Concise Review: Regulatory Influence of Sleep and Epigenetics on Adult Hippocampal Neurogenesis and Cognitive and Emotional Function

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ABSTRACT

Neural stem and progenitor cells continue to generate new neurons in particular regions of the brain during adulthood. One of these neurogenic regions is the dentate gyrus (DG) of the hippocampus, which plays an important role in cognition and emotion. By exploiting this innate neuronal regeneration mechanism in the DG, new technologies have the potential to promote resistance to or recovery from brain dysfunction or degeneration. However, a deeper understanding of how adult DG neurogenesis is regulated by factors such as sleep and epigenetic modifications of gene expression could lead to further breakthroughs in the clinical application of neural stem and progenitor cells. In this review, we discuss the functions of adult-born DG neurons, describe the epigenetic regulation of adult DG neurogenesis, identify overlaps in how sleep and epigenetic modifications impact adult DG neurogenesis and memory consolidation, and suggest ways of using sleep or epigenetic interventions as therapies for neurodegenerative and psychiatric disorders. By knitting together separate strands of the literature, we hope to trigger new insights into how the functions of adult-generated neurons are directed by interactions between sleep-related neural processes and epigenetic mechanisms to facilitate novel approaches to preventing and treating brain disorders such as depression, post-traumatic stress disorder, and Alzheimer's disease. STEM CELLS 2018;36:969–976

SIGNIFICANCE STATEMENT

New technologies utilizing neural stem cells in the adult hippocampus could potentially be used to promote innate resistance to or recovery from brain dysfunction or degeneration. Accumulating evidence indicates that adult hippocampal neurogenesis contributes to cognitive and emotional processing and is regulated by sleep and epigenetic modification of gene expression. Therefore, a richer understanding of how the interplay between sleep and epigenetics impacts adult hippocampal neurogenesis and thereby influences hippocampal function can help advance efforts to employ behavioral sleep interventions, epigenetic drugs, and novel neural stem cell-based therapeutic strategies for preventing or treating neurodegenerative and psychiatric disorders.

INTRODUCTION

The discovery of neurogenesis in the adult human brain [1] suggests the possibility of harnessing innate neuronal regeneration mechanisms to promote resistance to or recovery from brain dysfunction or degeneration across the lifespan. However, compared with recent advances in induced pluripotent stem cells and cell implantation techniques [2], the potential of utilizing intrinsic restorative mechanisms, such as the birth of new neurons within particular regions in the brain, seems overlooked. Thus, a deeper understanding of how adult neurogenesis is regulated by factors such as sleep and epigenetic modifications of gene expression could prompt new insights and lead to further breakthroughs in the translation of basic research findings to clinical practice. Here, we review the functions of adult-generated neurons in the dentate gyrus (DG) region of the hippocampus, describe the epigenetic regulation of adult DG neurogenesis, and explore interactions between sleep and epigenetic modifications that could impact adult DG neurogenesis and thereby improve cognitive and emotional function, with an emphasis on memory consolidation. By synthesizing this literature, we hope to inspire new approaches to understanding and clinically

applying the potential of adult-generated neurons to prevent or treat neurodegenerative and psychiatric disorders.

FUNCTIONS OF ADULT DG NEUROGENESIS

Anatomically, the DG is the gate to a major hippocampal pathway that originates from superficial layers of the entorhinal cortex (EC) through the perforant path and projects onward to the CA3, CA2, and CA1 hippocampal regions and outward to the subiculum and deeper EC layers (Fig. 1A). The principle cell layer of the DG is the granule cell layer, which is made up of densely packed granule neurons. The neural stem and progenitor cells (NSPCs) that give rise to DG neurons home at the border of the granular cell layer and hilus, called the subgranular zone (Fig. 1B). Intriguingly, these NSPCs not only contribute to initial DG development but also continue to produce new neurons throughout the lifespan in many mammalian species, including rodents, insectivores, carnivores, ungulates, and primates [3]. Whereas the rate of DG neurogenesis declines exponentially with age in most mammals [4], humans appear to exhibit a more modest age-related reduction in DG neurogenesis [5]. Evidence of adult neurogenesis has also been observed in other regions of the mammalian brain such as the subventricular zone, neocortex, hypothalamus, amygdala, and striatum [6].

Early rodent studies provided evidence of a connection between adult DG neurogenesis and cognition by showing that exercise enhances both adult DG neurogenesis and hippocampal-dependent learning and memory [7] and that hippocampal-dependent learning itself enhances adult DG neurogenesis [8]. Since then, additional evidence has indicated that adult-born DG neurons functionally integrate into hippocampal circuitry and play a special role in cognition during a period of heightened excitability and synaptic plasticity occurring 4–6 weeks after mitosis [9]. Moreover, recent studies employing sophisticated experimental techniques have generated compelling evidence for a critical role of adult DG neurogenesis in hippocampal-dependent cognitive function. For instance, transgene-mediated ablation of adult-born DG neurons [10] or optogenetic silencing of their activity [11] after learning impairs contextual fear and spatial memories in mice. Precisely how adult-born DG neurons contribute to cognition, however, remains to be determined. Some current theories are that adult-born DG neurons underlie the ability to discriminate between similar representations (i.e., pattern separation) [12], encode temporal information [13], allow the clearance of memories to minimize proactive interference [14], or promote cognitive flexibility [15]. Moreover, deficiencies in adult DG neurogenesis are linked to human disorders associated with cognitive deficits, such as Alzheimer's disease and schizophrenia [9, 16].

Adult DG neurogenesis may also play a role in emotional processing and mood disorders. For instance, rodent studies show that adult DG neurogenesis is reduced in depression- or anxiety-like states, is increased by antidepressive treatments, and mediates some of the effects of antidepressant drugs [17]. Consistently, postmortem studies report that human patients with major depressive disorder (MDD) have fewer NSPCs in the DG than non-MDD patients [18] and that antidepressant-treated MDD patients have more NSPCs in the DG than untreated MDD patients [19], although some studies report conflicting evidence [17]. Deficits in adult DG neurogenesis might also contribute to post-traumatic stress disorder (PTSD) by permitting the overgeneralization of fear via insufficient pattern separation [20]. This dual role of adult DG neurogenesis in cognition and emotion may arise from anatomical segregation of hippocampal function, with dorsal adult-born neurons being more involved in cognition and ventral adult-born neurons being more involved in emotion [21].

EPIGENETIC REGULATION OF ADULT DG NEUROGENESIS

Adult DG neurogenesis is regulated by a myriad of intrinsic and extrinsic factors, including drugs, diet, inflammation, physical activity, environmental enrichment, stress, and trauma [22]. Conceivably, many of these factors impact adult DG neurogenesis via dynamic epigenetic modifications that facilitate or suppress the expression of particular genes, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs [16, 23]. As an example, exposure to extremely low-frequency electromagnetic fields increases the proliferation and differentiation of adult-born DG neurons in mice, which is accompanied by enhanced long-term potentiation of perforant path-DG synapses and improved spatial learning and memory [24]. This increase in adult DG neurogenesis may result from the transcription of pro-proliferative (i.e., *Hes1*) and neuronal determination (i.e., *Mash1*, *Neurogenin1*, *NeuroD1*) genes in part through increased binding of CREB-binding protein (CBP), a histone acetyltransferase (HAT), at gene promoter regions [25]. In support of this possibility, direct pharmacological activation of CBP promotes the differentiation and dendritic branching of adult-born DG neurons and improves spatial memory [26], whereas CBP deficiency blunts the enhancing effects of environmental enrichment on adult DG neurogenesis, spatial learning and memory, and pattern separation [27]. Therefore, epigenetic mechanisms can mediate the regulatory effects of a variety of factors on adult DG neurogenesis, thus impacting hippocampal function and contributing to neurodegenerative and psychiatric disorders [16, 23].

ROLE OF SLEEP IN EPIGENETIC REGULATION OF ADULT DG NEUROGENESIS

Due to several key associations among sleep, hippocampal function, and factors that influence neurogenesis, sleep has been proposed to regulate the generation of new DG neurons during adulthood [28, 29]. We go one step further and propose that sleep regulates adult DG neurogenesis by inducing or being affected by epigenetic modifications of gene expression. Below, we highlight overlaps in existing knowledge about sleep, epigenetics, adult DG neurogenesis, and memory processing to help identify links between sleep and epigenetic modifications that can be exploited to prevent or treat symptoms of neurodegenerative and psychiatric disorders.

Brief Overview of Sleep

Sleep is defined as a homeostatically regulated and rapidly reversible state of immobility and low sensory responsiveness observed in many but not all animals [30]. In mammals, sleep consists of cycles of rapid eye movement (REM) and different
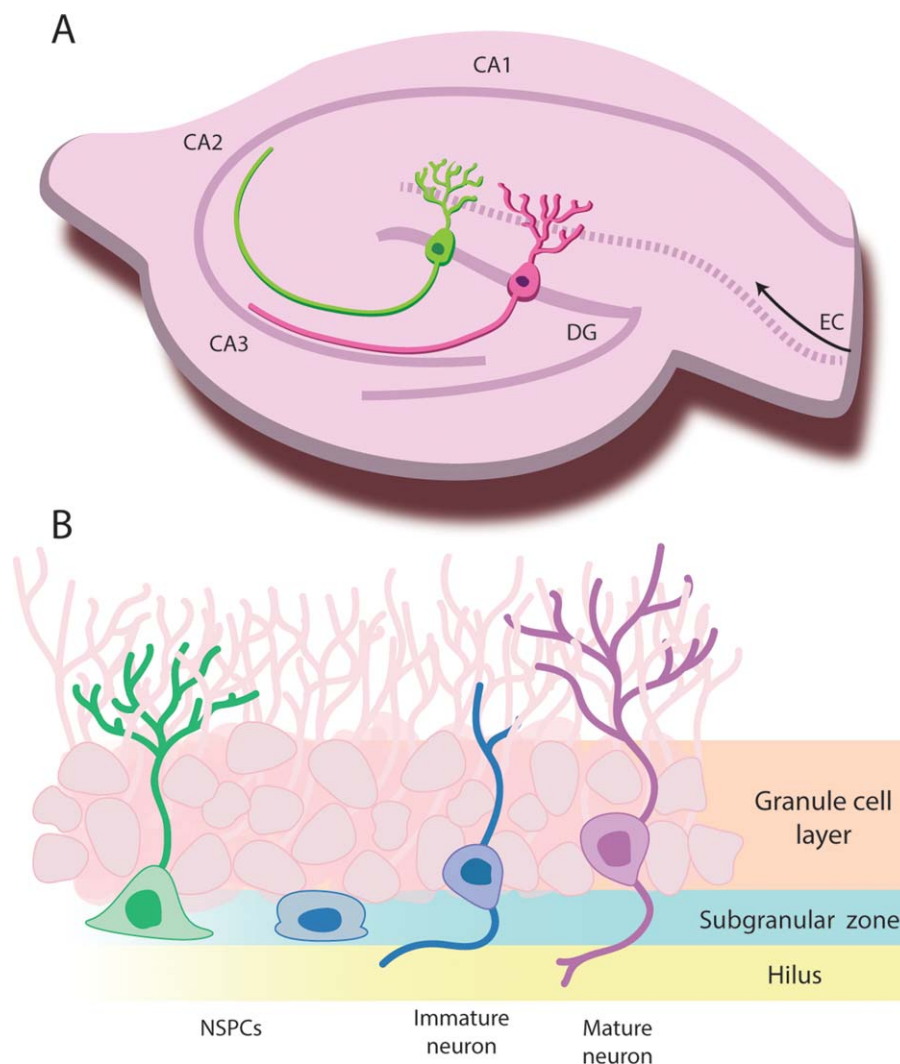
Figure 1. DG circuitry and generation of new neurons. **(A):** The DG receives input from the perforant path of the EC and sends output through mossy fibers to the CA3 region and additional longitudinal projections to the CA2. **(B):** NSPCs originate in the subgranular zone of the DG and gradually migrate into the granule cell layer as they mature. Abbreviations: DG, dentate gyrus; EC, entorhinal cortex, NSPCs, neural stem and progenitor cells.

stages of non-REM (NREM) sleep, with particular stage characterized by distinct patterns of cortical activity as detected by electroencephalography (EEG; Fig. 2). Certain patterns of coordinated neural activity occurring during sleep are observed in the hippocampus [31]. In rodents, sharp wave-ripples (SW-Rs) occurring during NREM sleep arise from the synchronous discharge of hippocampal CA3 pyramidal neurons, which causes fast depolarization ("sharp wave") and high-frequency oscillations (100–250 Hz "ripples") resulting from interactions between CA1 pyramidal neurons and inhibitory interneurons [32]. Also, theta rhythm (6–9 Hz) during REM sleep is observed throughout regions of the rodent hippocampus, including the DG, and may be paced by subcortical nuclei [33]. Interestingly, intracerebral EEG recordings from epileptic patients show the presence of hippocampal SW-Rs during NREM sleep but suggest that delta rhythm (0.5–4 Hz) may be the human analog of rodent theta rhythm during REM sleep [34]. Across species, however, the coordination of hippocampal and extra-hippocampal oscillatory activity during sleep is thought to promote the system-level consolidation of

memories formed during prior wakefulness, through which initially hippocampal-dependent memories become reorganized across distributed cortical networks for long-term storage [35].

Circadian Rhythms

The sleep-wake cycle is regulated by internal circadian clocks controlled by a master clock in the suprachiasmatic nucleus (SCN). Circadian clocks also regulate the homeostasis and function of stem cells, including adult NSPCs [36]. Core clock genes such as *mPer2* and *mBmal1* are present in NSPCs in the adult mouse subgranular zone and regulate adult DG neurogenesis by controlling the timing of cell cycle events [37]. Indeed, *mBmal1* knock-out mice, which show arrhythmic locomotor activity, exhibit abnormally high proliferation or survival of adult-born DG neurons [37, 38] and poor performance in a delayed nonmatching-to-place task [37], suggesting that this clock gene promotes optimal cognition function by placing restrictions on the rate of adult DG neurogenesis. A relationship between clock gene expression and adult DG neurogenesis
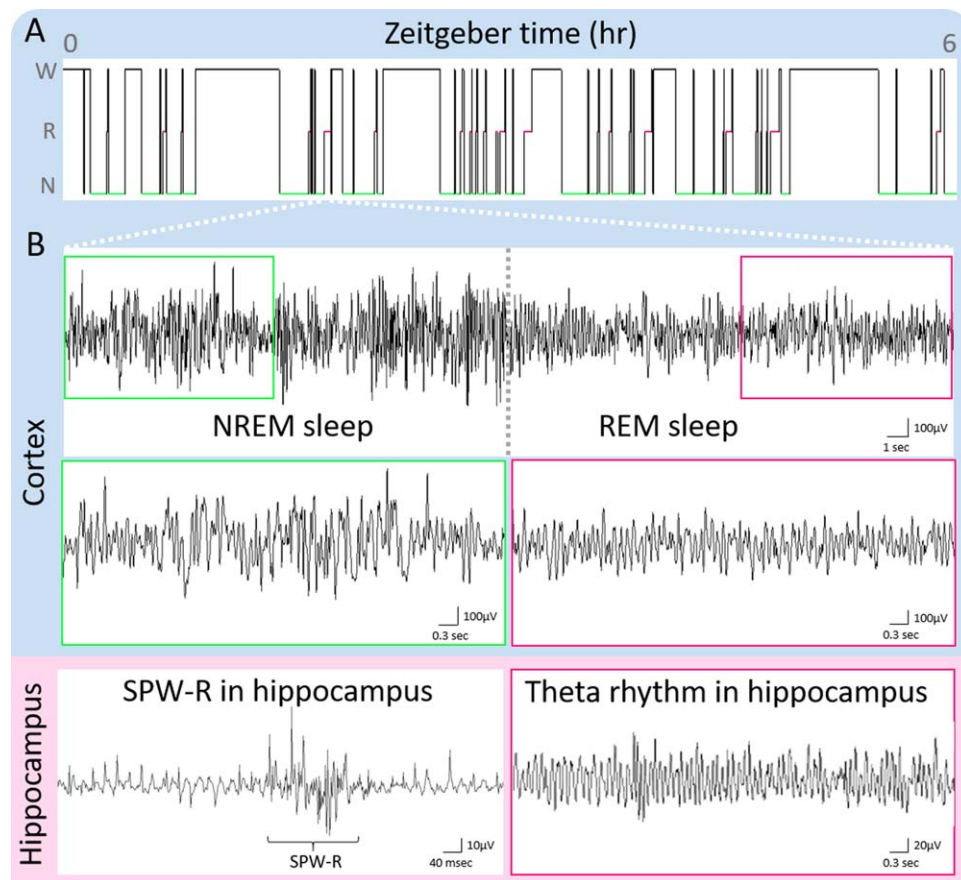
Figure 2. Basic features of sleep. **(A):** Hypnogram showing sleep architecture in rodents during a period of 6 hours. Sleep consists of several cycles of REM and NREM sleep. **(B):** EEG trace showing a transition from NREM to REM sleep. NREM sleep is characterized by high-amplitude and low-frequency waves in the cortex (0.5–4 Hz; green panel) and sudden bursts of high-frequency firing (100–250 Hz) called SPW-Rs in the hippocampus. REM sleep is characterized by low-amplitude and high-frequency waves in the theta range in both the cortex and hippocampus (6–9 Hz; pink panels). Abbreviations: W, wake; N, NREM sleep; R, REM sleep; SPW-R, sharp wave ripple.

may also have implications for emotional processing. For instance, SCN-specific *mBmal1* knock-down mice exhibit depression-like behaviors [39], whereas mice selectively bred for high anxiety- and depression-like behavior show decreased hippocampal mRNA levels of another clock gene, *mCry2* [40], and reduced survival and functional integration of adult-born DG neurons [41]. Accumulating evidence indicates that the transcription of circadian clock genes is epigenetically regulated through changes in DNA methylation, histone modifications, and structural chromatin alterations [42]. Therefore, epigenetic modifications of clock genes could be targeted for the prevention or treatment of neurodegenerative or psychiatric disorders involving circadian disruptions.

Sleep Deprivation

Despite recommendations to sleep at least 7 hours each night, over one-third of U.S. adults report regularly receiving insufficient amounts of sleep [43]. In experimental studies with human subjects, a single night of lost sleep has been found to impact a wide range of cognitive and emotional functions, including attention, working memory, processing of rewards and aversive stimuli, and hippocampal-dependent memory [44]. Neuroimaging studies show that acute sleep deprivation reduces learning-related activity in the hippocampus and functional coupling between the hippocampus and

cortical regions [44], consistent with the hypothesis that sleep promotes system-level memory consolidation by promoting interactions between the hippocampus and cortex [35]. Moreover, after several consecutive days of insufficient sleep, cognitive deficits exhibit a protracted course of recovery, with normal function not observed until after 3 or more nights of recuperative sleep [45]. Thus, the sleep disruptions often experienced by healthy aged individuals as well as patients with Alzheimer's disease have been proposed to contribute to declines in hippocampal-dependent cognitive function [31, 44, 46].

The effects of chronic sleep deprivation on hippocampal function have been extensively investigated using rodent models. A large body of evidence indicates that chronic sleep deprivation, sleep restriction, sleep fragmentation, or REM-specific sleep deprivation reduces adult DG neurogenesis, disturbs hippocampal signaling pathways, impairs hippocampal synaptic plasticity, and disrupts the consolidation of hippocampal-dependent memories [28, 47]. Although these effects have been argued to be an indirect outcome of elevated stress hormones, several studies report that the impact of sleep deprivation on hippocampal function is independent of the stress response [29]. For example, depriving adult rats of sleep for 96 hours reduces the proliferation of DG neurons, and this effect persists when rats are adrenalectomized and given low-dose corticosterone, indicating that sleep

deprivation affects adult DG neurogenesis by mechanisms other than an increase in stress hormones [48].

One route by which sleep deprivation could impact adult DG neurogenesis and thereby affect hippocampal function is through epigenetic modifications. Both acute and chronic sleep deprivation produce broad changes in epigenetic markers and patterns of gene transcription in rodents [49–52] and humans [53, 54]. Of particular interest, depriving mice of sleep for 3 days downregulates hippocampal CBP expression, reduces hippocampal histone acetylation levels at *Bdnf* promoter regions, and weakens spatial memory [49], suggesting that sleep deprivation can impair cognition by disrupting hippocampal BDNF signaling, which is important for the maturation and growth of adult-born DG neurons [55]. Also, genome-wide analysis of blood samples from healthy individuals after 1 night of sleep deprivation shows alterations in the methylation status of genes involved in Notch and Wnt signaling pathways [54], both of which play important roles in the regulation of adult DG neurogenesis. Therefore, insufficient sleep could produce epigenetic modifications that disrupt the generation of new DG neurons and hence impact hippocampal function, suggesting that epigenetic markers could be targeted to normalize adult DG neurogenesis and restore cognitive function in people who do not receive sufficient sleep.

Memory Replay During Sleep

In vivo neural recordings reveal that certain memories are replayed in the hippocampus during sleep, which may allow the further processing of memories during system-level consolidation [56]. For instance, hippocampal place cells that fire together while rats explore a spatial environment tend to also fire together during subsequent sleep [57], and patterns of hippocampal blood flow during virtual route learning in humans are reinstated during later sleep [58]. Although some studies have detected memory replay during REM sleep [59], memory replay is usually observed during NREM sleep and is tied to the occurrence of hippocampal SW-Rs [56]. Indeed, electrophysiological suppression of sleep-related hippocampal SW-Rs across several days of training in spatial tasks impairs task performance in rats [60], providing evidence that the replay of memories during NREM sleep promotes their consolidation.

In addition to spontaneous memory replay during sleep, specific memories can be reactivated during NREM or REM sleep via the covert presentation of an auditory or olfactory stimulus associated with a previously acquired memory, a phenomenon known as "cueing" or "targeted memory reactivation" [61, 62]. For example, when a person is sleeping, presenting an odor associated with a recent object-location memory causes hippocampal activation and enhances recall of that memory during subsequent wakefulness [63]. Whereas some studies show that cueing during sleep enhances memory, others report that cueing during sleep impairs memory (e.g., [64]). Therefore, additional research is needed to define the parameters under which targeted memory reactivation during sleep improves or impairs subsequent memory recall.

Although studies of targeted memory reactivation during sleep point toward the hippocampus as an important neural substrate [62], the underlying mechanisms are not yet clear. Therefore, insights into the cellular and molecular basis of targeted memory reactivation during sleep could come from studies of memory reactivation during wakefulness. Interestingly,

reactivation of a memory during wakefulness induces epigenetic modifications in the hippocampus, including alterations in histone acetylation and methylation, as well as DNA hydroxymethylation [65, 66]. For example, reactivation of a recent contextual fear memory in mice increases the abundance of H3K9/14 acetylation at the promoter region of *cFos* [66], suggesting that memory reactivation induces epigenetic changes that facilitate the transcription of plasticity-related genes. In parallel with epigenetic modifications, reactivation of a memory during wakefulness can also engage adult-born DG neurons. That is, immature adult-born DG neurons expressing the plasticity-related gene *Egr1* are preferentially recruited for the reactivation-mediated updating of an object recognition memory [67]. Taken together, these findings raise the possibility that the targeted reactivation and replay of a memory during sleep induces epigenetic modifications of gene expression in adult-born DG neurons that promote further memory processing and consolidation.

TARGETING SLEEP AND EPIGENETIC MARKERS AS TREATMENT STRATEGIES

The existence of a regulatory pathway through which the interplay of sleep and epigenetics impacts adult DG neurogenesis and thereby affects cognitive and emotional processing (Fig. 3) invites new thinking about approaches to preventing or treating neurodegenerative and psychiatric disorders.

As a most basic therapeutic strategy, it is important to ensure that patients with neurodegenerative or psychiatric disorders consistently receive sufficient amounts of high-quality sleep to allow optimal cognitive and emotional processing of memories. This may involve carefully choosing pharmacological treatments, such as those for depression [68] or aging-related disorders [69], that do not negatively impact sleep architecture. The timing of sleep may also be of strategic importance, as sleep immediately following exposure therapy can decrease fear in patients with phobia, presumably by promoting the consolidation of new, non-fearful memories [70]. On the other hand, restricting sleep can also be beneficial in some cases. Acute sleep deprivation following a traumatic experience might prevent the development of PTSD by disallowing the consolidation of traumatic memories [71], whereas a partial or full night of sleep deprivation can alleviate symptoms of depression or bipolar disorder [72], perhaps by resetting circadian rhythms via epigenetic modification of clock gene expression.

Targeted memory reactivation could also be employed as a clinical tool for modulating memory processing during sleep. Depending on factors such as the type of memory and the sleep stage in which a memory is reactivated, cueing during sleep can either enhance or impair later recall of a memory [61, 62]. Therefore, targeted memory reactivation could be used to bolster wanted memories in healthy or cognitively impaired individuals or weaken unwanted memories in individuals with PTSD, anxiety, or depression [62].

In addition to behavioral sleep therapies, epigenetic drugs such as DNA methylation inhibitors, histone deacetylase (HDAC) inhibitors, and HAT activators could override epigenetic modifications arising from life experiences or developmental perturbations and thus be used to treat neurodegenerative
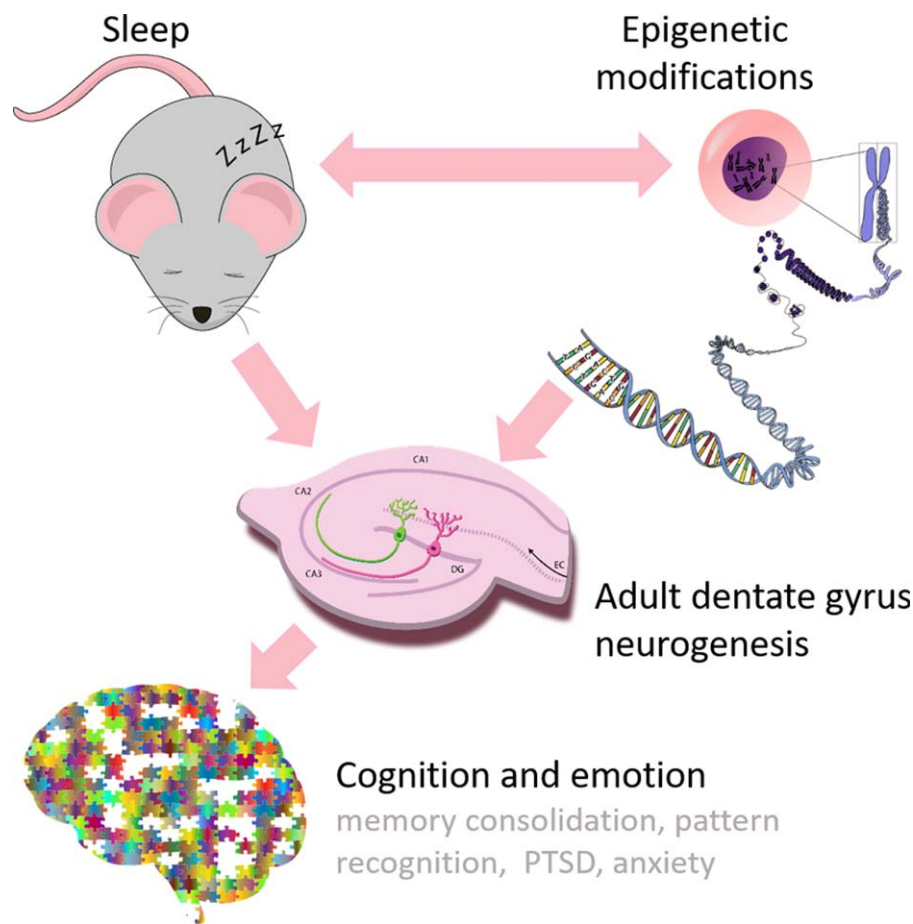
Figure 3. The interplay between sleep and epigenetic modifications of gene expression impacts adult dentate gyrus neurogenesis and thereby influences cognitive and emotional processing, suggesting new therapeutic avenues for preventing or treating neurodegenerative and psychiatric disorders. Abbreviation: PTSD, post-traumatic stress disorder.

and psychiatric disorders [73]. For example, by selectively downregulating HDAC5, the antidepressant imipramine increases histone acetylation at *Bdnf* promoter regions, upregulates *Bdnf* expression, and alleviates depression-like behavior in mice after social defeat [74], suggesting that HDAC inhibitors can exert antidepressant effects by reversing environmentally-induced epigenetic modifications. Given that depression also involves sleep disruptions [75] and abnormalities in adult DG neurogenesis [76], it is interesting to consider whether the beneficial effects of epigenetic drugs on cognitive and emotional processing could be mediated by improvements in sleep and/or the generation of adult-born DG neurons.

In particular, Alzheimer's disease might be well suited for the employment of both sleep and epigenetic interventions to alleviate cognitive impairment. Patients with Alzheimer's disease show altered levels of epigenetic markers in the hippocampus [77]; various sleep disruptions including nighttime sleep fragmentation, increased daytime napping, and less time spent in slow wave and REM sleep stages [78]; and impairments in DG neurogenesis [78]. These findings suggest that cognitive deficits in Alzheimer's disease could result in part from disruptions in DG neurogenesis caused by both suboptimal epigenetic modification of gene expression and poor sleep. Importantly, sleep disruptions often precede the clinical onset of Alzheimer's disease [46]. Therefore, the simultaneous and coordinated use of epigenetic drugs and behavioral

therapies that restore circadian rhythms (i.e., through clock gene transcription) and improve sleep duration and quality could not only treat established cognitive deficits but also delay the progression of cognitive decline in individuals at risk for Alzheimer's disease.

CONCLUSION

The literature discussed in this review hints at a complex interplay among sleep, epigenetic modifications of gene expression, adult DG neurogenesis, and cognitive and emotional function, indicating the potential value of future studies aimed at identifying and unraveling the interconnections among these processes as well as the additional modulatory influences of neurotransmitters, hormones (e.g., stress hormones), and cytokines. Here, we propose that interactions between sleep and epigenetics regulate the generation of new DG neurons in adulthood and thereby affect cognitive and emotional processing (Fig. 3). To advance our understanding of this regulatory pathway, it is imperative to perform deeper investigations into how adult-born DG neurons integrate into the existing neural circuitry and contribute to hippocampal-dependent function, which may soon be realized through advances in technology and computing. For instance, the activity of adult-born DG neurons in behaving mice can

now be monitored using two-photon calcium imaging [79]. Newly developed miniaturized fluorescence microscopes [80] could be used to show the firing patterns of adult-born DG neurons during different stages of sleep and their responses to cueing during sleep. Also, new analysis methods can unveil detailed and comprehensive maps of the connections (i.e., connectomes [81]) and functional dynamics (i.e., dynomes [82]) between adult-born DG neurons and pre-existing neural networks, which could aid in the targeted manipulation of specific memories during sleep.

In addition to pointing toward avenues for further basic research, our synthesis of the literature on adult DG neurogenesis and its regulation by sleep and epigenetic modifications suggests that future NSPC-based therapeutic strategies should at least consider, if not directly exploit, factors that control the process of adult DG neurogenesis with the aim of maintaining or improving cognitive and emotional function. By employing sleep interventions and epigenetic drugs alongside other therapies that promote the optimal survival, proper connectivity, and functionality of adult-born DG neurons, we will move closer toward realizing the full potential of hippocampal NSPCs for preventing and treating neurodegenerative and psychiatric disorders.

Author Contributions

K.G.A.: conception and design, manuscript writing, final approval of manuscript; Y.C.: manuscript writing, creation of figures, final approval of manuscript; Y.F., S.S., and T.S.: manuscript writing, final approval of manuscript; M.S.: conception and design, financial and administrative support, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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