable, consistent circadian rhythms, as compared to late chronotype mice (Wicht et al., 2014, Pfeffer et al., 2015, di Milia & Folkard, 2021). This same pattern is seen in humans, wherein late chronotype individuals have increased rhythm instability, but this has often been attributed to the mismatch between natural chronotype and social chronotype (Pfeffer et al.,2015). Considering these correlations of chronotype are seen in mice, it appears that late chronotype is damaging, even without the presence of societal expectations or societal "jet-lag". Overall, this is a developing field where further study is necessary to draw more concrete conclusions, but we can postulate from the current research that there is a conserved aspect to chronotypes across species. Despite the fact that social demands in rodents are not equivalent to those in humans, there is still evidence for a possible social aspect of circadian rhythms and chronotype. Specifically, there is research showing that social hierarchy may play an important role in determining circadian rhythmicity within a cage. Within group-housed cages, dominant male mice showed a larger percentage of daytime activity compared to their subordinate conspecifics, but this finding was not seen in females (Robbers et al., 2021). This finding paves the way for further research into individual differentiation in chronotypes amongst mice, and the impact of social demands on circadian rhythmicity within mice.

Additionally, it is important to note that several sex differences in circadian rhythmicity exist, although they fall outside the scope of focus of this review. These include, but are not limited to, circadian-mediated differences in heart rate, immune functioning, and body temperature (Walton et al., 2022). Of note, males also display later chronotypes than females from the approximate ages of 15-50, putting them at higher risk for affective disorders and chronic diseases (Roenneberg et al., 2004). However, all of this work has been done within humans, so it will be important to examine whether these sex differences translate across species.

Effects of disruptions in sleep/circadian rhythms in adolescents

The acute effects of circadian disruptions in adolescents are very similar to those seen in adults – fatigue, irritability, gastrointestinal distress, and more (Kansagra, 2020). Acute circadian and sleep disruption in adolescents has also been linked to poorer memory and worse academic performance (Vik et al., 2022). As adolescence is a period of rapid neuroanatomical and neuroelectrical maturation during which a number of changes to brain structure and circuitry occur. Therefore, it is likely that circadian or sleep disruptions during this period could have persistent consequences.

Despite the well-defined effects of acute circadian disruption in adolescence, there is a dearth of research on the long-term impacts of chronic circadian disruption during adolescence. Of the existing research, there is substantial evidence linking chronic circadian disruption in adolescence with increased drug-taking and a higher risk of affective disorders (Kuula et al., 2022; Atrooz et al., 2022; Anastasiades et al., 2022). These studies implicate differences in connectivity and neurocircuitry as the catalyst for future drug use and emotional regulation problems, with the reward pathway being one such example of a disrupted pathway. There is evidence showing that circadian disruptions in adolescence stunt the maturation of reward circuitry. An increase of neuronal activity within the NA and VTA, both of which are key reward circuitry structures, is seen following acute adolescent sleep deprivation, during developmental periods typically characterized by reduced synaptic and neuronal activity. This indicates a potential increase in the rewarding properties of drugs following sleep deprivation (Atrooz et al., 2022; García-García et al., 2021). Additionally, research has shown that mice who underwent circadian disruptions in adolescence showed impaired memory and an increase in anxiety-like behavior in adulthood, as well as neuroanatomical stunting within areas of the brain related to decision making, affective emotion, and spatial memory (Ameen et al., 2022). Although this is a promising start in looking at the longitudinal effects of circadian disruptions in adolescence, there is a lack of mechanistic studies in rodent models to identify the underlying molecular mechanisms causing these chronic circadian disruptions needs to be filled. Additionally, it is important that research be done in a variety of modalities, rather than just focusing on psychological disorders and drug use. The issue of chronic sleep and circadian disruptions in adolescence is an epidemic, with a Youth Risk Behavior survey carried out in 2018 reporting that 72.7% of adolescents surveyed received significantly less than the recommended hours of sleep regularly during the school week (Wheaton et al., 2018). It is therefore critical to understand if these circadian disruptions in adolescence have mechanistic, structural, and functional consequences that persist into adulthood.

Do disruptions in sleep and circadian rhythmicity in adolescence have long reaching impacts into adulthood?

Throughout this review, we have posited that disruptions to sleep and circadian rhythmicity during adolescence will have long-term impacts into adulthood, and indeed there is a body of evidence that supports this. In both human research and in rodent models, disruptions to the circadian rhythm and sleep during adolescence impact physiological functioning and behavioral

performance in adulthood. In one example, Ameen and colleagues (2022) used a paradigm of early life circadian disruption in which they placed mice on a rapidly shifting light-dark cycle. Once the mice reached adulthood, they were put through a behavioral battery to assess anxiety and depressive-like behaviors, as well as working and spatial memory. The researchers found that mice exposed to early-life circadian disruptions showed increased anxiety-like behaviors and a decrease in both spatial and working memory (Ameen et al., 2022). This suggests that severe circadian disruptions in adolescence can have persistent negative impacts that affect mood and memory in adulthood.

In another related study in rats, it was shown that adolescent sleep deprivation led to increased anxiety-like behavior and enhanced alcohol consumption in early adulthood (Atrooz et al., 2022). This finding has been replicated within humans, in which both poor quality of sleep and a shorter duration of sleep during adolescence were predictive of various substance-related issues in adulthood (Wong et al., 2015). Additionally, individuals who favor a late chronotype across the lifespan showed a higher prevalence of generalized anxiety disorder and other psychiatric disorders. Disrupting sleep in adolescence therefore seems to increase an individual's susceptibility to developing a substance use disorder.

In addition to behavioral deficits, disruptions to sleep and circadian rhythms in adolescence can cause long-term neural morphological consequences. In the study mentioned above, Ameen and colleagues also found that there was a decrease in neuronal complexity within areas associated with anxiety and memory (BLA, DH, mPFC) (2022). In humans, a reduction in hippocampal and amygdalar volume was seen in individuals who underwent early life stress and sleep disruption (Hanson et al., 2015; Teicher et al., 2018). These negative anatomical changes within memory relevant brain regions help to broaden our understanding of memory disruptions due to early life circadian disturbance, and their underlying mechanistic cause.

It is critically important that we better understand these long-term impacts, in order to create interventions aimed towards avoiding deleterious outcomes. By conducting more translational studies identifying molecular signatures of risk in these populations, we may be able to create positive interventions at the genetic level. Additionally, it is important to continue advocating school boards to set their school day schedules more in accordance with the late chronotype displayed by adolescents and young adults, in order to avoid the "social jetlag" caused by this misalignment between natural chronotype and social chronotype, which predisposes them to many of the risks in adulthood.

Conclusion

Adolescence is a key developmental stage in which a number of important physiological and neurological changes are occurring to allow us to transition into adulthood. We know that disruptions during this period can have long-term deleterious effects, as shown in studies of early life stress. Additionally, it is well-validated that disruptions to circadian rhythmicity and sleep in adolescence have negative acute effects, such as moodiness, fatigue, cognition issues, and more. Taken together, our review presents compelling evidence that disrupting the circadian rhythm or sleep in adolescence can have long-term detrimental impacts to the individual, including memory

issues and a higher risk for affective and substance use disorders in adulthood. These issues become endemic when we take into account the mismatch between most adolescents' chronotypes, and their enforced school schedule. It is vital that we dig further into the chronic negative outcomes of sleep and circadian rhythm disruptions in adolescence, so that we are better able to prevent them.

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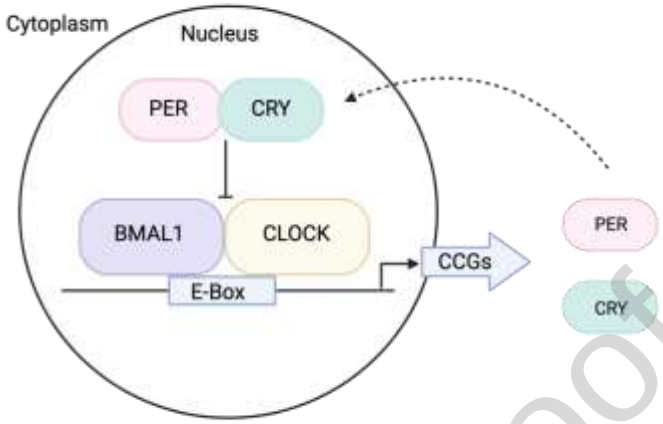

Figure 1. *The basic molecular clock. The molecular circadian clock is a self-regulatory feedback loop. First ,CLOCK and BMAL1 form a heterodimer and bind the E-box region upstream of two clock gene families:* Per *and* Cry*, inducing their transcription.* Per *and* Cry *genes are then translated in the cytoplasm, heterodimerize, and translocate back into to the nucleus, where they inhibit subsequent* CLOCK/BMAL1 *activity, essentially reducing their own transcription. As Per and Cry degrade, this inhibition of CLOCK-BMAL1 is released, and the loop begins again. The whole feedback loop takes around 24 hours to complete. PER:Period, CRY:Cryptochrome, BMAL1:Basic Helix-Loop-Helix ARNT Like 1, CLOCK:Circadian Locomotor Output Cycles Kaput, CCG:clock-controlled genes.*

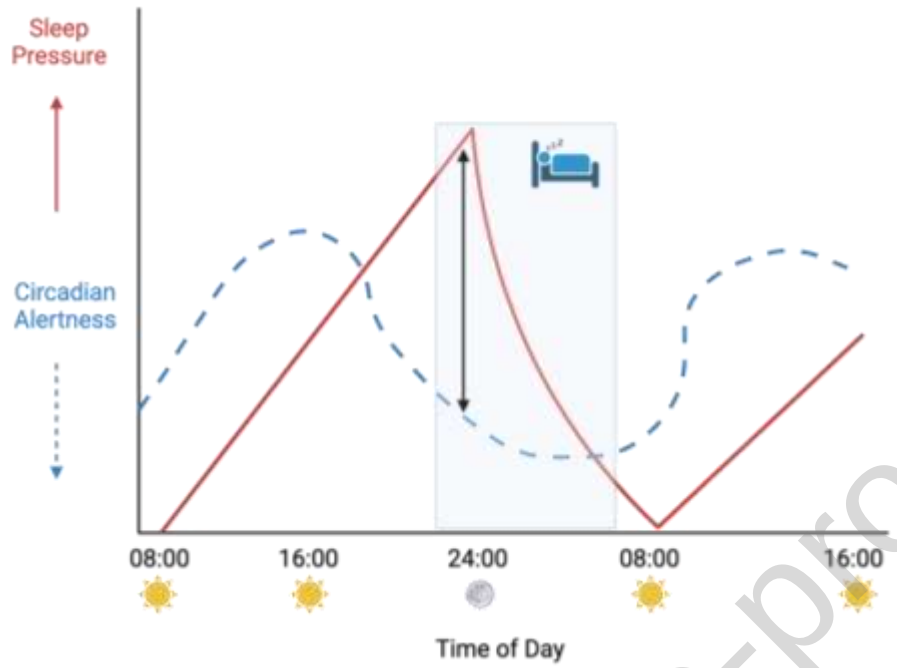

Figure 2. *Two-process model of sleep regulation (adapted from van Bommel, 2021). The greatest urge to sleep occurs in the shaded area, where there is the largest distance between processes.*

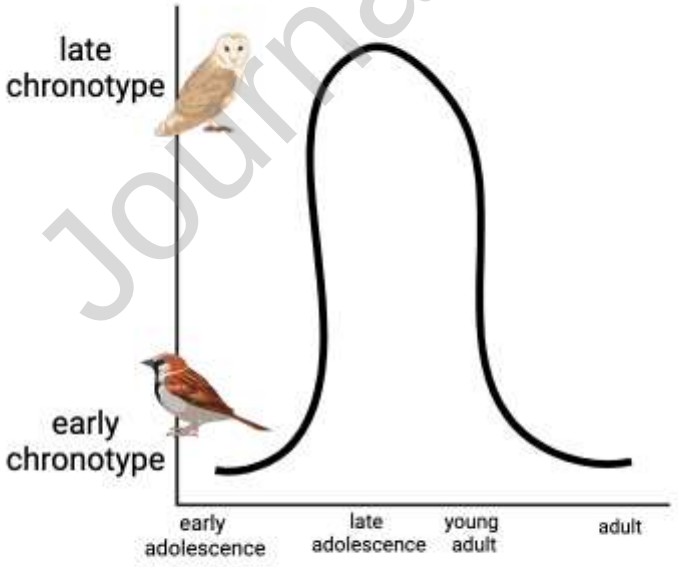

Figure 3. *Typical chronotype changes seen across the human lifespan.*

Declaration of Competing Interest

The authors have no declarations of interest.

Highlights

- Circadian rhythms regulate a number of biological systems including memory
- Many brain structures important for memory are developing during adolescence
- In adolescence, a mismatch between circadian and societal time develops
- Disrupted circadian rhythms in adolescence may have lasting consequences