

# Synchrony and desynchrony in circadian clocks: impacts on learning and memory

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Circadian clocks evolved under conditions of environmental variation, primarily alternating light dark cycles, to enable organisms to anticipate daily environmental events and coordinate metabolic, physiological, and behavioral activities. However, modern lifestyle and advances in technology have increased the percentage of individuals working in phases misaligned with natural circadian activity rhythms. Endogenous circadian oscillators modulate alertness, the acquisition of learning, memory formation, and the recall of memory with examples of circadian modulation of memory observed across phyla from invertebrates to humans. Cognitive performance and memory are significantly diminished when occurring out of phase with natural circadian rhythms. Disruptions in circadian regulation can lead to impairment in the formation of memories and manifestation of other cognitive deficits. This review explores the types of interactions through which the circadian clock modulates cognition, highlights recent progress in identifying mechanistic interactions between the circadian system and the processes involved in memory formation, and outlines methods used to remediate circadian perturbations and reinforce circadian adaptation.

Circadian clocks permit organisms to anticipate recurring daily environmental events through the coordination of metabolic, physiological, and behavioral rhythms. Conservation of the core principles through which circadian oscillators are organized across eukaryotic phyla suggests strong selective pressures for both circadian clocks and the mechanisms through which circadian oscillators operate. Intracellularly, transcription/translation feedback loops involving core circadian components set the stage for transcriptional regulation of thousands of genes in individual cells and tissues (Balsalobre et al. 2000b; McDonald and Rosbash 2001; Panda et al. 2002; Yoo et al. 2004; Doherty and Kay 2010; for recent review of mammalian circadian oscillators, see Buhr and Takahashi 2013). Circadian oscillators operate within single cells using neuropeptide communication to promote synchronization and coordination of output regulation, primarily vasoactive intestinal peptide (VIP) for coordination of circadian pacemaker neurons within the suprachiasmatic nucleus (SCN) in mammals with other contributing neurotransmitters (Aton et al. 2005; Maywood et al. 2006, 2011; Evans et al. 2013) and pigment-dispersing factor (PDF) in fruit flies (Renn et al. 1999; Duvall and Taghert 2012). At a systems level, the SCN within the hypothalamus broadly acts as the master circadian clock in mammals synchronizing circadian oscillators in multiple tissues such as pancreas, adipose tissue, lungs, skeletal muscles, adrenal glands, ovaries, and cell types including neurons, fibroblasts, and islet cells (Honma et al. 2012; Mohawk et al. 2012; Pulimeno et al. 2013; Sellix 2015). This hierarchy stands in contrast to the circadian system in lower vertebrates such as fish or invertebrates, e.g., *Drosophila melanogaster*, in which independently entrainable oscillators may be found throughout the organism (Plautz et al. 1997; Whitmore et al. 2000). Nonetheless, even in mammals independent peripheral oscillators exist including the food-entrainable oscillator in the liver (Stephan 2002; Saper and Fuller 2007; Mistlberger 2011) and oscillators in the olfactory bulb (Granados-Fuentes et al. 2004; Abraham et al. 2005; Miller et al. 2014).

Circadian rhythms have been observed for centuries in plants (McClung 2006) and animals (for review, see Moore-Ede et al. 1982); however, our understanding of the impact of the circadian clock on disease remained limited for much of the last century despite rapid progress identifying the molecular mechanisms underlying the circadian oscillator. In *Drosophila*, circadian mutants exhibited few negative consequences altering health, fecundity, or longevity, although more recently reductions in lifespan have been observed for circadian mutants in a sex-specific manner or under stressful conditions (Shaw et al. 2002; Hendricks et al. 2003). Similarly, no adverse health impacts initially were observed in *tau*, the first identified short period mutant in mammals (Ralph and Menaker 1988), although later studies identified longevity impacts (Hurd and Ralph 1998), significant cardiovascular disease issues (Martino et al. 2007), and a correlation between shorter period length and smaller body size (Refinetti 2014).

## Desynchronization of the circadian clock

Under conditions of circadian perturbation in which environmental conditions abruptly change, e.g., flying across multiple time zones, the temporal synchronization of circadian oscillators with the environment is suspended. Within the SCN, circadian neurons become desynchronized from each other with resynchronization taking 5–7 d after long-phase delays and 9–13 d after long-phase advances (Nagano et al. 2003). Similarly, peripheral oscillators across tissues and organs also need to resynchronize with each other and the SCN, and generally take longer to resynchronize than the SCN (Yamazaki et al. 2000). However, the length of time necessary to achieve stable phases attuned to the new photoperiod varies between tissues and organs (for review, see Harrington 2010), with ~8 d necessary for full

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peripheral resynchronization following a 6 h phase advance (Davidson et al. 2009; Kiessling et al. 2010).

Throughout the last two centuries, technological advances have dramatically changed individual work and rest patterns. (Luckhaupt 2012; Alterman et al. 2013) Individuals increasingly work longer hours with progressively more individuals working nontraditional schedules. In 2004, 17.7% of US workers (~15 million full-time employees) worked hours outside of a traditional day shift (U.S. Bureau of Labor Statistics 2005; McMenamin 2007; Alterman et al. 2013) with that number increasing to 28.7% by 2010 demonstrating a rapid increase in the scope of nontraditional shift work (Alterman et al. 2013). On a global level, individuals performing shift-work comprise >15% of the workforce in many developed countries (for review, see Wright et al. 2013). Across professions and industries, career and economic pressures often extend an individual's working hours with 18.7% of Americans working >48 h per week and 7.2% working 60 h or greater (Alterman et al. 2013). However, this number probably underestimates the number of individuals with shift work or extended work-weeks (Grosch et al. 2006; Alterman et al. 2013).

Individuals working traditional schedules also suffer from circadian desynchronization through social jet lag, a phenomenon in which individuals shift their activity and sleep patterns between the work week and the weekend with most individuals sleeping considerably later on weekends (Wittmann et al. 2006; Roenneberg 2013). Social jet-lag results in a bi-weekly phase shifting of the circadian clock similar to individuals with shift-work schedules rotating between day and afternoon-evening shifts. Shift-work and social jet-lag affect individual health, and increase safety risks and economic costs to businesses and society. Misalignment of the circadian system with scheduled work results in increased industrial and occupational accident rates, decreased work productivity, increased traffic accidents, and increases the risk for performance errors with adverse impacts for individuals in healthcare, transportation and public safety professions (Lockley et al. 2007; Keller 2009; Wright et al. 2013).

In the past decade, the adverse impacts of circadian dysfunction on human health have become clear. Desynchronization or aberrant functioning of circadian oscillators result in significant health consequences with increased risk and incidence of obesity, diabetes, cancer, and heart disease as well as other diseases (Barnard and Nolan 2008; Preuss et al. 2008; Arble et al. 2010; Bass and Takahashi 2010; Karatsoreos et al. 2011; Evans and Davidson 2013; Orozco-Solis and Sassone-Corsi 2014; Pluquet et al. 2014). Furthermore, circadian dysfunction may increase susceptibility to mood disorders or the incidence of drug abuse (Logan et al. 2014; Zelinski et al. 2014).

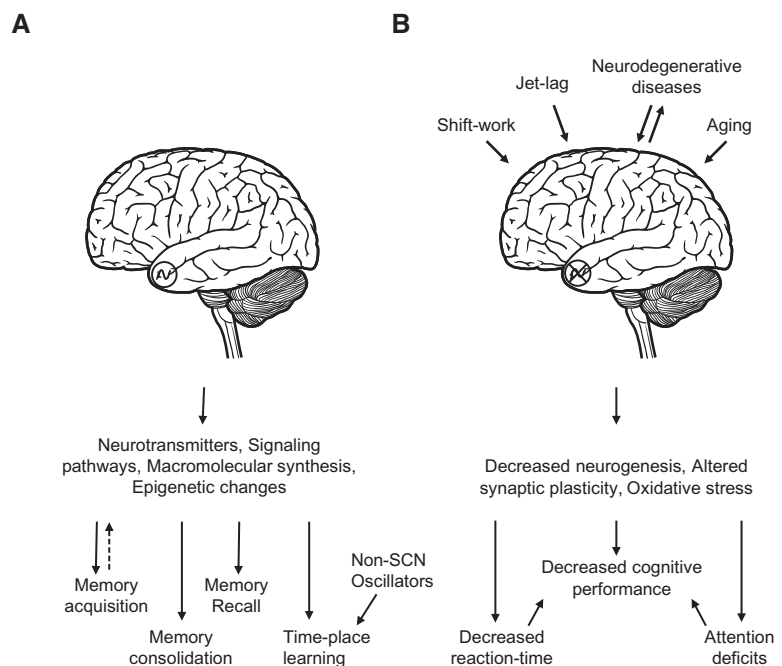
## Types of circadian interactions with learning and memory

The circadian clock broadly affects metabolic and physiological processes with adverse consequences to the individual when circadian oscillators are desynchronized, so it is not surprising that memory and cognitive performance

also are under circadian control. There is a critical need for identifying and understanding the mechanisms through which the circadian clock affects memory and cognitive performance. Four major interactions of the circadian clock with the processes of learning and memory will be reviewed (Fig. 1): (1) the impact of circadian dysfunction on memory, (2) circadian modulation of memory formation or recall, (3) daily time place learning, a temporal-spatial form of learning that incorporates time-stamping, and (4) interactions between the circadian clock, aging, and neurodegenerative diseases.

## Circadian dysfunction and memory

Desynchronization or misalignment of circadian oscillators causes decrements in cognitive function as observed in animal models and humans. Chronic jet lag lasting several years decreases cognitive performance in flight crews compared with flight crews routinely crossing less than three time zones (Cho et al. 2000). Moreover, these cognitive decrements were accompanied by higher cortisol levels and temporal lobe atrophy (Cho 2001). Experimental jet-lag conditions in hamsters also resulted in persistent long-term cognitive deficits in spatial memory accompanied by significant decreases in cell proliferation and hippocampal neurogenesis (Gibson et al. 2010). The severity of neurogenesis deficits are direction dependent with phase advances resulting in greater suppression of hippocampal neurogenesis (Kott et al. 2012). Circadian disruption through constant light conditions (Daan and Pittendrigh 1976) decreases performance in the Morris water maze along with hippocampal neurogenesis (Fujioka et al. 2011). In wild-type hamsters with the SCN intact, induction of circadian dysrhythmia impairs spatial and recognition memory (Fernandez et al. 2014). Acute experimental jet lag also disrupts recall of long-term contextual fear conditioning in mice (Loh et al. 2010). As seen with many learning paradigms, acute circadian phase shifts



**Figure 1.** Interactions between the circadian oscillator and memory. (A) The circadian clock modulates learning and memory by interacting with underlying molecular mechanisms. (B) Desynchronization of the circadian clock by environmental and behavioral factors leads to cognitive impairments.

following training produce deficits in memory recall and retrograde amnesia (Tapp and Holloway 1981; Fekete et al. 1985; Devan et al. 2001; see Smarr et al. 2014 for additional examples and discussion of rodent models).

Recent occupational studies found significant cognitive impairments in long-time shift workers (Rouch et al. 2005; Marquié et al. 2015), with a cognitive loss equivalent of 6.5 yr compared with age-related decline cohorts (Marquié et al. 2015). While these deficits are, at least, partially reversible (Rouch et al. 2005), the cognitive decrements in long-time shift workers (> 10 yr) persist for 5 yr after the conclusion of shift work (Marquié et al. 2015). Even for experienced shift workers, short-term memory (STM) is compromised after night work (Meijman et al. 1993). Thus, the desynchronization and misalignment of the circadian system caused by shift work or jet lag significantly decreases memory and performance in addition to increasing the incidence and risk of many diseases.

### Circadian rhythms in memory acquisition, recall, and extinction

Under normal conditions, daily modulation of learning and memory is observed across species ranging from invertebrates to humans. The scope and complexity of circadian modulation can be illustrated using invertebrate models of learning. In the diurnal *Aplysia californica*, peak intermediate (ITM) and long-term memory (LTM) formation for nonassociative and associative learning paradigms occur during the day in coordination with the animal's activity period (Fernandez et al. 2003; Lyons et al. 2005, 2008) while LTM in nocturnal *Aplysia fasciata* peaks during the night (Lyons et al. 2005). However, circadian modulation of memory may occur independently of circadian regulation of rest/activity cycles. Despite the difference in activity between crepuscular *Drosophila* and nocturnal cockroaches, short and long-term olfactory memory arising from classical conditioning in both models is modulated by the circadian clock with peak performance during the early (subjective) night (Decker et al. 2007; Lyons and Roman 2009; Fropf et al. 2014). Bees demonstrate more robust learning when trained and tested early in the day relative to other time points and independent of the feeding schedule (Lehmann et al. 2011). Thus, the phase of circadian peaks and troughs in memory varies between learning paradigms and species, potentially entwined with coordination of related behaviors and processes.

In rodents, acquisition of hippocampal-dependent learning paradigms such as Morris water maze, contextual fear conditioning, and the radial arm maze, is higher during the night (Hauber and Bareiss 2001; Valentinuzzi et al. 2001, 2004). Similarly in hippocampal long-term potentiation, the amplitude of population spikes is significantly greater during the night (Chaudhury et al. 2005). Furthermore, memory persistence is dependent upon time of training with increased retention observed when nocturnal rodents were trained during the night for spatial learning or an operant sustained attention task (Gritton et al. 2012). In all of these studies, time of training appears to be the critical factor in predicting memory strength suggesting that circadian clock regulates training-induced processes in memory formation. However, the circadian clock may independently modulate the recall of memory. Recall of cued fear conditioning in mice peaks in the early day irrespective of the time of training (Chaudhury and Colwell 2002). Likewise in cockroaches, the recall of operant olfactory conditioning rather than memory formation is regulated by the circadian clock (Garren et al. 2013).

Multiple factors, including homeostatic sleep pressure, sleep inertia, and circadian modulation, interact to affect memory and

cognitive performance and discriminating between these elements can be difficult in humans. However, forced desynchrony models in which circadian rhythms are disconnected from rest periods have allowed researchers to separately analyze contributions of homeostatic sleep pressures, sleep inertia, and circadian processes on cognitive performance (Czeisler et al. 1994; Lee et al. 2009; Cohen et al. 2010; Grady et al. 2010; Silva et al. 2010). Upon awakening and early in the day, cognitive performance is lower due to sleep inertia and low circadian stimulation of brain arousal (for review, see Wright et al. 2012). Throughout the day alertness and performance decrease in response to extended time awake indicative of homeostatic regulation and fatigue. Persisting circadian up-regulation of arousal, alertness, and cognitive performance counteracts the homeostatic drive, particularly during the late afternoon and evening (Wright et al. 2002, 2012; Reid et al. 2011). In humans, the circadian clock regulates cognitive performance such that learning and performance are lower during the night (Wright et al. 2006; Gerstner et al. 2009).

In addition to memory acquisition and recall, the extinction of memory and even memory forgetting are active regulated processes (Hardt et al. 2013; Berry and Davis 2014). In rodent models, extinction of conditioned fear peaks in the early night similar to the rhythm observed for the initial contextual conditioned fear memory (Valentinuzzi et al. 2001; Woodruff et al. 2015). In studies of healthy men, extinction learning was faster with more robust memory apparent when learning trials occurred in the early morning compared with the late evening (Pace-Schott et al. 2013). Furthering our understanding of the circadian modulation of memory processes and extinction learning could facilitate improved treatments of post-traumatic stress disorder and other mood disorders.

Bidirectional interactions occur between the circadian system and memory processes with more complex learning paradigms affecting circadian entrainment. For a sustained attention task, repeated training out of phase with the animals' activity pattern in rats shifted and entrained circadian locomotor activity rhythms (Gritton et al. 2009, 2012, 2013). Entrainment through this non-photic signal relied primarily upon basal forebrain cholinergic projections to the SCN (Gritton et al. 2013). Interestingly, cognitive entrainment of locomotor activity rhythms also occurred in SCN-lesioned arrhythmic animals demonstrating the potential for entrainment through extra-SCN oscillators (Gritton et al. 2013). Thus, the circadian clock modulates the acquisition and formation of memory, but the performance of complex learning tasks out of phase with an animal's activity patterns may also reset circadian activity patterns. Potentially, for long-term shift workers increasing cognitive demand and sustained attention tasks during work could facilitate and maintain circadian alignment with the scheduled work shift.

### Time-stamping and circadian time place learning

The time of day a learning event occurs also can become part of the memory framework. In time-stamping and circadian time place learning, the time of day becomes incorporated into the context during memory formation such that animals demonstrate significantly greater memory at the same circadian time that training occurred (i.e., at 24-h intervals), presumably when the memory would be ethologically relevant (Cain et al. 2004, 2008; Valentinuzzi et al. 2008). Time-stamping effects have been broadly observed for active and passive avoidance learning (Holloway and Wansley 1973), conditioned place preference (Ralph et al. 2002; Valentinuzzi et al. 2008; Monclaro et al. 2014), and

conditioned place avoidance (Cain et al. 2004, 2008). In the golden hamster, temporal encoding of information as a contextual component of memory can be independent of the SCN as animals with lesioned SCNs demonstrate time of day memory similar to wild-type animals (Ko et al. 2003; Cain and Ralph 2009). Both the canonical SCN oscillator and nontraditional oscillators may encode temporal information for time-stamped memories as *tau*-mutant animals with a behaviorally short period of 20 h demonstrate peak recall of conditioned place avoidance at both 20 and 24 h after training, with the 20-h rhythm eliminated in SCN-lesioned animals (Cain et al. 2014).

In more complex learning situations in which the animal chooses between multiple spatial locations at different times of day, circadian or daily time place learning provides the animal with the ability to link events (rewarding or aversive) in a spatio-temporal manner (Biebach et al. 1991; Mistlberger et al. 1996; Van der Zee et al. 2008). In the 1920s, Beling's detailed observations of bees demonstrated that honeybees returned to specific locations at times associated with food reward (Moore-Ede et al. 1982). Mice use circadian time place learning in risk assessment paradigms in which the animal associates the spatial location (maze arm) and time of day with a negative cue (footshock) (Van der Zee et al. 2008). Circadian time place learning permits optimization of resource localization with risk assessment such as predator avoidance. In time place learning, the incorporation of temporal information may also occur through extra-SCN or non-canonical oscillatory mechanisms as rats with lesioned SCNs continue to show time-of-day discrimination in a two-lever T-maze test (Mistlberger et al. 1996). When food comprises the reward component in time place learning, the food-entrainable oscillator may be responsible for conveyance of temporal information (Aragona et al. 2002; Mulder et al. 2013). However, the mechanism through which temporal information in time place learning remains unknown as animals with mutations in two of the circadian period genes (*Per1*<sup>-/-</sup>;*Per2*<sup>-/-</sup>) show no difference in time place learning when compared with wild-type mice (Mulder et al. 2013). Reception and transmission of temporal information to the unknown oscillator still appears to require Cryptochrome (CRY), a light sensitive clock molecule and core component of the mammalian circadian clock, as CRY double knockout mice (*Cry1*<sup>-/-</sup>;*Cry2*<sup>-/-</sup>) are unable to acquire time place learning (Van der Zee et al. 2008).

## The circadian clock, aging, and neurodegenerative diseases

Dampening of circadian rhythms, phase alterations, and circadian desynchrony occur with aging across species ranging from invertebrates to humans (Sloan et al. 1999; Yamazaki et al. 2002; Cajochen et al. 2006; Nakamura et al. 2011; Zhdanova et al. 2011; Farajnia et al. 2012). Furthermore, aging decreases the ability of circadian pacemaker neurons within the SCN to resynchronize following circadian perturbation and increases the time necessary for resynchronization of central and peripheral oscillators (Davidson et al. 2008; Sellix et al. 2012). Prolonged circadian desynchronization can lead to increased mortality in aged animals (Davidson et al. 2006). Age-associated alterations in circadian rhythms also impact memory and performance in animal models (Haley et al. 2009; Kondratova et al. 2010; Nakamura et al. 2011), while in older individuals, fragmentation of rest-activity cycles is correlated with cognitive decline in mental speed, memory, and executive function (Oosterman et al. 2009). The interaction between circadian rhythms and cognitive function in aged individuals represents an area of escalating concern given the rising age of modern societies.

In addition to circadian alterations occurring with normal aging, neurodegenerative disorders associated with aging, including Alzheimer's, Parkinson's, and Huntington's diseases, are correlated with disordered circadian rhythms and disrupted sleep patterns (Hatfield et al. 2004; Nieoullon et al. 2008; Wulff et al. 2010; Cermakian et al. 2011; Videnovic et al. 2014; Musiek 2015). Traditionally, circadian and sleep disorders associated with neurodegenerative diseases have been viewed as symptomatic of these diseases as circadian disorders often correlate with disease severity and rhythms deteriorate with disease progression. However, recent research suggests circadian dysfunction contributes to and escalates neurodegenerative pathologies (Musiek 2015). In clinical studies, dampened or shifted circadian rhythms in aging individuals were predictive of increased risk of mild cognitive impairments and dementia (Tranah et al. 2011; Schlosser Covell et al. 2012). Similarly, weaker circadian rhythms were also predictive of future cognitive impairments in older individuals without dementia (Walsh et al. 2014). The predictive value of dampened circadian rhythms for future impairments suggests that age-associated circadian dysfunction aggravates cognitive decline introducing the possibility of circadian rhythm reinforcement as a therapeutic component during treatment of age-related memory impairments. In a mouse model of Huntington's disease, pharmacological manipulation of rest/activity cycles or scheduled feeding as reinforcement of circadian rhythms mitigated metabolic, circadian, and cognitive impairments (Pallier et al. 2007; Oosterman et al. 2009; Pallier and Morton 2009; Maywood et al. 2010). Reinforcing or strengthening circadian rhythms may represent potential treatment options to slow progression of neurodegenerative diseases and the accompanying cognitive declines.

## Function of circadian interactions with memory

The numerous interactions between the circadian system and memory make discernment of the function(s) of circadian modulation challenging. Circadian regulation of memory presumably arose and was maintained through natural selection. In molluscan models, peak memory formation for intermediate and long-term memory occurs in phase with the animal's activity period (Fernandez et al. 2003; Wagatsuma et al. 2004; Lyons et al. 2005, 2008; Michel et al. 2013). Similarly in rodents, peak performance in the Morris water maze for the diurnal grass rat occurs during the day, while peak performance at night is observed for nocturnal animals (Valentinuzzi et al. 2004; Martin-Fairey and Nunez 2014). However, core circadian gene expression in the SCN appears similarly phased in nocturnal and diurnal rodent species, suggesting that the contrasting phases of memory formation are regulated downstream from the master circadian clock. Neurons of the hippocampus and the amygdala exhibit rhythms in core circadian gene expression (Lamont et al. 2005; Wang et al. 2009; Li et al. 2013) with the hippocampal circadian gene expression anti-phasic for the diurnal grass rat and nocturnal rodents (Ramanathan et al. 2010; Martin-Fairey and Nunez 2014). Phase differences in gene expression also occur in brain regions downstream from the SCN for diurnal versus nocturnal *Debus* (Otalora et al. 2013). Potentially, phase-specific coordination of physiological processes occurs locally in the brain regions generating or regulating those behaviors. Indeed, analysis of hippocampal circadian gene and protein expression reveals cyclic coordination of gene expression suggesting that hippocampal gene expression may form a temporal framework for memory formation (Jilg et al. 2010; Rawashdeh et al. 2014). In a mouse model used to represent evening-type individuals, the *clock* mutation in a Jcl/ICR background, in which the animals have long periods and

phase delays, the animals demonstrate an impaired learning ability in the Morris water maze during the early dark phase (morning for the mice) along with damped hippocampal acetylcholine release (Sei et al. 2003, 2006).

In contrast, peak short and long-term olfactory memory in *Drosophila* occurs in the early to mid-night seemingly out of phase with the crepuscular activity of these insects (Lyons and Roman 2009; Fropf et al. 2014). Although the peak performance in olfactory memory is not dependent upon rhythms in olfactory sensitivity (Krishnan et al. 1999; Lyons and Roman 2009), the phase regulation of olfactory memory may be coordinated with olfactory-dependent behaviors such as courtship or predator avoidance. Mice exhibit peak recall for contextual fear conditioning in the early morning hours normally associated with periods of rest (Chaudhury and Colwell 2002). Increased memory for aversive stimuli may be coordinated with increased defensive behavioral responses when the animal is more vulnerable to predation and settling into its rest period. For example, ducks demonstrate vigilance during sleep to reduce predation risk (Zimmer et al. 2011). In humans, the circadian system increases arousal toward the late afternoon/early evening counteracting the homeostatic drive for sleep (Wright et al. 2012). Thus, variance of circadian regulation of memory between learning paradigms or in a species' restricted manner may be dependent upon intertwined metabolic processes or related behaviors.

Circadian peaks and troughs in memory and performance may represent separate functions of circadian regulation. Suppression of memory formation during specific phases may have evolved in conjunction with energy conservation. Neuronal activities and memory formation are metabolically expensive with the brain consuming ~20% of an organism's total energy budget (for review, see Harris et al. 2012). The higher cost of synaptic plasticity can be observed in *Drosophila* in which an inverse relationship between longevity and improvements in memory and performance has been shown (Burger et al. 2008; Lagasse et al. 2012). Memory formation also decreases stress resistance (Mery and Kawecki 2005) and longevity is significantly decreased when long-term memory formation is forced on flies under starvation stress (Plaçaïs and Preat 2013).

## Mechanisms linking the circadian clock and memory

At a circuit level, circadian modulation of memory processes could arise from rhythmic changes in synaptic connections, synapse number, or structure. Circadian changes in synapse number have been observed at *Drosophila* neuromuscular junctions along with circadian changes in motor neuron morphology (Mehnert and Cantera 2011; Ruiz et al. 2013). Dendrite length also is circadianly regulated in the optic lobe with larger dendritic trees observed early in the (subjective) day (Weber et al. 2009; Damulewicz and Pyza 2011). Notably for the regulation of output processes, the small ventral lateral circadian pacemaker neurons of *Drosophila* form differential synaptic contacts dependent upon the time of day (Fernández et al. 2008; Gorostiza et al. 2014). Rhythmic axonal remodeling occurs through matrix metalloproteinase regulation of the circadian neurotransmitter PDF (Depetris-Chauvin et al. 2014), presumably due to the circadian regulation of matrix metalloproteinases (Kadener et al. 2007; Nagoshi et al. 2010). Thus, circadian regulation of neuronal connections as well as the strength of synaptic contacts represent likely mechanisms through which circadian pacemaker neurons could coordinate different physiological and behavioral processes across the day and night.

In vertebrate models, in vivo circadian regulation of synaptic morphology has been studied using the transparent zebrafish lar-

vae (Appelbaum et al. 2010; Elbaz et al. 2013). Researchers found the greatest number of synaptic boutons for hypocretin neurons projecting to the pineal gland observed during the (subjective) day with an oppositely phased rhythm observed for hypocretin neurons projecting to the hindbrain (Appelbaum et al. 2010). In Siberian hamsters, diurnal rhythms in dendritic spine density occur with opposite phases in the hippocampal CA1 and the dentate gyrus (Ikeno et al. 2013). Antiphase circadian regulation of neuronal projections supports the hypothesis that local brain regions regulate rhythmicity of behaviors and processes specific to that region.

The circadian clock could regulate learning and memory at a circuit level through hormonal signaling. Melatonin, a circulating hormone rhythmically secreted by the pineal gland, functions in the circadian system through the SCN and also functions in neural plasticity (for review, see Rawashdeh and Maronde 2012). In pharmacological studies, acute administration of melatonin inhibits long-term potentiation (Wang et al. 2005) and affects hippocampal neuronal plasticity (El-Sherif et al. 2002, 2003); whereas melatonin receptor antagonists phase-specifically enhance nighttime memory in diurnal animals (Rawashdeh et al. 2007). In rats, melatonin phase-specifically enhances memory during the day and impairs memory at night (Takahashi et al. 2013). In mice with genetic deletions of both high-affinity G-protein coupled melatonin receptors ( $MT_1^{-/-}$ ;  $MT_2^{-/-}$ ), animals exhibit enhanced cognitive performance (O'Neal-Moffitt et al. 2014). However, the action of melatonin on cognitive performance may vary between  $MT_1$  and  $MT_2$  signaling as a  $MT_2$  receptor deletion results in impairments in hippocampal long-term memory (Larson et al. 2006). In Alzheimer's disease models, melatonin or  $MT_2$  agonists appear to have a therapeutic effect on cognitive performance and hippocampal neuroplasticity (Bahna et al. 2014; Ali and Kim 2015; Stefanova et al. 2015). While melatonin has the potential to link the circadian system with memory and performance, the actions of melatonin may vary with circadian phase, task specificity, or receptor signaling.

Glucocorticoids promote synaptic development, neuronal plasticity (Liston and Gan 2011), and cell proliferation, and themselves have the capacity for resetting circadian oscillators in peripheral tissues (Balsalobre et al. 2000a; Dickmeis and Foulkes 2011). Diurnal release of glucocorticoids occurs in synchrony with the animal's activity cycle (Dickmeis and Foulkes 2011). In mice, training during peak glucocorticoid levels increases learning-induced spine formation, while training during the circadian trough does not (Liston et al. 2013). Furthermore, disruption of glucocorticoid cycling following learning by increasing trough glucocorticoid levels reduces survival of learning-induced spines and impairs long-term memory (Liston et al. 2013). Prolonged increases in glucocorticoid levels mediate, at least in part, the effects of chronic jet lag on decreased neurogenesis in rodent models (Gibson et al. 2010) and temporal lobe atrophy in humans (Cho 2001). Chronic exposure to high levels of glucocorticoids disrupts previous memories and eliminates new spines induced by learning as well as previously present spines (Liston et al. 2013). Thus, rhythmic regulation of stress hormones alters the efficacy of learning-induced synaptogenesis and is necessary for long-term synaptic stability and robust memories.

Circadian suppression of memory at night also may result from synaptic scaling during rest periods. The synaptic homeostasis hypothesis of sleep emphasizes physical changes in synaptic structure that occur during sleep permitting decreased energy consumption and restoration of cellular homeostasis (for review, see Tononi and Cirelli 2014). Structural evidence for synaptic scaling comes from *Drosophila* in which decreased synapse number and size may be observed after sleep (Bushey et al. 2011). Widespread long-term memory formation accompanied by

synaptic strengthening and morphological changes during normally inactive periods could be counterproductive to sleep and rest homeostatic functions.

At the molecular level, circadian modulation of memory could occur at multiple levels through regulation of sensory gating, neurotransmission, kinase signaling cascades, macromolecular synthesis, or epigenetic modifications. Circadian gating of sensory processes, as observed for olfaction in insects (Krishnan et al. 1999) and mammals (Granados-Fuentes et al. 2006; Miller et al. 2014), could alter salience and perception of sensory stimuli resulting in differential learning acquisition. Downstream, molecular processes can serve as a bridge between the circadian clock and memory either through circadian regulation of basal expression and activity levels, rhythms in cellular compartmentalization, or rhythms in training-inducible activity or expression (Table 1). Neurotransmitters with circadian rhythms in basal expression and activity in brain regions associated with memory formation include acetylcholine, nitric oxide, serotonin, and GABA. Neurotransmitters can also function in conveyance of temporal information in memory context as suggested for acetylcholine in time-stamping (Hut and Van der Zee 2011) and GABA synthesis in fear memory (Bergado-Acosta et al. 2014). An example of circadian regulation of training-induced neurotransmitter release comes from *Aplysia*, in which sensitization training-induced serotonin release is circadianly regulated with higher levels of serotonin observed in the hemolymph following training during the subjective day (Lyons et al. 2006). Circadian regulation of inhibitory pathways may also modulate memory processes. In rats, disinhibition of recurrent GABAergic inhibition is suggested as a

mechanism for regulating circadian rhythmicity of LTP in hippocampal CA1 (Nakatsuka and Natsume 2014). In hamsters, circadian rhythmicity is necessary for declarative learning and memory as increased SCN GABAergic inhibition to the hippocampus in arrhythmic animals impairs memory (Ruby et al. 2008, 2013; Fernandez et al. 2014).

The phylogenetically conserved mechanisms of memory formation include intracellular second messenger and kinase signaling pathways. The MAPK/ERK signaling cascade comprises a necessary component of nonassociative (Sharma et al. 2003; for review, see Hawkins and Byrne 2015) and associative learning paradigms in invertebrate models (Michel et al. 2011), and associative memory such as contextual fear conditioning in vertebrates (Atkins et al. 1998). In the hippocampus, circadian cycling of phospho-ERK with peaks during the subjective day promotes memory formation and persistence of long-term memory (Eckel-Mahan et al. 2008; Eckel-Mahan 2012). Although a basal circadian rhythm in phospho-MAPK is not observed in *Aplysia* ganglia, sensitization training during the (subjective) day induces significantly greater MAPK activity compared with training during the night (Lyons et al. 2006). Potentially, second messenger-dependent kinase pathways such as the cAMP/PKA pathway may also transduce circadian signals in learning acquisition or memory formation. Diurnal rhythms in cAMP levels, presumably due to adenylyl cyclase activity, occur in the hippocampus with peak levels during the day (Eckel-Mahan et al. 2008). Hippocampal rhythms in adenylyl cyclase and ERK activity are dependent upon SCN rhythms as SCN ablation abolishes these rhythms and impairs spatial memory persistence (Phan et al. 2011).

**Table 1.** Examples of molecular interactions between circadian systems and learning and memory

	Model system	Type of interaction	References
<b>Neurotransmitters</b>			
Acetylcholine	Rats	May convey time-stamp information from the SCN	Hut and Van der Zee (2011)
	Rhesus Monkeys	Muscarinic receptors associated with diurnal rhythms in spatial learning	Haley et al. (2011)
GABA	Golden Hamsters	GABA <sub>A</sub> Receptor—basal circadian rhythm in cerebral cortex GABA output from SCN to hippocampus regulates rhythms in spatial learning; inhibits learning in arrhythmic animals	Kanterewicz et al. (1995); Ruby et al. (2008, 2013)
	Mice	GAD65 dependent GABA synthesis implicated in phase-specific learning	Bergado-Acosta et al. (2014)
Nitric oxide	<i>Manduca sexta</i>	Inhibition of nitric oxide phase specifically inhibits short and intermediate-term memory	Gage and Nighorn (2014)
Serotonin	<i>Aplysia</i>	Circadian modulation of training-induced release	Lyons et al. (2006)
<b>Second Messengers and Signaling Pathways</b>			
cAMP/adenylyl cyclase	Mice	Rhythms in hippocampus, dependent on SCN; necessary for LTM formation and maintenance	(Eckel-Mahan et al. 2008; Phan et al. 2011)
	<i>Aplysia</i>	Phase-specific activation after training	(Lyons et al. 2006)
MAPK	Mice	Rhythms in hippocampus; necessary for LTM formation and persistence	Eckel-Mahan et al. (2008); Phan et al. (2011); Wardlaw et al. (2014)
	Mice	Activity rhythms in hippocampus; absent in <i>per1</i> mutants	Rawashdeh et al. (2014)
PKA	<i>Aplysia</i>	Circadian phase-specific inhibition of ITM	Michel et al. (2013)
<b>Transcription factors and epigenetic changes</b>			
CREB	<i>Drosophila</i>	Diurnal rhythms in Mushroom Bodies; may underlie rhythms in olfactory memory	Fropf et al. (2014)
	Rats	Diurnal phosphorylation in hippocampus	Hsieh et al. (2015)
C/EBP	Mice	Hippocampal rhythms in phosphorylation	Eckel-Mahan et al. (2008); Rawashdeh et al. (2014)
	<i>Aplysia</i>	Phase specifically increased after training	Lyons et al. (2006)
Acetylation/methylation of H3	Mice	Basal rhythms in histone markers; learning-induction phase specific and absent in <i>per1</i> mutants	Rawashdeh et al. (2014)
	Mice	Diurnal rhythms; peaks promote dendritic spine formation after learning; troughs promote dendritic spine maintenance.	Liston et al. (2013)
Melatonin	<i>Danio rerio</i> , Rats	Diurnal rhythm; circadian phase-specific learning.	Rawashdeh et al. (2007); Rawashdeh and Maronde (2012); Takahashi et al. (2013)

Conversely, circadian regulation of memory may also occur through protein phosphatase activity. In *Aplysia*, inhibition of protein phosphatases rescues the induction of intermediate-term memory during the late subjective day and night (Michel et al. 2013). In mammals, Suprachiasmatic Oscillatory Protein (SCOP), an oscillatory protein first identified in the SCN, is a serine/threonine phosphatase enriched in the hippocampus (Shimizu et al. 2010) that is regulated by calpain-dependent protein degradation (Shimizu et al. 2007). SCOP suppresses the ERK pathway through its binding to Ras (Shimizu et al. 2003, 2007, 2010; Gao et al. 2005). Through its protein phosphatase activity, SCOP also regulates AKT pathway activation in the hippocampus (Jackson et al. 2010). Thus, the circadian regulation of intracellular signaling cascades through kinase and phosphatase regulation provides broad mechanisms through which the circadian clock can impact multiple types of learning and memory.

The induction of gene expression, a necessary occurrence for LTM, provides multiple junctures through which the circadian clock can regulate memory formation. Rhythmic oscillations in pERK or cAMP/PKA pathways provide a mechanism for circadian regulation of learning-induced gene transcription through the transcription factor CREB (cAMP element response binding protein). In the hippocampus, phospho-CREB levels oscillate in phase with the pERK and cAMP (Eckel-Mahan et al. 2008). More recently, hippocampal circadian rhythms in CREB activation have been shown to be dependent upon the *Period1* gene (Rawashdeh et al. 2014). In *Aplysia*, training animals during the subjective day results in significantly increased protein levels of the CREB-dependent immediate early gene *ApC/EBP* (Lyons et al. 2006), a transcription factor in nonassociative (Alberini et al. 1994), and associative memory formation (Levitan et al. 2008). In *Drosophila* mushroom bodies, a region necessary for many forms of memory, dCREB2 exhibits circadian oscillations in gene expression, nuclear protein levels and activity, likely mediating rhythms in LTM formation (Tanenhaus et al. 2012; Fropf et al. 2014).

Recent studies have highlighted the role of epigenetic modifications affecting gene transcription in the circadian regulation of memory formation. Acetylation of histone protein, particularly H3, enhances the induction and formation of long-term memory (Levenson et al. 2004), while trimethylation of H3 at lysine 4 marks active transcription (Gupta et al. 2010). The circadian clock regulates H3 acetylation at lysine 14 in phase with trimethylation of H3 at lysine 4 providing a mechanism for circadian regulation of learning-induced gene transcription (Rawashdeh et al. 2014). SIRT1, a NAD-dependent deacetylase, which regulates CLOCK mediated chromatin remodeling and circadian rhythms (Asher et al. 2008; Nakahata et al. 2008) also functions in learning and memory (Gao et al. 2010). SIRT1 oscillates in the hippocampus with alterations in SIRT1 rhythm resulting in memory deficits (Rawashdeh et al. 2014). Thus, circadian regulation of learning-induced transcription necessary for LTM through epigenetic mechanisms or transcription factor activation provides a key mechanism through which the circadian clock targets memory formation. The identification of modulated steps and targets of the circadian clock potentially may serve as the foundation for future therapies to improve memory and performance.

## Countermeasures for circadian desynchrony

Circadian modulation of human performance results in high economic costs to businesses attributable to industrial and occupational accidents, decreased worker productivity, and increased health costs for employees (Rajaratnam et al. 2013; Wright et al. 2013) besides posing a serious health risk to individuals when shift work induces circadian misalignment. Moreover, technolog-

ical advances have resulted in increased human exposure to artificial light at night, particularly blue wavelengths that most affect the circadian clock, compounding the problems of circadian disorders in modern society (for review, see Bonmati-Carrion et al. 2014; Stevens and Zhu 2015). Consequently, identifying methods to maintain circadian rhythms or minimize circadian misalignment are necessary both at home and the workplace.

Recommendations by the American Academy of Sleep Medicine to ameliorate the problems of shift work are designed to minimize individual circadian misalignment and to increase alertness and performance (Morgenthaler et al. 2007). In brief review, these strategies include: (1) the use of bright light therapy to enhance circadian re-entrainment (Burgess et al. 2002; Gooley 2008; Dodson and Zee 2010) combined with morning light restriction through the use of dark goggles to improve circadian adaptation (Crowley et al. 2003; Smith et al. 2009; Sasseville and Hébert 2010; Boivin et al. 2012). (2) Scheduled napping to counter fatigue and sleepiness during night shifts (Purnell et al. 2002; Schweitzer et al. 2006), although sleep inertia upon awakening may induce cognitive impairments (Wertz et al. 2006; Signal et al. 2013). (3) Melatonin administration to promote daytime sleep. Readily passing through the blood brain barrier, melatonin increases daytime sleep duration with little effect on sleep latency for night-shift workers (Sharkey et al. 2001; Liira et al. 2015) and phase-shifts circadian rhythms in simulated night-shift studies (Sharkey and Eastman 2002). During the day, the circadian system maintains arousal in the face of increased time awake with decreased arousal at night due, in part, to rising melatonin levels which target MT<sub>1</sub> and MT<sub>2</sub> receptors in the SCN to dampen SCN driven arousal signals (Dodson and Zee 2010; Carocci et al. 2014). Melatonin is used as a treatment of circadian perturbations including jet lag, shift work, or delayed sleep disorder (Pandi-Perumal et al. 2008; Brown et al. 2009; Srinivasan et al. 2010) and can be used in combination with bright light therapy, to accelerate reentrainment for jet lag (Dodson and Zee 2010; Zee and Goldstein 2010). Newly developed selective MT<sub>1</sub>/MT<sub>2</sub> receptor agonists (Srinivasan et al. 2010; Carocci et al. 2014) include Ramelteon which effectively acts as a phase shifting agent in humans (Richardson et al. 2008; Carocci et al. 2014) and animal models (Rawashdeh et al. 2011) as well as Tasimelteon which facilitates entrainment to a 24-h cycle maintaining melatonin rhythms, sleep latency, and sleep quality (Carocci et al. 2014; Neubauer 2015). (4) The use of wakefulness promoting drugs to increase arousal and performance in circadian disorders include caffeine and modafinil. In forced desynchrony studies, repeated low doses of caffeine counteracted homeostatic sleep pressures, enhanced alertness, and ameliorated reductions in cognitive performance, particularly at the circadian troughs of performance (Walsh et al. 1990; Wyatt et al. 2004; Schweitzer et al. 2006). Modafinil and its R-enantiomer armodafinil improve attention and alertness, cognitive performance, long-term memory, and reduce sleepiness associated with night-shift work (Walsh et al. 2004; Czeisler et al. 2005, 2009; Grady et al. 2010; Roth 2012; Liira et al. 2014, 2015) with little effect on sleep efficiency, quantity, or quality following shift work (Walsh et al. 2004; Czeisler et al. 2005; Grady et al. 2010). In addition to the above strategies designed to enable permanent shift workers to maintain regular rhythms minimizing circadian misalignment and enhancing performance, exercise during a night shift also may facilitate phase shifting and maintenance of circadian rhythms (Eastman et al. 1995; Barger et al. 2004). For further review of strategies for managing shift work, see Boivin and James (2005), Morgenthaler et al. (2007) and Boivin and Boudreau (2014).

For individuals engaged in rotating shift work given the length of time necessary for complete resynchronization of central and peripheral oscillators, reentrainment to the work cycle

may not be optimal. For these individuals, managing the direction of the rotation may reduce some negative health effects associated with shift work or even maintaining entrainment to a daytime light dark cycle through minimizing the effects of workplace lighting at night on melatonin secretion and hormonal rhythms. Recent research has suggested that the wearing of glasses with optical filters to block wavelengths shorter than 480 or 500 nm may attenuate circadian misalignment, improve mood disorders, enhance cognitive performance during shift work, and sleep upon cessation of shift work (Rahman et al. 2013; Casper and Rahman 2014). New applications and software also are becoming available to provide optical filters for personal electronic devices and home computers to minimize circadian perturbations from electronic devices during evening use. The realities of technological advancements in a modern, global society, and the risks to individual and public health due to circadian modulation of cognitive function or circadian desynchronization, emphasize the critical need for continued research to understand the molecular mechanisms underlying circadian and memory interactions, developing new therapeutic treatments and identifying practical measures to minimize individual circadian stresses.

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