Chapter 9
Sleep, Ageing, and Cognitive Decline

Krishna Melnattur

9.1 Introduction

This chapter focuses on changes in sleep architecture, physiology, and function in healthy ageing. We begin with a description of the phenomenology of age-dependent changes in sleep distribution and oscillations and discussion of potential underlying neurobiological mechanisms. We next consider two candidate consequences of sleep—glymphatic brain clearance and learning and memory. This chapter focuses largely on work on humans and rodents. However, in each section, we will also briefly consider parallels with invertebrate models. Specifically, we will draw comparisons with sleep in the fly *Drosophila* as a canonical example of an invertebrate. In the last 20 years, *Drosophila* has emerged as powerful model to study sleep regulation and function and is certainly the best studied invertebrate sleep model.

9.2 Age-Dependent Changes in Sleep Distribution and Oscillations

Sleep in humans undergoes characteristic ontogenic changes, with the prototypical young adult pattern of sleep distribution and oscillatory activity only emerging by late adolescence.

Newborn infants spend a large proportion of their day asleep (16–18 h). Infant sleep is, however, not consolidated into a single sleep bout. Instead, bouts of sleep alternate with bouts of feeding. Further, each sleep cycle lasts ~ 50 min and consists of equal amounts of rapid eye movement (REM) sleep and non-rapid eye movement

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(NREM) sleep. Sleep onset is also frequently into REM sleep (Daftary et al. 2019; Grigg-Damberger et al. 2007; Grigg-Damberger 2016; Ohayon et al. 2004). Sleep stages in newborns and infants do not exhibit all of the characteristics seen in young adults. Muscle atonia is thus incomplete in infant REM sleep, and the slow waves that are an important characteristic of NREM sleep in adults (see below) are not present in every cycle (Grigg-Damberger 2016; Bes et al. 1991). REM and NREM sleep in infants are classified as active sleep and quiet sleep to reflect this fact (Grigg-Damberger 2016).

By one to four years of age, total sleep time decreases to about 11–12 h a day. Sleep is also more consolidated, consisting of one primary sleep bout at night, and one to two naps during the day (Ohayon et al. 2004). Important differences remain in characteristics of different sleep stages in young children versus young adults. NREM is typically much deeper in young children versus young adults (Busby and Pivik 1983).

As children get older sleep duration further decreases. Teenage sleep shares many traits with sleep in young adults discussed below, with the important exception that the timing of sleep is delayed.

In young adults, sleep is characterised by a single consolidated bout at night and a regular cyclical pattern of alternation between sleep stages. Each sleep cycle lasts ~ 90 min, with a regular alternation between NREM and REM sleep (Fig. 9.1a). The sleep stages are defined by characteristic signatures in the electro encephalogram (Carskadon and Dement 2016).

9.2.1 Age-Dependent Changes in Sleep

Healthy normal ageing is associated with characteristic changes in sleep duration, quality, and timing. Overall sleep duration decreases in older adults. Sleep is more fragmented and associated with more awakenings and arousals. Further, the timing of sleep onset and offset is advanced, and sleep latency is increased. In addition, ageing is also associated with changes in sleep stage architecture. Thus, ageing is associated with lower amounts of deep slow wave sleep, more time in lighter NREM stages 1 and 2, and fewer NREM-REM cycles (Fig. 9.1) (Landolt et al. 1996; Zepelin et al. 1984; Feinberg and Carlson 1968; Kales et al. 1967; Klerman and Dijk 2008; Van Cauter et al. 2000).

Further, it is not just sleep at night that is altered with age. Daytime sleep is also altered with age. Older adults report increased frequency of daytime naps, and daytime sleepiness severe enough to impair normal functioning (Foley et al. 2007).

9.2.1.1 Anatomical Basis of Age-Dependent Sleep Changes

What might be the neurobiological basis for these phenomena? We begin our discussion of this question, with a little historical background.

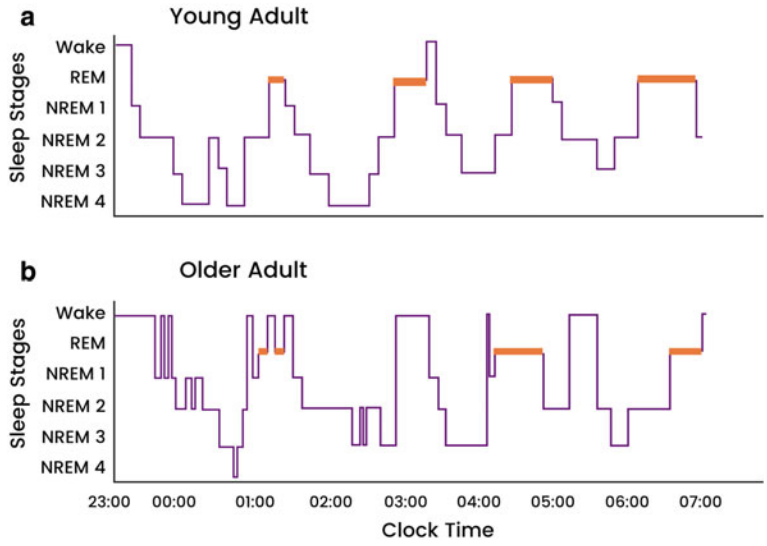

Fig. 9.1 **a** Sleep hypnogram of a young adult. Sleep consists of a single consolidated bout at night and is characterised by a ~ 90 min cycle of NREM and REM sleep (orange). The relative time spent in REM sleep increases through the night, concomitant with a decrease in time spent in deeper NREM stages. **b** Sleep hypnogram of an older adult. Sleep of older adults is characterised by longer sleep latency, more fragmented sleep with greater awakenings from sleep, and less time in deeper slow wave sleep stages. Figure adapted from Mander et al. (2017)

The study of the anatomical basis of sleep and wakefulness in mammals owes a lot to an unfortunate epidemic of *encephalitis lethargica* almost a 100 years ago. Upon examining encephalitis patients who presented with insomnia, von Economo observed inflammatory lesions in the preoptic area (POA). Patients with hypersomnia presented with lesions in the posterior hypothalamus (PH) (von Economo 1930). Based on these results, von Economo postulated a sleep-promoting area in the POA and a wake promoting region in the PH. Subsequent lesion studies in animal models supported this idea and suggested a model, whereby sleep-promoting POA neurons inhibit arousal promoting PH neurons (Nauta 1946). Around the same time, electrical stimulation of the reticular formation was shown to induce a wake like state in anaesthetised cats (Moruzzi and Magoun 1949).

Since these classic studies, application of more modern circuit dissection techniques has led to a more nuanced understanding of the circuitry for sleep and wakefulness (Scammell et al. 2017; Szymusiak and McGinty 2016) (Fig. 9.2). The sleep-promoting area in the POA was shown to comprise of GABA and galaninergic neurons in the ventrolateral preoptic area (VLPO) (Kroeger et al. 2018; Sherin et al. 1996). The idea of an undifferentiated reticular formation has been replaced by the identification of multiple arousal promoting systems distributed along the neuraxis. These include serotonergic neurons from the Dorsal Raphae, noradrenergic neurons in the Locus Coeruleus, dopaminergic neurons from Ventro Tegmental Area,

histaminergic neurons from the Tubero Mammillary Nucleus, orexinergic neurons in the hypothalamus, and cholinergic neurons in the basal forebrain. These arousal promoting systems innervate broadly in the cortex enabling the brain to transition to a wake state. Interestingly, wake and sleep-promoting systems inhibit each other, resulting in what has been termed a flip-flop switch, that enables rapid transitions between sleep and wake with little time spent in an in-between state (Saper et al. 2010).

Perhaps unsurprisingly, ageing affects both sleep and arousal promoting centres. The number of galanin expressing neurons in the POA was shown to decline with age in humans, with the severity of loss correlating with extent of sleep fragmentation (Lim et al. 2014). Further, the number of orexinergic neurons in the lateral hypothalamus was also reduced in both aged rodents and older humans (Kessler et al. 2011; Hunt et al. 2015). A recent study in rodents found that neuronal excitability of orexinergic neurons was causally linked to age-dependent sleep disruptions (Li et al. 2022). Oxerinergic neurons in aged mice were found to have a lower resting membrane potential. They were also found to express lower levels of the voltage gated potassium channel subfamily Q member 2 subunit (KCNQ2) and a lower basal M current (I_m). Disrupting KCNQ2 in young mice fragmented sleep, conversely increasing KCNQ2 activity increased sleep stability in aged mice (Li et al. 2022). These results provide an interesting and detailed mechanistic explanation for sleep

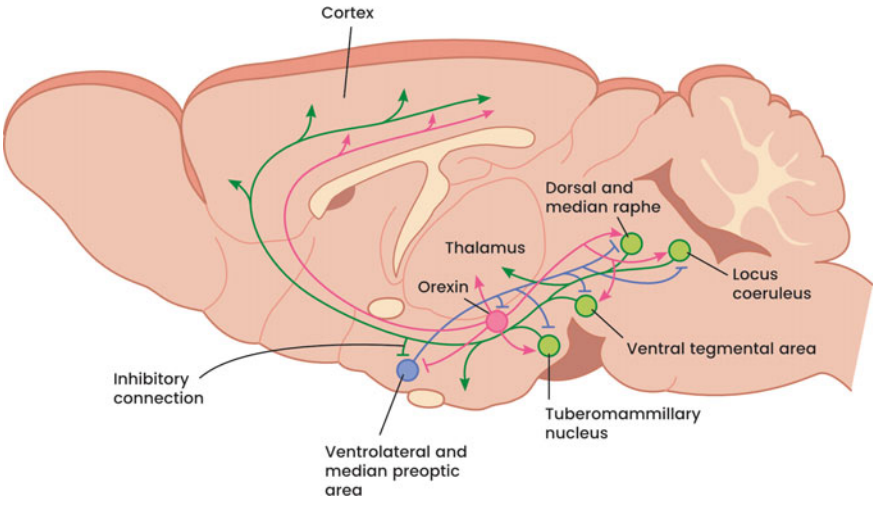

Fig. 9.2 Schematic highlighting select sleep and arousal promoting nuclei in the mouse brain. Green is arousal promoting monoaminergic nuclei, including norepinephrine secreting nuclei in the Locus Coeruleus, serotonergic neurons in the Dorsal Raphae, dopaminergic neurons in the Ventro Tegmental Area, and histaminergic neurons in the TuberoMammalary Nucleus. Pink is arousal promoting orexinergic neurons of the Lateral Hypothalamus. Blue is the sleep-promoting GABA and galanin positive neurons of the ventrolateral preoptic area. Sleep and arousal promoting neurons have mutually inhibitory connections that result in a sleep–wake 'flip-flop' switch that enables rapid transitions between sleep and wake. Figure adapted from Scammell et al. (2017)

deficits in ageing and suggest potential therapeutic avenues for improving sleep in older human subjects.

Another, non-exclusive possibility to explain some of the age related sleep deficits is changes in neurogenesis. Neurogenesis has been reported in the hypothalamus of rodents (Lee and Blackshaw 2012; Haan et al. 2013; Robins et al. 2013). Ageing affects hypothalamic neurogenesis (Zhang et al. 2017; Matsuzaki et al. 2015). Chronic suppression of neurogenesis and gliogenesis by administration of an antimitotic agent disrupted sleep in young animals (Kostin et al. 2019). These animals exhibited reduced NREM and REM sleep amount, sleep fragmentation, and altered sleep homeostasis—all sleep deficits also associated with ageing (Kostin et al. 2019). The molecular processes that underlie the effects of ageing on neurogenesis are not very well understood. However, there are some hints that changes in neuroinflammatory products might explain some of these effects (Rosano et al. 2012; Ekdahl et al. 2003, 2009; Vallières et al. 2002). Further, systemic changes, such as in exercise and calorie restriction, that reduce inflammation, can improve neurogenesis and mitigate sleep deficits (Varrasse et al. 2015; Stangl and Thuret 2009; Blanco-Centurion and Shiromani 2006; Salin-Pascual et al. 2002). These manipulations, however, can affect multiple systems. The field will likely thus benefit from a more targeted means of enhancing neurogenesis, which would be expected to help better establish a causal link between neurogenesis and ageing-related deficits.

9.2.2 Age-Dependent Changes in Sleep Oscillations

In addition to changes in overall sleep amounts, substantial changes are observed in the electrical oscillations of sleep–slow wave activity and sleep spindles.

9.2.2.1 Changes in Slow Waves with Age

One important measure of slow waves is the spectral power in the slow and delta frequency range (0.5–4 Hz) that has been termed slow wave activity (SWA). SWA is most associated with drive to sleep and the phenomenon of homeostatic rebound sleep. Sleep pressure or the drive to sleep is classically modelled as increasing in proportion to time spent awake and dissipating during subsequent sleep (Borbély 1982; Borbely and Tobler 2011). SWA is highest in the early part of the sleep period and reduces over the length of the sleep period as sleep pressure dissipates.

Substantial SWA reductions are seen in baseline sleep of older adults. Further, the process of homeostatic SWA increase and decrease is also altered in older adults. Specifically, homeostatic increases in SWA in response to time awake are blunted (Landolt and Borbély 2001; Münch et al. 2004), and the slope of SWA dissipation across the night is also shallower (Landolt and Borbély 2001; Landolt et al. 1996).

SWA changes are accompanied by changes in slow wave amplitude and density. Both amplitude and density of slow waves are reduced in older adults (Carrier et al.

2011; Dubé et al. 2015). These changes suggest that ageing might diminish synchronised firing—the switching between a depolarised up state and a hyperpolarised down state that might underlie slow wave changes.

9.2.2.2 Neurobiological Basis of Slow Wave Impairments

In mammals, adenosine in the basal forebrain plays an important role in sleep homeostasis (Porkka-Heiskanen et al. 1997). Prolonged wakefulness increases adenosine levels in the basal forebrain. Adenosine levels in the basal forebrain, however, appeared higher in older rodents versus younger siblings (Mackiewicz et al. 2006; Murillo-Rodriguez et al. 2004). This finding is surprising given the age-dependent impairments in homeostasis discussed above. However, there is also age-dependent loss of adenosine A1 receptors and A1 receptor gene expression (Ekonomou et al. 2000; Pagonopoulou and Angelatou 1992; Cheng et al. 2000). This receptor loss may decrease sensitivity to adenosine and thus may form the basis for the observed age-dependent defects in homeostasis. Interestingly, age-dependent impairments in slow wave features correlated with structural atrophy in prefrontal cortex (PFC) areas in older adult humans (Mander et al. 2013; Varga et al. 2016). These structural changes thus might also at least partially explain the observed defects in slow wave features discussed above.

9.2.2.3 Changes in Sleep Spindles with Age

Sleep spindles are oscillatory activity in the 12–15 Hz range, thought to be generated by thalamocortical activity (Huguenard and McCormick 2007; De Gennaro and Ferrara 2003). Power in this 12–15 Hz range is decreased in older versus younger adults (Dijk et al. 1989; Landolt et al. 1996). This power reduction could be explained in part by a reduction in the number of generated spindles (Mander et al. 2014; Martin et al. 2013). Other features of the spindle waveform, e.g. duration and peak amplitude are also decreased in older versus younger adults (Mander et al. 2014; Martin et al. 2013).

9.2.2.4 Neurobiological Basis of Spindle Impairments

What might be the neurobiological basis for age-dependent spindle defects? This is less clear. Reductions in hippocampal grey matter predict spindle defects in older adult humans (Fogel et al. 2017). Although spindles are classically thought to result from thalamocortical activity, they are also linked to burst firing of sharp wave ripples in hippocampus so these structural defects in the hippocampus could plausibly underlie the observed defects in spindles (Fell et al. 2001).

9.2.3 Connection to Invertebrates

Drosophila was also shown to exhibit age-dependent changes in sleep amount, quality, and homeostasis (Shaw et al. 2000; Vienne et al. 2016; Melnattur et al. 2021). The anatomical basis of these age-dependent sleep changes in the fly has not been systematically investigated. The extrinsic fan-shaped lateral (ExFl2) neurons of the dorsal fan shaped body are a particularly interesting candidate in this regard (Donlea et al. 2011). These sleep-promoting neurons secrete GABA and allatostatin (Ni et al. 2019; Donlea et al. 2018). Allatostatin is the invertebrate analogue of mammalian galanin. Further, they have been proposed to form the output arm of the fly homeostat and are thought to be analogous to mammalian VLPO neurons (Liu et al. 2012, 2016; Donlea et al. 2011, 2014, 2018; Pimentel et al. 2016). It would thus be interesting to investigate whether there is age-dependent loss of these ExFl2 neurons in flies as has been reported for VLPO neurons in mammals.

9.3 Consequences of Age-Dependent Sleep Loss

The previous sections clearly demonstrate that ageing leads to sleep deficits. But are these defects of any consequence? To get at this question, we need to examine some functional outcome of sleep (Dissel et al. 2015).

9.3.1 Glymphatic Clearance

One interesting idea about the function of sleep comes from a flurry of papers over the last 10 years that describe a system for fluid flow in the brain that has been termed the glymphatic system (Nedergaard and Goldman 2020). To appreciate the significance of these discoveries, we first have to take a brief detour into anatomy. Brain neuropil lacks lymphatic capillaries that enable fluid flow as is common in other organ systems. Directional flow is instead achieved by means of astrocytic processes that constitute a glia—lymphatic or 'glymphatic' conduit for cerebrospinal fluid (CSF) flow (Iliff et al. 2012; Xie et al. 2013). CSF flows into periarterial spaces in the brain driven by arterial pulsations that result from pulse waves along arteries driven by heart beats (Mestre et al. 2018; Iliff et al. 2013). Perivascular spaces are channels that run along the vasculature enclosed by endfeet of astrocytes (Wardlaw et al. 2020). Astrocytic endfeet expresses the water channel Aquaporin 4 (AQP4) (Hasegawa et al. 1994; Jung et al. 1994; Nielsen et al. 1997; Rash et al. 1998). Glymphatic flow consists of CSF entering periarterial space, mixing with interstitial fluid (ISF), carrying solutes and exiting the brain via perivenous spaces, cranial nerves, etc. Importantly, for the purposes of this review, glymphatic flow was dramatically higher (up to a fold higher) in sleep versus wake (Xie et al. 2013). This increase in flow also correlated

with increased AQP4 at astrocytic endfeet. Further, the flow was AQP4 dependent as deletion of AQP4 dramatically reduced flow (Iliff et al. 2012).

In parallel, recent studies reported the discovery of lymphatic vessels in the meningeal dura and clearance of injected tracers via lymphatic vessels (Aspelund et al. 2015; Louveau et al. 2015). Glymphatic clearance along perivenous spaces could drain into sinus lymphatics as veins merge (Fig. 9.3a) (Wardlaw et al. 2020; Ma et al. 2017), suggesting an anatomical connection between glymphatic and lymphatic systems.

9.3.1.1 Impairment of Glymphatic Flow with Age

Glymphatic flow is reduced with sleep deprivation (Plog et al. 2015; Eide et al. 2021) and with ageing (Da Mesquita et al. 2018; Kress et al. 2014; Zhou et al. 2020). Ageing was also associated with mislocalisation of AQP4 away from endfeet towards soma and perisynaptic processes (Kress et al. 2014). Tortuosity of the vasculature was also increased in aged animals, providing another mechanism by which CSF flow could be reduced with age (Fig. 9.3e). Further, brain lymphatic vessels also degenerate with age (Ma et al. 2017; Ahn et al. 2019), thereby possibly providing another mechanism for reduction of flow. These age-dependent reductions in flow could have important consequences as glymphatic clearance has been implicated in clearance of toxic metabolites such Amyloidβ (Aβ)—the toxic fragment associated with Alzheimer's disease (Iliff et al. 2012; Xie et al. 2013). Decreased glymphatic flow increased Aβ (Iliff et al. 2012; Xie et al. 2013), conversely increased Aβ decreased flow (Da Mesquita et al. 2018; Peng et al. 2016), suggesting a vicious cycle. Indeed, polymorphisms in AQP4 are also linked to Alzheimer's disease (Zeppenfeld et al. 2017; Burfeind et al. 2017).

9.3.1.2 Connection to Invertebrates

A sleep stage associated with brain clearance was recently reported in *Drosophila* (van Alphen et al. 2021). This sleep stage was defined by characteristic proboscis extension and retraction movements and elevated arousal thresholds. The proboscis extensions appear to causally drive haemolymph flow facilitating clearance and supported recovery from brain injury, suggesting parallels with mammalian glymphatic clearance (van Alphen et al. 2021).

9.3.2 Learning and Memory

Brain clearance is clearly one important function of sleep. Another very influential theory of sleep function is that sleep is critical for learning and memory (Diekelmann and Born 2010; Walker and Stickgold 2004).

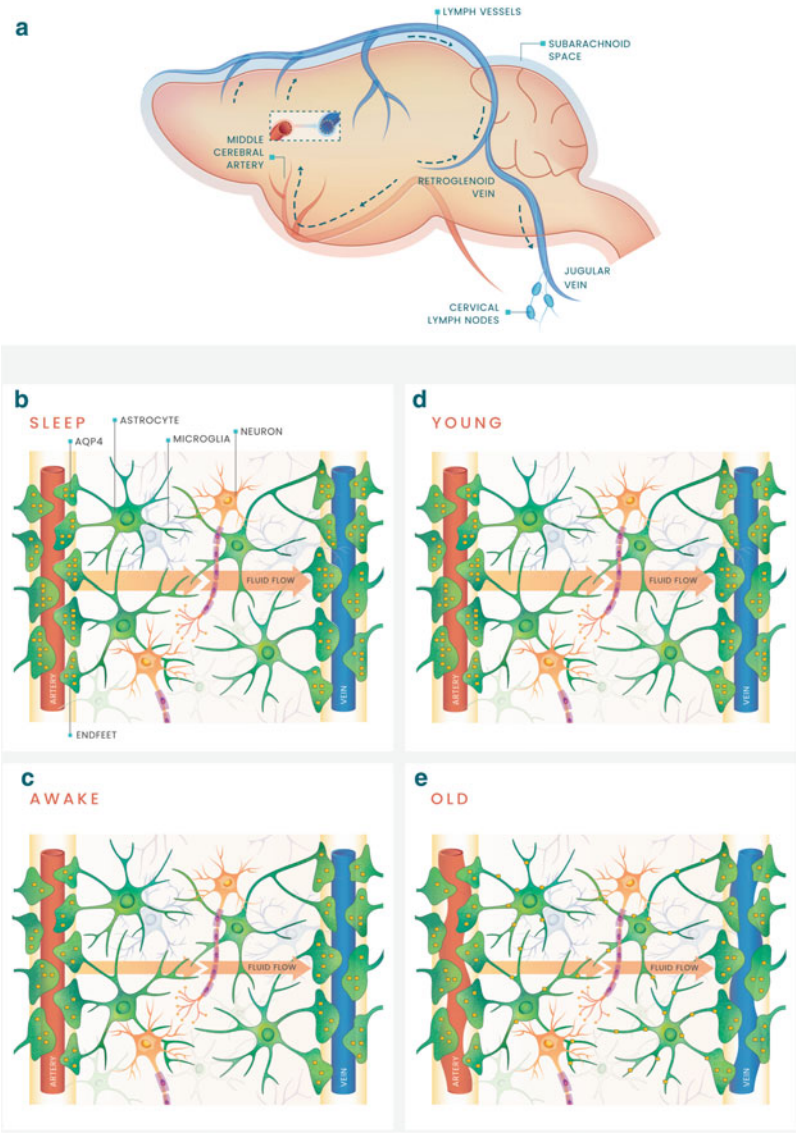

Fig. 9.3 **a** Anatomy of glymphatic and meningeal lymphatic systems. Arrows depict direction of CSF flow. Arteries are in red, veins in dark blue, and lymph vessels in light blue. Figure adapted from (Iliff et al. 2015). **b–e** Insets highlighting the glymphatic system that facilitates fluid flow in the neuropil. Astrocytic endfeet tile the vasculature, astrocytic processes create a conduit for CSF + ISF flow across the neuropil. Increased AQP4 at astrocytic endfeet during sleep (**b**) versus wake (**c**) facilitates increased fluid flow. AQP4 is mislocalised away from endfeet towards the soma in old (**e**) versus young (**d**) animals. AQP4 mislocalisation combined with arterial tortuosity decreases fluid flow in old versus young animals. **b–e** Artery—red, Veins—Blue, astrocytes—green, AQP4—gold. Figure adapted from Nedergaard and Goldman (2020)

9.3.2.1 Learning

In humans, although sleep supports many kinds of memories, hippocampus-dependent declarative memories appear to particularly benefit from sleep (Diekelmann and Born 2010). Thus, sleep loss in young adults was shown to impair learning of new episodic memories and verbal memories (Yoo et al. 2007; Drummond et al. 2000). Ageing also similarly disrupted encoding of hippocampus-dependent declarative memories and spatial memories (Jennings and Jacoby 1997; Toth and Parks 2006; Newman and Kaszniak 2000).

9.3.2.2 Age-Dependent Learning Defects

In older adults, the extent of overnight sleep impairments correlated with the extent of next day encoding impairments (Lo et al. 2016; Cavuoto et al. 2016). Consistent with these findings, in rodents, ageing disrupted hippocampus-dependent spatial learning but not hippocampus independent non-spatial learning (Rapp et al. 1987; Barnes 1979; Bach et al. 1999).

9.3.2.3 Memory Consolidation

Sleep is clearly important for learning new information, but the idea that sleep is critical for memory and plasticity perhaps only really took flight after the discovery of hippocampal place cell replay in rodents by Wilson, McNaughton, and colleagues (Wilson and McNaughton 1993, 1994). In these classic experiments, rats were trained to run along a linear track. The trajectory of the rat along the track was shown to be represented as a sequence of activation of place cells in the rat's hippocampus (Wilson and McNaughton 1993). This sequence was shown to be replayed during subsequent sleep in a kind of 'fast-forward' replay (Wilson and McNaughton 1994; Lee and Wilson 2002; Nadasdy et al. 1999). Hippocampal replay was accompanied by sequence reactivations in the cortex, and this dialogue between hippocampus and cortex consolidated the experience into a memory (Siapas and Wilson 1998; Sirota et al. 2003; Ji and Wilson 2007; Rothschild et al. 2017). Further, disrupting sleep-dependent replay impaired memory, thus establishing causality (Girardeau et al. 2009; Ego-Stengel and Wilson 2010).

9.3.2.4 Age-Dependent Memory Consolidation Defects

Ageing impaired sleep-dependent sequence reactivation in rodents and resulted in lower memory scores (Gerrard et al. 2008). Ageing was also shown to impair long-term potentiation and Ca^{2+} signalling in hippocampal neurons (Barnes 1988; de Souza et al. 2012). Further, in older adult humans, impairment in SWA was associated

with a continued reliance on hippocampal storage rather than cortical representations (Mander et al. 2013) indicating that ageing might disrupt replay in humans as well.

9.3.2.5 Age-Dependent Declines in Hippocampal Neurogenesis

In small mammal systems, adult neurogenesis has been reported in the dentate gyrus (DG) of the hippocampus (Altman and Das 1965, 1967; Caviness 1973, Guéneau et al. 1982). Neurogenesis in the DG has been associated with context encoding and memory, including REM sleep-dependent memory consolidation (Shors et al. 2001; Danielson et al. 2016; Kumar et al. 2020). Neurogenesis in rodents is impaired with sleep deprivation and fragmentation (Guzman-Marin et al. 2007; 2003). Ageing also impairs rate of neurogenesis in the DG at least in rodents (Seki and Arai 1995; Kuhn et al. 1996). Impairments in neurogenesis might thus explain some of the age-related cognitive deficits. That said, clearly not all hippocampal-dependent memories require neurogenesis (Shors et al. 2002). Further, the extent of neurogenesis in the adult human hippocampus remains somewhat unclear (Sorrells et al. 2018; Boldrini et al. 2018). Additional experiments might help clarify the roles of neurogenesis in age-related impairments in cognition and sleep-dependent processes.

9.3.2.6 Enhancing Sleep to Restore Learning

Ageing clearly impairs sleep, learning, and sleep-dependent memories. This suggests that enhancing sleep could potentially be a viable strategy to restore functioning to aged brains. Indeed enhancing sleep of older adults was shown to improve memory (Papalambros et al. 2017; Westerberg et al. 2015).

9.3.2.7 Connection to Invertebrates

Sleep is critical for learning and memory in *Drosophila* as well (Dissel et al. 2015). Flies also exhibit age-dependent declines in learning, including spatial learning (Tamura et al. 2003; Rieche et al. 2018; Melnattur et al. 2021). Interestingly, enhancing sleep of aged flies was sufficient to ameliorate age-dependent spatial learning defects (Melnattur et al. 2021), indicating that in flies as in mammals, sleep can restore functioning to impaired brains. Enhancing sleep might thus be widely applicable as a viable therapeutic strategy in a range of different contexts.

9.4 Conclusions

Age-dependent changes in sleep architecture and physiology are fairly well characterised. The precise neurobiological mechanisms underlying these changes in sleep

and sleep outcomes are still being worked out. The emergence of powerful invertebrate models of sleep such as the fly *Drosophila* holds promise as vehicles to solve some of these problems.

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Compliance with Ethical Standards: This article does not contain any studies with human participants performed by any of the authors.

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