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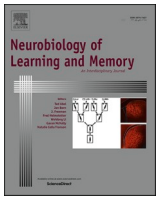

Time to learn: The role of the molecular circadian clock in learning and memory

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ABSTRACT

The circadian system plays an important role in aligning biological processes with the external time of day. A range of physiological functions are governed by the circadian cycle, including memory processes, yet little is understood about how the clock interfaces with memory at a molecular level. The molecular circadian clock consists of four key genes/gene families, *Period*, *Clock*, *Cryptochrome*, and *Bmal1*, that rhythmically cycle in an ongoing transcription-translation negative feedback loop that maintains an approximately 24-hour cycle within cells of the brain and body. In addition to their roles in generating the circadian rhythm within the brain's master pacemaker (the suprachiasmatic nucleus), recent research has suggested that these clock genes may function locally within memory-relevant brain regions to modulate memory across the day/night cycle. This review will discuss how these clock genes function both within the brain's central clock and within memory-relevant brain regions to exert circadian control over memory processes. For each core clock gene, we describe the current research that demonstrates a potential role in memory and outline how these clock genes might interface with cascades known to support long-term memory formation. Together, the research suggests that clock genes function locally within satellite clocks across the brain to exert circadian control over long-term memory formation and possibly other biological processes. Understanding how clock genes might interface with local molecular cascades in the hippocampus and other brain regions is a critical step toward developing treatments for the myriad disorders marked by dysfunction of both the circadian system and cognitive processes.

1. Introduction

Most animals have developed a circadian system to synchronize their internal physiological processes with the external time of day. Historically, the circadian field has largely focused on understanding how circadian oscillations control the sleep/wake cycle, but a wide range of biological processes are affected by the circadian system, including feeding behavior, body temperature, metabolism, and memory formation. Memory strength in particular has been largely neglected as an oscillating physiological process; very little is understood about the mechanisms that drive diurnal fluctuations in memory. This is surprising, as the mechanisms that support memory formation are relatively well-characterized, as are the individual mechanisms involved in the molecular circadian clock. The relationship between these two molecular cascades, however, is unclear despite a well-documented relationship between circadian rhythms and cognitive function (Davies et al., 1973; Fekete et al., 1985; Folkard et al., 1983; Holloway and Wansley, 1973; Monk et al., 1983; Monk et al., 1984; Tapp and Holloway, 1981). Recent research has suggested that circadian clock genes function outside the brain's central pacemaker to control local functions, possibly serving as a mechanism to provide circadian control over biological processes including memory formation and expression.

Here, we will discuss how circadian genes function within and outside of the brain's central pacemaker to exert circadian control over memory. Following a brief overview of the key genes involved in generating the brain's circadian rhythm, we will discuss the limited work suggesting these genes might also function to modulate memory across the 24-hour day in rodents, focusing largely on work in the hippocampus, an important memory-relevant brain region. We will then outline how the molecular clock interfaces with key mechanisms known to support memory formation and discuss how this interaction might serve to integrate time-of-day information with memory processes across the brain.

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2. Circadian rhythms and the central pacemaker

Circadian rhythms are intrinsic oscillations that drive the cycling of a body's biological processes over a 24-hour period. This internal pacemaker is vital to the physiology of most living organisms, as it synchronizes the internal state of the body and brain with the external time of day. Driven by changes in the environment due to the earth's daily rotation, diurnal oscillations give organisms several evolutionary advantages, including the synchrony and coordination of biological functions and responses (Sharma, 2003). From cyanobacteria (Johnson et al., 2017; Swan et al., 2018; Woelfle et al., 2004) to humans (Duffy and Wright, 2005; Scheer et al., 2007), most organisms can synchronize physiological events to regular diurnal events in the environment.

The brain's master circadian pacemaker is the suprachiasmatic nucleus (SCN), located in the hypothalamus (Repper and Weaver, 2002). Made of approximately 20,000 neurons that oscillate autonomously, the SCN is coordinated by a complex communicative network that ensures synchrony to the external environment (Mieda, 2020; Noguchi et al., 2013). The SCN sets the pace for downstream "satellite clocks," including other areas of the brain and peripheral tissues like the liver, pancreas, and lungs. Liver cells, for example, use these oscillations to guide an organism's metabolism over a 24-hour cycle (Mukherji et al., 2019; Tong and Yin, 2013).

Zeitgebers, or time-givers, are cues that allow an organism to align internal or behavioral rhythms to environmental stimuli, such as the 24-hour day. The most potent zeitgebers are light/dark cues (i.e. photic zeitgebers) that are typically provided by the sun rising and setting or, in a laboratory setting, the daily onset and offset of the overhead lights (Golombek and Rosenstein, 2010). Light is a particularly potent zeitgeber because the SCN receives direct input from photosensitive retinal ganglion cells (pRGCs) via the retinohypothalamic tract (RHT). Photic input can therefore adjust the phase of the master pacemaker in the SCN, which then can indirectly impact the phase of downstream satellite clocks in peripheral tissues. The ability to entrain to photic zeitgebers is particularly important, considering most animals have endogenous circadian rhythms that are slightly shorter or longer than 24 h (for example, the free-running period of a C57Bl/6J mouse is ~ 23.6 h (Eckel-Mahan and Sassone-Corsi, 2015). Entraining to the actual light/dark rhythms of the environment allows for a daily readjustment of the animal's circadian system, ensuring internal synchrony with the external world.

There are also many examples of non-photic zeitgebers that can serve to entrain the clock, including feeding time, temperature, social interactions, or even the arousal evoked by caretaker work that consistently occurs each day (such as cage changes or feeding; Kusumoto-Yoshida et al., 2015; Moriya et al., 2009; Mrosovsky, 1989; Opiol et al. 2015; Peng-Li et al., 2022; Ribeiro et al., 2009). Indeed, any stimulus that happens around the same time every day can potentially serve as a zeitgeber to the SCN. The SCN in turn uses the timing information provided by these different zeitgebers to align the organism to the external time of day, functioning as the master pacemaker for satellite clocks throughout the rest of the brain and body. Accordingly, SCN lesions drastically impair free-running activity patterns in rodents (Moore and Eichler, 1972; Stephan and Zucker, 1972a; Tahara et al., 2012) and affect circadian gene oscillations in peripheral tissues. Typically, SCN lesions ablate clock gene oscillations in satellite tissues (Akhtar et al., 2002; Guo et al., 2005; Hara et al., 2001; Iijima et al., 2002; Kudo et al., 2004; Terazono et al., 2003;), although some researchers report that SCN lesions reduce peripheral clock gene oscillation amplitude without affecting their endogenous phase (i.e. SCN lesions reduce the difference between gene expression peaks and troughs without affecting *when* those genes peak and trough across the 24 h day; Tahara et al., 2012), and others have shown intact rhythms in peripheral tissues even when the SCN is removed (Yoo et al., 2004). These disparate results across studies may be from differences in the experimental design, including the methods through which the circadian activity pattern is monitored (e.g. with running wheels that provide exercise versus passive infrared sensors), differences in how oscillations are monitored (e.g. luciferase expression versus qPCR/microarray), and even how the SCN is removed (via electrolytic lesion or thermal lesion). Although it is not clear why different labs have observed varying effects of SCN lesions on peripheral clock gene oscillations, recent studies have suggested that the SCN may be specifically required to maintain synchrony across peripheral organs but may not be required to maintain oscillations within each organ (Sinturel et al., 2021). Even when peripheral clocks are dampened or destroyed by SCN lesions, however, rodents can successfully entrain to non-photic zeitgebers like food presentation, although this rhythmicity is lost in the absence of these cues or when only photic zeitgebers are provided (Saini et al., 2013;Tahara et al., 2012). The ability of animals with SCN lesions to entrain to non-photic external cues demonstrates the power and complexity that zeitgebers have in driving diurnal rhythmicity. Zeitgebers can therefore modulate circadian rhythmicity by providing time-of-day information even when the brain's central pacemaker is offline.

3. Oscillations of the molecular clock

Although the SCN functions as the brain's master pacemaker, every cell in the brain and body maintains some time-of-day information in the form of a rhythmic molecular clock. This molecular clock is primarily driven by four key circadian clock genes/gene families: Circadian Locomotor Output Cycles Kaput (*Clock*), Brain and Muscle ARNT-Like 1 (*Bmal1*), Period (*Per1-3*), and Cryptochrome (*Cry1-2*) (Fig. 1). At the most basic level, circadian information is encoded in the rhythmic expression and inhibition of these genes, as they interact in a core negative transcription-translation feedback loop (TTFL) that rhythmically oscillates within every cell. The TTFL begins when a heterodimer of two transcription factors, CLOCK and BMAL1, bind to Ebox motifs upstream of the *Per* and *Cry* gene families (Fig. 1). The CLOCK-BMAL1 heterodimer drives transcription of the *Per* and *Cry* genes, which are subsequently translated in the cytoplasm, where they heterodimerize. Phosphorylation of PER proteins via CK1δ/ε allows the PER-CRY complex to move into the nucleus (Fu et al., 2002; Gallego and Virshup, 2007; Isojima et al., 2009; Lee et al., 2011) where it interacts with transcriptional repressors to block CLOCK/BMAL1 activity, inhibiting subsequent transcription of the *Per* and *Cry* genes. Over time, PER and CRY proteins are degraded, relieving the inhibition of CLOCK-BMAL1, and ultimately resetting the molecular clock to enable a new round of *Per* and *Cry* transcription. Importantly, this entire TTFL takes approximately 24 h to complete, roughly matching the organism's internal clocks with the external time of day (for review see Ko & Takashi, 2006; Virshup and Forger, 2007).

In addition to this core feedback loop, there are accessory feedback loops that help to fine-tune the rhythm to ensure close synchrony with the external environment (Buhr and Takahashi, 2013). Most notably, the CLOCK-BMAL1 heterodimer can also bind to Ebox regions upstream of two nuclear orphan receptor genes, *Rev-erbα*, and *RORα*, which compete to bind at retinoic acid-related orphan receptor response elements (ROREs) in the *Bmal1* promoter. REV-ERBα and RORα binding have opposite effects on *Bmal1* transcription; RORα promotes *Bmal1* transcription whereas REV-ERBα inhibits *Bmal1* transcription via recruitment of the repressive histone deacetylase HDAC3 (Zhao et al., 2016; for review see Mohawk et al., 2012). This accessory loop can therefore help adjust the molecular clock by tightly controlling *Bmal1* expression.

While we understand a lot about how these mechanisms function in regulating circadian oscillations within SCN, the role of these clock genes outside of the SCN is largely unclear. As these genes are found throughout the brain and body, it is likely that they function to set local clocks within peripheral tissues, with the SCN functioning as a "master regulator" that synchronizes these satellite clocks. It is possible that these individual clock genes serve other, tissue-specific functions in downstream satellite clocks, as well, locally controlling different

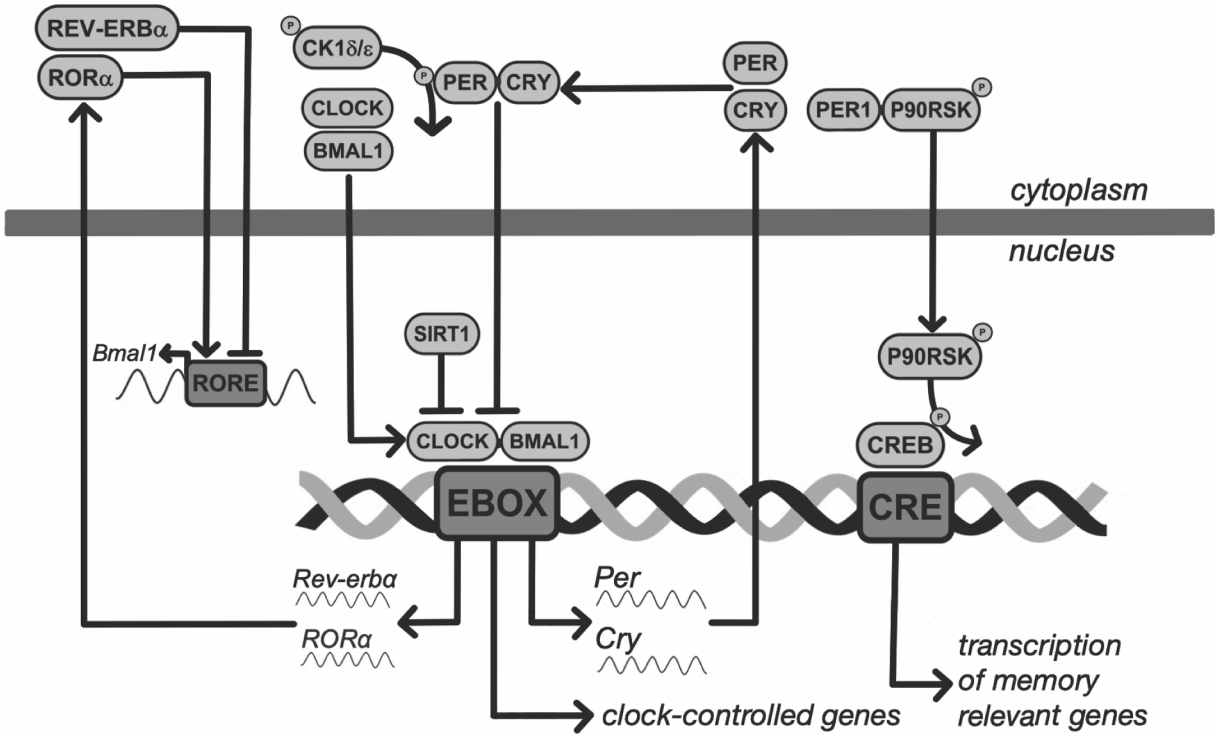

Fig. 1. The molecular interface between the clock and memory. The molecular clock begins when the CLOCK-BMAL1 heterodimer binds to EBox motifs in the *Per* and *Cry* promoters, driving their transcription. After translation in the cytoplasm, PER and CRY form a heterodimer that inhibits the CLOCK-BMAL complex to reduce further *Per/Cry* transcription. Eventually, degradation of PER and CRY alleviates this repression, starting a new round of transcription. As a major accessory loop, *Rev-erbα* and *RORα* compete to bind ROREs upstream of *Bmal1* to promote and inhibit *Bmal1* transcription, respectively, fine-tuning the clock. Importantly, PER1 also physically binds to phosphorylated P90RSK to allow it to move into the nucleus to phosphorylate CREB to regulate the transcriptional program necessary for memory formation. Diurnal oscillations in PER1 may therefore modulate memory consolidation by regulating CREB-mediated transcription.

physiological functions in distinct regions. Memory formation, which is strongly influenced by the circadian system, is one such process that may be directly modulated by circadian gene function in distinct areas of the brain.

4. The molecular mechanisms of Long-Term memory

Memory consolidation, the time-limited process through which memory is stabilized into long-term storage, is well-characterized at a molecular level. Many of the key molecular cascades necessary for memory consolidation oscillate across the 24-hour day, possibly modulating memory formation and/or consolidation across the day/night cycle (Gerstner et al., 2009). In addition, memory-relevant brain structures, such as the hippocampus (Jilg et al., 2010), amygdala (Savalli et al., 2014), prefrontal cortex (Chun et al., 2015), and retrosplenial cortex (Niu et al., 2021), show rhythmic oscillations in many of the core clock genes described above. How these oscillating cascades interact to exert diurnal control over memory formation is currently unknown.

One consistent requirement for memory consolidation is transcription (Alberini and Kandel, 2014). Although this is an incredibly complex process, several specific genes have been identified as necessary for long-term memory formation, a topic that has been reviewed extensively elsewhere (e.g. Johansen et al., 2011). In particular, the mitogen-activated protein kinase (MAPK; also called ERK)/cAMP-binding protein (CREB) cascade is a major signaling pathway necessary for memory formation (Alberini and Kandel, 2014; Alberini, 2009; Kandel, 2012; Silva et al., 1998). Inhibition of MAPK/ERK, CREB, or other key molecules in this cascade around the time of learning leads to long-term memory impairments (Kelly et al., 2003; Ortega-Martínez, 2015; Selcher et al., 1999; Vogtet al., 2014). CREB is also an important mechanism that directly interfaces with the molecular clock. The CREB cascade shows a rhythmic diurnal oscillation, with hippocampal CREB phosphorylation peaking during the day (Rawashdeh et al., 2016). In addition, the two phosphorylated MAPK isoforms, pERK1 and pERK2 oscillate relative to total MAPK (which does not change across the day/night cycle), also peaking in the hippocampus during the daytime, around ZT4-8 (ZT = Zeitgeber Time, where ZT0 = light onset in the colony room; Eckel-Mahan et al., 2008). CREB directly interacts with the TTFL by promoting the transcription of *Per* genes (Tischkau et al., 2003) and is also downstream of *Per1* (see Fig. 1; discussed later in this review), providing a compelling interface between the molecular signaling cascades that regulate the circadian system and the mechanisms that regulate memory.

4.1. The effect of circadian rhythms on memory

It is indisputable that circadian rhythms influence long-term memory formation. Memories are strongly influenced by the time of day when they are formed or retrieved (Chaudhury and Colwell, 2002; Eckel-Mahan et al., 2008) and manipulations that disrupt the circadian system typically produce marked impairments in memory formation (for review see Smarr et al., 2014). Memory oscillates across the day/night cycle and typically peaks during the day in rodents (Chaudhury and Colwell, 2002; Eckel-Mahan et al., 2008; Gerstner and Yin, 2010; Rawashdeh et al., 2014 Urban et al., 2021), although this varies across task and lab (Liu et al., 2022; Loss et al., 2015; Morales-Delgado et al., 2018; Tsao et al., 2022; Winocur and Hasher, 2004). Further, disrupting the circadian system through SCN lesions or jet lag experiments usually impairs memory and cognition (Cho et al. 2000; Cho 2001; Davidson et al. 2006). Jet lag, caused by abruptly advancing a light or dark phase by > 3 h, temporarily disrupts both clock gene oscillations in the SCN and memory performance until the rodent re-entrains to the new light/dark schedule. (Reddy et al., 2002; Sellix et al., 2012). Finally, a wide

range of neuropsychiatric disorders, including Alzheimer's disease (Homolak et al., 2018), depression (Vadnie and McClung, 2017), PTSD (Albrecht and Stork, 2017), and even normal aging (Antoniadis et al., 2000) is accompanied by disruptions in both memory and the circadian system, suggesting that these two biological processes are linked. Memory is therefore tightly coupled to the organism's circadian cycling and a dysfunctional circadian system typically leads to impaired memory. As the goal of this review is to describe the molecular interface between the circadian system and memory formation, we will primarily focus on research using rodent models in which the circadian rhythm and memory have both been extensively profiled at molecular and behavioral levels. Although human circadian and memory studies have been conducted, they are unable to provide the detailed molecular resolution achieved in rodent studies and are less helpful in describing this molecular interface. In both rodents and humans, however, memory shows a similar circadian oscillation, with better memory typically observed during the daytime (Chaudhury and Colwell, 2002; Eckel-Mahan et al., 2008; Evans et al., 2017; Gerstner and Yin, 2010; Groeger et al., 2008; Harrison et al., 2007; Horowitz et al., 2003; McHill et al., 2018; Rawashdeh et al., 2014; Urban et al., 2021; Wright et al., 2002).

Although it is not currently clear *how* the circadian system governs memory formation, there are some major intersections between the genes that support memory formation and those that regulate circadian rhythms. One compelling idea is that rhythmic oscillation of clock genes in memory-relevant structures (like the hippocampus, retrosplenial cortex, prefrontal cortex, and amygdala) may function to exert circadian control over memory formation (Hartsock and Spencer, 2020). A massive number of transcripts (>80% of protein-coding genes in the baboon (Mure et al., 2018) and ~ 43% of protein coding genes in the mouse (Zhang et al., 2014)) show circadian oscillations in at least one tissue type. This includes a host of diverse "clock-controlled genes" that are directly transcriptionally regulated by the core clock genes themselves. E-box regions are found upstream of non-clock genes, for example, enabling enhanced expression of these genes when the CLOCK-BMAL heterodimer peaks in that local tissue (Hartsock and Spencer, 2020). Although clock-controlled genes in the brain have not yet been characterized in detail, it is very likely that many of these genes impact neuronal activity and plasticity and therefore can affect memory formation. Further, other key genes *known* to play a role in memory formation (like the MAPK/ERK/CREB cascade (Eckel-Mahan et al., 2008; Rawashdeh et al., 2014; Rawashdeh et al., 2016)) oscillate in a circadian manner, despite not being directly transcriptionally coupled to the TTFL itself. To understand how the circadian clock regulates memory, therefore, it will be critical to determine how the molecular clock interfaces with the signaling cascades necessary for memory consolidation in the hippocampus and other memory-relevant brain structures.

5. Core circadian clock genes and their roles in memory

Clock gene oscillations are best characterized in the SCN, where *Clock*, *Bmal1*, *Per1-3*, and *Cry1-2* rhythmically oscillate to establish the animal's circadian activity pattern. Clock genes are present in every cell of the body, however, and these genes show oscillatory expression in many other tissues, including within memory-relevant structures in the brain, including the hippocampus (Chun et al., 2015; Harbour et al., 2014), amygdala (Chun et al., 2015; Harbour et al., 2014), retrosplenial cortex (Urban et al., 2021), and prefrontal cortex (Chun et al., 2015; Jilg et al., 2010; Woodruff et al., 2018) possibly providing a mechanism through which circadian information is communicated locally to these satellite clocks.

Disrupting circadian gene oscillations within the SCN itself can cause an indirect impairment in memory by disrupting the organism's circadian system and sleep/wake cycle. As the SCN controls the circadian functioning of a wide range of bodily processes like immunity, metabolism, mood, and sleep, any disruption of the central circadian pacemaker within the SCN can have widespread consequences on the function of the organism that can indirectly impact memory. To determine whether individual clock genes function locally within memory-relevant structures, therefore, it is important that the manipulation is spatially restricted to the region of interest to avoid disruption of the brain's central pacemaker. To date, only a few studies have tested the effects of local manipulations of individual clock genes on memory formation outside of the SCN (Kim et al., 2021; Kwapis et al., 2018; Mukherjee et al., 2010; Urban et al., 2021; Woodruff et al. 2018). These existing studies, however, all demonstrate behavioral effects in response to local manipulation of an individual clock gene outside the SCN, consistent with the idea that clock genes function to exert local circadian control over memory and other biological processes across the brain. In the next section, we will review what is currently known about the role of each individual clock gene in memory and outline the gaps in our knowledge to guide future studies on these molecules.

5.1. Clock

Clock is one of the four circadian genes that comprise the basic TTFL. As described above, CLOCK heterodimerizes with BMAL1 to drive transcription of the *Per* and *Cry* genes (King et al. 1997; Takahashi, 1995; Vitaterna et al. 1994), initiating the positive limb of the feedback loop (*see* Fig. 1). As with the other clock genes, *Clock* also rhythmically oscillates in cells outside the SCN, although its expression is often shifted in satellite clocks. In the SCN, *Clock* expression peaks at ZT22 whereas its expression peaks in the hippocampus, for example, at ZT18 (Jilg et al., 2010). This out-of-phase oscillation in *Clock* (and the other core clock genes) could function to exert circadian control over other local functions regulated by specific regions of the brain.

CLOCK is ubiquitously expressed throughout the mouse brain and rhythmically oscillates in the hippocampus (Jilg et al., 2010), making it a possible mechanism that could exert local circadian control over memory. Indeed, *Clock*$^{-/-}$ mice (in which *Clock* is globally deleted) show deficits in long-term spatial memory in the hippocampus-dependent Morris water maze task (Oishi et al., 2006). Importantly, however, these *Clock*$^{-/-}$ mice also have disrupted activity patterns (i.e., longer circadian periods and two-hour phase delays; Sei et al., 2001) that may indirectly affect memory. Typically, global knockout or disruption of *Clock* causes arrhythmia (King et al., 1997), although some studies have shown compensation from a second gene, *Npas2* (DeBruyne et al., 2006). NPAS2, a CLOCK paralog, can bind with BMAL1 to support rhythmic oscillation of the molecular clock in the forebrain (Reick et al., 2001) even in the absence of *Clock* (Debruyne et al., 2006; Debruyne et al., 2007). Although there is some debate about the effects of *Clock* deletion on a rodent's behavioral and molecular rhythms, loss-of-function studies demonstrate that CLOCK is necessary for accurately maintaining 24-hour rhythms and NPAS2-mediated compensation is not as effective as CLOCK itself. For example, *Per2* remains arhythmic in peripheral tissues of CLOCK-deficient mice, likely due to the slightly lower binding affinity of NPAS2 to BMAL1 compared to CLOCK, (Landgraf et al., 2016; Mitchell and Tjian, 1989). Together, this indicates that global deletion of *Clock* impacts SCN function, even if this impact is subtle. Global *Clock* deletion may therefore affect hippocampal memory via either local mechanisms (direct functioning within the hippocampus) or indirectly by disrupting the animal's circadian system.

CLOCK can also function as a histone acetyltransferase (HAT; Doi et al. 2006), a chromatin modifier that adds acetyl groups to histone tails. CLOCK primarily acetylates histone H3, but can also acetylate its own binding partner, BMAL1, to activate the complex's ability to positively regulate the transcription of *Per* and *Cry* (Doi et al., 2006; Hirayama et al., 2007; Nakahata et al., 2008; Sahar and Sassone-Corsi, 2012). Little work has investigated whether CLOCK's HAT activity is important for memory, however, despite the well-documented requirement for HAT activity in memory formation (Chatterjee et al., 2020; Peixoto & Abel, 2012; Pirooznia & Elefant, 2013; Stefanko et al., 2009).

As CLOCK is known to interact with CREB-binding protein (CBP) (Eckel-Mahan and Sassone-Corsi, 2013; Hardin and Yu, 2006), a HAT that plays a key role in memory consolidation, this molecule is well-positioned to serve as an epigenetic interface between the circadian clock and memory.

To counterbalance its HAT activity, CLOCK also interacts with the histone deacetylase SIRT1, which itself is important for memory formation (Nakahata et al. 2008). The acetylation of the CLOCK-BMAL1 dimer promotes gene expression, and SIRT1 (a nicotinamide adenosine dinucleotide (NAD)-dependent, Class III HDAC) acts on CLOCK and the CLOCK-BMAL1 dimer to regulate this expression. Studies in the liver have shown that SIRT1 functions to maintain and regulate the amplitude of circadian gene expression, possibly acting as a "rheostat" to carefully regulate core circadian gene expression in tandem with the HAT activity of CLOCK (Asher et al., 2008; Nakahata et al., 2008). Importantly, SIRT1 is also critical for long-term memory, in part because it regulates CREB expression (Gao et al., 2010). Accordingly, SIRT1 knockout mice show impaired hippocampal memory and synaptic plasticity in hippocampal neurons (Michán et al., 2010). Thus, CLOCK may also affect memory through its interactions with SIRT1.

To date, all of the work on *Clock* manipulates its expression in a global manner, affecting *Clock* both in memory-relevant structures and within the SCN itself. It is therefore impossible to determine whether *Clock* plays a local role within the hippocampus in regulating spatial memory formation, or whether its effects on memory occur indirectly due to disruption of the circadian system. Future studies should therefore manipulate *Clock* directly within the hippocampus or other memory-relevant brain regions to directly test whether it plays a role in memory formation that is distinct from its circadian function within the SCN. Further, future studies should determine whether hippocampal *Clock* interacts with SIRT1, HDAC3, and other epigenetic mechanisms during memory formation and whether these interactions change across the day/night cycle.

5.2. *Bmal1*

The second core clock molecule, BMAL1, which binds to CLOCK to drive *Per* and *Cry* transcription, seems to be particularly indispensable for the circadian system. *Bmal1*$^{-/-}$ mice fail to entrain to light/dark cycles and display complete arrhythmia under constant-dark conditions (Bunger et al., 2000), indicating that this gene is critical for normal rhythmicity, even in the presence of light/dark zeitgebers.

Consistent with its vital role in the circadian system, global *Bmal1* knockout causes widespread physiological consequences, including drastic impairments in memory. Wardlaw and colleagues (2014) demonstrated that *Bmal1*$^{-/-}$ mice show impaired learning and memory in multiple hippocampus-dependent tasks, including the Morris water maze and context fear conditioning (Wardlaw et al., 2014), although these mice show intact object recognition memory, which is often reported to be hippocampus-independent (Broadbent et al. 2004; Clark et al. 2000; Good et al. 2007; McNulty et al., 2012; Winters et al., 2004). Additionally, using the open-field task, Kondratova and colleagues (2010) showed that *Bmal1* knockout mice show impairments in habituation both within and between sessions, suggesting that both short- and long-term memory, respectively, are impaired. Hippocampal long-term potentiation (LTP) is also impaired in *Bmal1*$^{-/-}$ mice, suggesting that *Bmal1* knockout might limit memory formation by impairing plasticity within hippocampal synapses (Wardlaw et al., 2014). These impairments in both memory and LTP may stem from disruptions in the MAPK pathway, which is critically important for hippocampal long-term memory (Atkins et al., 1998; Berman et al., 1998; Cammarota et al., 2000; Crow et al., 1998; Kelly et al., 2003; Marin et al., 1997; Selcher et al., 1999; Sharma et al., 2003). *Bmal1*$^{-/-}$ mice show no diurnal oscillation in either MAPK activity or cAMP levels and, strikingly, fail to show learning-induced increases in MAPK phosphorylation in the hippocampus (Wardlaw et al., 2014). Therefore, *Bmal1* seems to play a critical role in hippocampal memory formation via its regulation of the cAMP/MAPK signaling pathway in the hippocampus.

Although organism-wide knockout of *Bmal1* produces impairments in hippocampal long-term memory, again it is not clear whether these effects are from *Bmal1* deletion within the hippocampus *per se*. Because *Bmal1* plays a key, indispensable role in the organism-wide circadian system, its disruption causes widespread effects on the health of the animal, including a complete disruption of the animal's circadian activity pattern. As circadian system disruptions alone can negatively impact memory, it is not possible to dissociate whether the observed effects are due to *Bmal1* disruption within the hippocampus or whether they stem from the disruption of the SCN-mediated circadian system itself. To address this, Snider and colleagues (2016) crossed *Bmal1*$^{flox/flox}$ mice with *CAMKII-Cre* mice to selectively delete *Bmal1* throughout the hippocampus, cortex, and other forebrain regions while sparing *Bmal1* expression in the SCN. Unlike global Bmal1$^{-/-}$ mice, these forebrain-specific *Bmal1* knockout animals displayed normal circadian activity patterns but showed impairments in short-term memory in the hippocampus-dependent object location memory task and disruptions in hippocampal long-term memory in the spatial Barnes maze task. Thus, selective deletion of *Bmal1* in the forebrain impairs learning and memory without affecting the core circadian system in the SCN, suggesting that *Bmal1* may function independently in memory-relevant structures to modulate memory formation. As this deletion was still relatively widespread, however, removing *Bmal1* across the entire forebrain, it is still somewhat unclear whether *Bmal1* functions specifically in the hippocampus to regulate memory. Thus, future studies will need to test whether site-specific deletion of *Bmal1* in the hippocampus and other memory-relevant structures is indeed sufficient to impair long-term memory formation.

5.3. *Cryptochrome*

As part of the negative loop of the molecular circadian clock, CRY1 and CRY2 heterodimerize with the three PER homologs (PER1, 2, and 3) to turn off CLOCK-BMAL1-mediated transcription, ultimately repressing their own expression. In *Drosophila,* CRY1 acts as a photoreceptor, oscillating based on light exposure and entraining the circadian system to the external environment (Emery et al., 1998). In mammals, however, there is little evidence to suggest that CRY1 and CRY2 work in a light-dependent manner. Instead, they function independent of light exposure (Griffin et al. 1999), and their expression is not altered even in constant-dark conditions (Miyamoto and Sancar, 1998).

It is interesting to note that in contrast to *Bmal1* knockout mice, which show early mortality rates alongside other health complications (Wardlaw et al., 2014), global *Cry1/2* knockout mice are behaviorally arrhythmic under constant-dark conditions but can successfully maintain rhythmic activity patterns with 12-hour light/dark cues (van der Horst et al., 1999). In addition, *Cry1/2*$^{-/-}$ mutants show an altered behavioral phenotype including increased locomotion in the dark phase, impaired object recognition memory, and increased anxiety levels, but do not show any change in auditory fear memory (de Bundel et al., 2013), suggesting that the effects of *Cry* knockout are more subtle compared to other clock gene knockouts.

One putative role for the *Cry* genes is to control time-place learning, the ability to learn that a specific event occurs in a particular time and place. To test this idea, Van der Zee and colleagues (2008) developed a novel time-place learning paradigm in which a 3-arm maze is baited with food but also has one arm that delivers a footshock, with the aversive arm changing based on the time of day. Despite being able to learn both the aversive and appetitive information normally, *Cry1/2*$^{-/-}$ mice failed to learn to avoid the shock-delivering arm based on time-of-day information. Thus, *Cry1/2* knockout mice were unable to learn the time-place information necessary to avoid a particular arm at a specific time of day, indicating they have deficient time-place learning.

Together, the data suggest that global deletion of the *Cry* genes

impairs some forms of memory, but not others. Time-place learning (Van der Zee et al., 2008), object recognition memory (de Bundel et al., 2013), and contextual fear conditioning (Van der Zee et al., 2008) are impaired by *Cry* deletion, although auditory fear conditioning is intact (de Bundel et al., 2013). As it is unclear whether time-place learning requires the SCN, the hippocampus, the cortex, or multiple brain regions, it is difficult to make a conclusion about why the *Cry* genes support some types of memories and not others. Further, because all of the work to date uses global disruption of the *Cryptochrome* genes, it is not possible to conclude with any certainty whether *Cry1* or *Cry2* function directly within memory-relevant structures to regulate memory formation. As with the other clock genes, site-specific disruption will be necessary to determine whether *Cry1* or *Cry2* plays a role in memory formation outside of the SCN.

5.4. Period

The *Period* gene family (*Per1-3*) plays a well-established role in the negative arm of the circadian TTFL, in which the PER homologs bind to CRY proteins to shut down *Per/Cry* transcription by blocking the activity of CLOCK/BMAL. Most of the research conducted on *Per* genes focuses on *Per1* and *Per2*, as *Per3*$^{-/-}$ mice show normal circadian activity patterns (Bae et al., 2001; Pendergast et al., 2010; Shearman et al., 2000), although some studies suggest that *Per3* could play a role in tissue-specific clock function outside the SCN (Pendergast et al., 2012). In contrast, global deletion of both *Per1* and *Per2* produces severe arrhythmia (Bae et al., 2001; Zheng et al., 2001), indicating that these genes are critical for normal circadian cycling.

Per1 and *Per2* each play a key role in memory and in generating the circadian activity pattern, although loss of either *Per* homolog has a much less severe effect on the animal's circadian system compared to loss of both *Per1* and *Per2*. Global *Per1*$^{-/-}$ mice show a rhythmic but slightly shortened (~1 h) activity period that is spared in the presence of photic-zeitgebers (Cermakian et al., 2001). Similarly in the absence of *Per2* (Per2$^{-/-}$), animals show a shortened circadian activity period that is lost entirely during complete darkness (Zheng et al., 1999). Interestingly, global *Per1* knockout animals also show shifted oscillations of core clock genes in peripheral tissues (including in the hippocampus (Jilg et al., 2010)), although the expression of these clock genes is spared in the SCN (Cermakian et al., 2001), suggesting that *Per1* may specifically function to regulate circadian output to satellite clocks.

Of all the clock genes, the *Per* genes have the most extensive evidence demonstrating they play a local role in memory-relevant structures to regulate memory. For one, *Period* family genes are known to oscillate in the dorsal hippocampus across the day/night cycle. In the hippocampus, *Per1* mRNA expression peaks around ZT12-16 and troughs at ZT22, whereas PER1 protein shows its highest expression at ZT22 and its lowest expression at ZT6 (Jilg et al., 2010). In the hippocampus, *Per2* mRNA is expressed but does not rhythmically oscillate. PER2 protein levels also do not show a rhythmic oscillation in the hippocampus, although a dip in PER2 expression has been observed at ZT10 (Jilg et al., 2010). Finally, although the diurnal dynamics of *Per3* have not been fully characterized in the hippocampus, its expression in the SCN peaks during the daytime, at ZT6-9, and shows a trough at night, between ZT15-21 (Zylka et al., 1998), whereas *Per1* and *Per2* peak at ZT6 and ZT12, respectively (Albrecht et al., 1997; Sun et al., 1997; Zheng et al., 2001) and both *Per1* and *Per2* trough in the subjective night (Albrecht et al., 1997; Yan & Okamura, 2002).

Perhaps most convincingly, research exists that directly manipulates *Per1* within memory-relevant structures (the dorsal hippocampus (Kwapis et al., 2018), the ventromedial prefrontal cortex (Woodruff et al., 2018), and the retrosplenial cortex (Urban et al., 2021)) to show that this clock gene plays a key role in long-term memory formation that is independent of its pacemaker function within the SCN. The Stehle group first identified *Per1* as a clock gene that also plays an important role in memory formation (2010). Specifically, they found that global *Per1*$^{-/-}$ mice showed long-term memory impairments in a hippocampus-dependent radial arm maze task (Jilg et al., 2010), suggesting that *Per1* regulates memory formation. In subsequent studies, these researchers uncovered a potential mechanism through which *Per1* could provide local control over memory: by regulating the activity of CREB (Rawashdeh et al., 2014; Rawashdeh et al., 2016). As previously described, CREB plays a well-documented role in memory formation, functioning as a transcription factor that promotes the expression of a number of genes necessary for long-term memory (Kandel, 2012). Further, hippocampal CREB phosphorylation at Ser133 is known to oscillate across the day/night cycle, peaking during the daytime in mice (Eckel-Mahan et al., 2008) along with its upstream activator, MAPK/ERK, which also shows increased phosphorylation during the daytime (Eckel-Mahan et al., 2008). Rawashdeh and colleagues showed that global deletion of *Per1* disrupts the diurnal oscillation of both CREB and MAPK phosphorylation in the hippocampus, suggesting that *Per1* may regulate memory formation by controlling CREB activity (2014). Indeed, subsequent work by this group demonstrated that PER1 protein directly interacts with the CREB kinase P90RSK when it is phosphorylated (pP90RSK), shuttling this kinase to the nucleus where it can phosphorylate and activate CREB to initiate the transcriptional program necessary for long-term memory (Fig. 1; Rawashdeh et al., 2016). Thus, this group has proposed that *Per1* functions as a "gate" within the dorsal hippocampus, controlling the sensitivity of CREB-mediated transcription in the hippocampus to modulate the likelihood of long-term memory formation across the circadian cycle. In all of this work, however, *Per1* was deleted throughout the brain, not just in the dorsal hippocampus. It is, therefore, possible that the observed effects on memory and gene expression were due to disruption of the molecular clock within the SCN, rather than disruption within the hippocampus.

Evidence for a site-specific role of *Per1* within a memory-relevant brain region was demonstrated by the Wood Lab in 2018. Kwapis and colleagues (2018) independently identified *Per1* as a key gene regulated by the repressive histone deacetylase HDAC3 during memory formation. Specifically, the authors found that deleting HDAC3 in the dorsal hippocampus ameliorated age-related impairments in memory formation. Using an unbiased RNA-seq approach, they identified *Per1* as one of four key genes restored by HDAC3 deletion, suggesting that HDAC3 might impair memory in the old hippocampus by repressing *Per1* expression. To test this, they bidirectionally manipulated *Per1* levels directly within the dorsal hippocampus and found that tissue-specific repression of *Per1* impaired spatial memory in young mice whereas local overexpression of *Per1* improved memory in old mice. Importantly, the SCN was not thought to be impacted by these manipulations, as the SCN-dependent free-running periods were unaffected in response to local genetic deletion of HDAC3 (a major regulator of *Per1*) within the dorsal hippocampus, consistent with the idea that *Per1* is able to function autonomously within the dorsal hippocampus, possibly providing local circadian control over memory formation. Similar work from Woodruff and colleagues (2018) has demonstrated that site-specific knockdown of both *Per1* and *Per2* in the ventromedial prefrontal cortex prevents enhancements in fear extinction typically observed at night, suggesting that *Per1* may also exert circadian control over extinction memory in the prefrontal cortex. Finally, our group has recently demonstrated that *Per1* knockdown within the retrosplenial cortex, another key brain region necessary for spatial memory, impairs memory for context fear conditioning (Urban et al., 2021), suggesting that *Per1* may exert circadian control over memory in a number of different memory-relevant brain regions. Surprisingly, we found that *Per1* overexpression in the RSC actually impaired memory in young male mice but had no effect in females, suggesting that this clock gene may have sex-specific functions. While there is clearly a need to further investigate sex differences in peripheral clock gene function, overall this work suggests that *Per1* is a key interface between the molecular clock and memory across the brain.

Together with the work from Rawashdeh and colleagues, this suggests that *Per1* may function independently within memory-relevant

brain regions to modulate memory formation across the day/night cycle. *Per1* is therefore particularly well-positioned to integrate the circadian system with memory, although much work remains to determine how widespread this role is across the brain and to determine the precise mechanisms through which *Per1* regulates memory. Further, because these site-specific manipulations of *Per1* are not limited to one phase of memory, it is difficult to determine whether these manipulations affected acquisition, consolidation, or retrieval of the memory, an outstanding question that will need to be addressed. Moving forward, it will also be important to establish how this system is altered in aging individuals, who typically show severe impairments in both long-term memory and circadian rhythmicity as well as reduced levels of hippocampal *Per1* (Kwapis et al., 2018). *Per1*, which may function as an interface between memory and the circadian rhythm, could therefore represent a novel therapeutic target for improving both memory and circadian rhythmicity in old age.

6. Conclusion

The circadian system plays a key role in regulating physiological processes across the brain and body. One major function controlled by the circadian system is memory formation, which is directly affected by circadian gene expression. Despite this connection, the role of circadian genes in memory outside of the SCN is largely unexplored, as most of the work to date investigates memory in global knockout animals that lack circadian gene expression throughout the brain, including in the brain's central pacemaker, the SCN. Recent work has begun to explore the effects of local clock gene manipulations directly within memory-relevant brain structures, however. The results to date demonstrate that clock genes, most notably *Per1*, may function autonomously within memory-relevant brain regions, including the hippocampus and retrosplenial cortex, to modulate memory across the 24 h day/night cycle. Circadian genes may therefore play very different roles outside of the SCN, exerting circadian control over memory by locally functioning in satellite clocks across the brain.

CRediT authorship contribution statement

Chad W. Smies: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Kasuni K. Bodinayake:** Conceptualization, Visualization, Writing – original draft. **Janine L. Kwapis:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors declare that they have no conflicts of interest.

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