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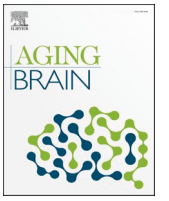

Invited Opinion

Sleep-dependent memory consolidation in young and aged brains

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ABSTRACT

Young children and aged individuals are more prone to memory loss than young adults. One probable reason is insufficient sleep-dependent memory consolidation. Sleep timing and sleep-stage duration differ between children and aged individuals compared to adults. Frequent daytime napping and fragmented sleep architecture are common in children and older individuals. Moreover, sleep-dependent oscillations that play crucial roles in long-term memory storage differ among age groups. Notably, the frontal cortex, which is important for long-term memory storage undergoes major structural changes in children and aged subjects. The similarities in sleep dynamics between children and aged subjects suggest that a deficit in sleep-dependent consolidation contributes to memory loss in both age groups.

Introduction

Research on the role of sleep in memory consolidation has received increasing attention in recent years (for a comprehensive overview, see [1]). Many studies emphasize the importance of sleep for memory consolidation in human and rodent brains. However, at the extremes of the aging spectrum, sleep and memory systems are in a state of flux – developing or declining, in young and aged individuals, respectively; these changes likely impact the process of sleep-dependent memory consolidation. Given that memory loss is prevalent in young children and older individuals, more research on sleep-dependent memory consolidation in those age groups into the scope of forgetting research is needed. Information gained from such research can provide insights into related disorders such as intellectual and developmental disabilities [2] and dementias such as Alzheimer's disease [3]. This review compares sleeping habits, sleep architecture, and sleep-dependent brain oscillations in young children and aged individuals and discusses their relevance for understanding age-related memory deficits.

Rapid memory loss in the young brain could occur because key structures for memory storage are insufficiently mature at the time of memory storage to process new memories ("immature brain" theories). Alternatively, it is also possible that the process of ongoing maturation interferes with memory storage ("ongoing brain maturation" theories) [4]. Some earlier theories falling into the "immature brain" category ascribe failure in long-term memory storage to the fact that the infant cortex is not fully "online". Support for this theory comes from findings that, although much of the human brain is fully formed at birth, the cortex undergoes significant postnatal development ([5] for review, [6]). Interestingly, the cortex also shows the most substantial old age-related structural change [5]. Accordingly, we here also review age-dependent structural changes in the cortex in the context of memory loss.

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Sleep-dependent memory consolidation

Sleep in mammals consists of two main stages: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM and REM sleep may have different roles in the memory process. Memory stabilization occurs during NREM sleep [7], whereas memory integration into the existing knowledge base occurs during REM sleep [8]. However, there is also a hypothesis that the NREM and REM sleep stages consolidate different types of memories [9]. It has been suggested that declarative memory benefits from NREM sleep, whereas consolidation of nondeclarative or procedural memories is supported by REM sleep. Contrasting with this notion, emotional declarative memory appears to be supported by REM sleep [10]. Overall, findings on the specific role of REM and NREM sleep in consolidating different memory types are inconsistent in the literature.

The long-term consolidation of memory depends on the interaction between the hippocampus and cortex, and sleep-dependent oscillations act as vehicles of memory transfer and stabilization [11,12]. Many excellent reviews have summarized the sleep-dependent memory consolidation process [13,14]. Below we will focus specifically on current advances in understanding the prominent hippocampal and cortical oscillations that support sleep-dependent memory consolidation.

Hippocampal activity during sleep-dependent memory consolidation

The hippocampus exhibits prominent oscillations, including sharp wave ripples (SWR) in NREM sleep and theta wave during REM sleep. Sharp waves are large-amplitude negative polarity deflections (40–100 ms) in CA1 of the hippocampus that are most often associated with short-lived fast (110–200 Hz) oscillatory patterns in CA1 known as ripples [15]. Some direct evidence for the role of ripples in memory consolidation comes from studies investigating the effects of their direct manipulation. Two animal studies indicated that depletion of ripple activities by electrical stimulation impair memory in rodents [16,17]. Furthermore, in social memory tasks, disruption or enhancement of ripples by optogenetic stimulation suppress and prolong social memory, respectively [18]. These findings indicate the necessity of SWR for memory consolidation. It is generally considered that the remarkable features of SWR contribute to the neural substrate of memory consolidation. During SWR, hippocampal neurons that are active during recent learning behavior are reactivated (“replay”), allowing a gradual strengthening of memory traces [19]. Also, SWR occurrence down-regulates the synaptic strength of previously potentiated synaptic circuits [20], which, in turn, may refine memory by reducing memory-irrelevant neuronal activity. Thus, SWRs represent important time epochs for offline hippocampal activity, and are required for plasticity and memory consolidation in rodent brains. Clear evidence for the role of SWR in memory consolidation in the human hippocampus is still needed.

During REM sleep, hippocampal activity is concentrated in the theta rhythm (6–10 Hz). Theta wave arises from the interaction between the medial septum (MS) – the diagonal band of Broca (DbB) and intra-hippocampal neuronal and circuit oscillations [21,22]. Cholinergic, gamma-aminobutyric acid (GABA), and glutamatergic MS –DbB neurons project to the hippocampus [23,24], and optogenetic manipulation of MS-DbB cholinergic or GABAergic neurons modulates hippocampal theta rhythms [25,26].

The first evidence for the role of theta rhythms in memory consolidation during REM sleep came from a study in which medial septal GABAergic neurons were optogenetically inactivated to specifically silence theta oscillations during REM sleep. Such silencing after learning impaired contextual memory consolidation in mice. Silencing theta oscillations for a similar duration during NREM or wakefulness did not affect memory. These results thus demonstrated that theta oscillation during REM sleep is required for normal memory consolidation [26]. While previous studies indicated that REM sleep theta oscillations associate with reorganization of neural excitability [27], the specific types of hippocampal cells that enable memory consolidation during the theta rhythm in REM sleep were not definable. It is also worth noting that some earlier studies associated “neuronal replay” of awake hippocampal activity during REM sleep with memory consolidation [28–30]. In this context, one of our own studies revealed that adult-born hippocampal neurons (ABNs) are activated during learning and reactivated in subsequent REM sleep. Optogenetic silencing of ABN activity during REM sleep impaired contextual memory consolidation. Silencing of ABN during NREM sleep or wakefulness did not affect memory. These findings provide a causal link between ABN activity during REM sleep and memory consolidation [30]. Nevertheless, the relationship between theta oscillation-dependent ABN activity and memory consolidation requires further study and understanding.

Theta oscillations are less prevalent during human REM sleep, which is characterized by desynchronized EEG activity, but the specific effects of theta stimulation on memory consolidation during REM sleep are yet to be studied. Recent studies suggest theta transcranial alternating current stimulation during the post-learning wake period enhances early consolidation of episodic memory [31]. Also, a previous study reported that event-related changes in spectral theta power during memory formation in the evening before sleep lead to overnight improvement in subsequent cued recall of word pairs in humans [32].

Cortical activity during sleep-dependent memory consolidation

The cortex is dominated by low-frequency synchronous delta (0.1–4 Hz) and slow waves (<1Hz) during NREM sleep. Past work has highlighted the importance of slow oscillations and delta waves in memory consolidation in both rodents and humans. In the rat, the EEG power of slow oscillation was found to be positively correlated with performance on an episodic-like memory task [33]. Miyamoto et al. showed that memory consolidation depends on the phase synchrony of slow waves. Their investigations indicated that consolidation of perceptual memory requires synchronized coactivation of cortical areas, enabled by slow oscillation in NREM sleep. Using optogenetics, they found that synchronous co-activation of cortical areas with slow oscillation prolongs memory retention. Alternatively, anti-synchronous activation resulted in a decrease in performance in memory tasks [34]. Triggering delta waves can also boost memory consolidation [35,36]. Todorova et al., showed the involvement of delta spike in memory consolidation [36]. Delta

spikes are isolated spikes found during the down-state of oscillation. Since the down-state of delta waves results in periods of complete cortical silence, occasional spikes have been routinely escaped detection [37]. Todorova et al., found that in natural sleep or stimulation-induced delta waves, delta spikes always coincide with the timing of hippocampal ripples which are required for memory consolidation, as discussed earlier. Consistent with this, a slight delay in the induction of the delta wave, to isolate the delta spike, failed to allow memory consolidation.

In humans, the frequency of slow oscillations peak between 0.7 and 0.8 Hz [38]. Evidence for a causal role of slow oscillations in memory consolidation comes from a study in which inducing slow oscillation by transcranial application of 0.75 Hz oscillations during early nocturnal NREM sleep enhanced the retention of hippocampus-dependent declarative memory in healthy humans [39]. Similar findings were subsequently reported by other authors [40–42]. In addition to enhanced overnight memory, such stimulation also increased power in the delta range, a phenomenon often referred to as slow wave activity (SWA). Several studies have suggested a positive correlation between EEG power in SWA and overnight improvement in memory [43,44].

Spindle (spindle-shaped 0.3–2 s burst of approximately 11–16 Hz), another thalamocortical oscillation during NREM sleep, is also thought to be involved in sleep-dependent memory consolidation [45,46]. Several studies have shown a positive correlation between spindle characteristics and memory improvement following the night of sleep [47]. To determine the causal role of spindles in declarative and procedural memory consolidation, researchers have experimentally modulated this oscillation via transcranial direct current stimulation (tDCS). Interestingly, that research revealed that tDCS stimulation enhanced motor memory consolidation and was correlated with stimulation-induced changes in spindle activity [48]. Therefore, slow oscillation and spindles appear to play a key role in memory consolidation [49]. Overall, the current trend of thought postulates that functional coupling of slow oscillation, spindles, and SWRs during NREM sleep [50] facilitates local synaptic potentiation and interregional communication, both of which are required for memory consolidation [50,51]. In this context, a recent study showed that enhancing hippocampal-prefrontal cortex synchrony during sleep improves memory consolidation in humans [52].

Memory consolidation during sleep in infants and young children

Studying sleep-dependent memory consolidation in infants is challenging. One major problem researchers face is to reliably measure declarative memory in preverbal children. Traditional tests of declarative memory rely on verbal reports and are better suited for older children and adults. A recent study explored whether sleep in 14- to 17-month-old infants supports the consolidation of object–word pairings as specific episodic-like memories [53]. The infants were exposed to a set of object-word pairs, for which lexical-semantic memories are expected to be present at a given age. The infants either napped or were awake during the post encoding retention period. Memory was subsequently evaluated by exposing infants to familiar objects before napping as well as to novel objects. Memory was assessed by analyzing event-related potentials (ERPs) that were time-locked to words [54]. Infants who were awake after encoding did not retain detailed memories of the individual pairings of objects and words. In contrast, infants who napped after encoding retained the information. Another study indicated that timely sleep is essential for declarative memory consolidation in infants [55]. Researchers examined the declarative memory of 6- and 12-month-old infants for novel action (imitation paradigm) after 4-hour and 24-hour delays. The infants in the nap condition took more than 30 min to nap within 4 h after learning, whereas the infants in the no-nap condition were not allowed to nap. A comparison with age-matched control groups revealed that after both delays, only infants who napped after learning remembered the target action during the test. Additionally, after a 24-hour delay, the memory performance of infants in the nap condition was significantly higher than that of infants in the no-nap condition. While these findings suggest that sleep-dependent memory consolidation, at least for short periods, starts at early ages, children nevertheless show deficits in memory retrieval at remote times due to infantile (or childhood) amnesia, the phenomenon where adults have few, if any, memories of events during the early years of their lives, typically before 7 years of age [56,57], although the average age of first memories may hover between 3 and 4 years of age. Human adults cannot remember episodic experiences from their first three years of life and tend to have sparse recollections of episodic experiences that occurred before the age of 10. It is thought that it is not the long time interval that is responsible for this, but rather due to the limited ability of infants and toddlers to maintain long-term memories [57].

How can one explain the labile nature of memories acquired in young brains? Both human and rodent studies suggest that infantile memories are not eliminated; rather, they are simply inaccessible by natural reminders [58–60]. This raises the possibility that infantile memories are perhaps not successfully consolidated and stored. Several characteristics of children's sleep that differ from those of adults may be associated with deficits in long-term memory consolidation and storage.

Sleep characteristics of infants and young children

Daytime napping

Naps are more common in infancy and continue into childhood. A study that recorded the sleep logs of Japanese children revealed that 100 % of the children who habitually took a nap were under 1 year old, and 96.8 % and 81.8 % were 1- and 2-year-old toddlers, respectively. There was a significant relationship between nap duration and bedtime on the corresponding night in 2-year-old toddlers. The "two hours or more" nap group showed a significantly later bedtime in 2-year-old children [61]. The number of daytime naps decreases with age. Infants aged 0–5 months old require a maximum of 5 naps/day, 3–4 daily naps at 6–11 months, and 2 naps/day at 1–2 years [62]. Increased sleep pressure is a major factor for increased daytime napping in young individuals. In a study of napping in 2-, 3-, and 5-year-old children who had naps in the morning, afternoon, and evening, varied sleep pressure was observed. Increased sleep pressure results in longer naps, accompanied by increased slow wave activity, in younger children; this finding indicates that

young children need more sleep depth during daytime naps [63]. Daytime napping is also influenced by genes (although minimally) and the environment [64,65]. There is evidence that changes in the environment alter the onset of melatonin and the duration of sleep [66]. One study proposed a novel hypothesis regarding napping, learning, and memory in the young brain. According to this hypothesis, early childhood is a time of competing demands for learning, which loads the brain—there is an overproduction of synapses that escalate energy demand. Nap provides a solution to meet energy challenges and may unload synapses across the brain [67].

Naps in children are generally considered beneficial for memory [67]. However, one finding also suggests that more frequent naps are associated with lower cognitive development in children [68]. One interpretation of this finding is that it is not the increased daytime napping itself that causes reduced memory and cognition, but rather the reduced sleep at night, which is a key period of memory consolidation. In fact, children who nap more also show reduced nighttime sleep [61].

Fragmented nighttime sleep

Infants do not have long, sustained sleep periods (sleep without awakening) during the night. One study reported that, at six months (n = 388) of age, 37.6 % of the infants sleep for less than six consecutive hours at night, whereas 43 % sleep for eight consecutive hours. At 12 months (n = 369), 72.45 % sleep for six consecutive hours at night, and 56.6 % sleep over eight consecutive hours [69]. Frequent nocturnal awakening is one of the main reasons for reduced nighttime sleep. In a longitudinal study of 6-month-old infants (n = 11500), approximately 13 % had 1–2 awakenings per night, and 10 % had 3 or more awakenings [70]. In a similar study, the prevalence of nighttime awakening was higher, with 46 % of infants waking 1–2 times per night and 21 % waking 3 or more times per night [71]. These awakenings serve primarily to meet infants' nutritional needs. In addition, nighttime awakening is related to several extrinsic factors, such as separation distress, frequent daytime crying, co-sleeping, and breastfeeding [72].

Neonatal sleep is classified as active sleep (AS), quiet sleep (QS), and indeterminate sleep (IS). Active sleep is also called paradoxical sleep; it is characterized by rapid eye movements, irregular breathing, body and limb movements, low-voltage EEG, and high variability in heart rate [73]. QS is characterized by reduced eye movements, regular breathing, decreased body movements, slow wave EEG activity, and low variability in heart rate. After two months of age, AS becomes REM sleep, and QS becomes NREM sleep. When elements of both AS and QS are present, it is described as indeterminate sleep. AS occupies a significant percentage of the total sleep time from birth. QS occurs less than half of the time and IS occupies 5–13 % of the time. As sleep matures during the first year of life, the percentage of total sleep time (TST) spent in AS and IS decreases, whereas the percentage of QS increases to 35–50 % [74]. At about the age of three, the percentage of REM sleep over TST further declines and stabilizes around 20 % for REM and 80 % for NREM. The complex neurophysiologic process that regulates sleep and waking patterns in infants changes remarkably over the first years of childhood [75].

It can be predicted that the memory consolidation process in children is affected as their sleep undergoes a transition phase during which the balance between REM and NREM sleep is reset and when sleep fragmentation evolves.

Instability in sleep-dependent oscillations

It is believed that the instable nature of sleep-dependent oscillations can affect memory and cognitive performance in children [76]. Below we discuss the unstable EEG features of various frequency bands during first year of human life.

All night polysomnographic recordings at 2 weeks and at 2, 4, 6, and 9 months after birth (analysis of 7 infants) revealed progressive changes in low delta (0.75–1.75 Hz), theta (6.5–9 Hz), and sigma (11.5–13.25 Hz) activity [77]. Initially, low delta and theta activity show similar variation of activity over time at the ages of 2 weeks and 2 months, with dissociation becoming apparent at 4 months of age. At 6 and 9 months, theta activity tends to decrease across consecutive sleep episodes. In contrast, low delta activity shows an alternating pattern, with a high value every second in the NREM episode.

Sleep spindles are not found at 2 weeks of age, and, accordingly, sigma activity is very low. From month 2 onward, when sleep spindles (waxing and waning oscillations of 11.0–16.0 Hz) can be visually detected during NREM, sigma power exhibits high values in NREM episodes. Additionally, the sigma peak frequency changes as infants develop. The sigma peak frequency increases from 12.6 Hz at 2 months to 13.1 Hz at 9 months [77]. Fattinger et al. examined slow wave slopes (i.e., negative half wave) in the EEG dataset published by Jenni and coworkers [77] and found that age-dependent changes in the slope of slow waves decrease overnight in infants starting at the age of 2 months [78].

The EEG feature continues to change in the later years of childhood. At 2 years of life, REM theta increases, and delta spectral power decreases. Also, a peak in the theta bandwidth emerges at 5 Hz at this time [79]. In a longitudinal study in which EEG data was recorded in children aged 2, 3, and 5 years, Olbrich et al., observed an age-related decrease in spectral power and event ratio of the delta/theta range and increase in the sigma frequency range; further, these authors found a waning of theta bursts and ultra-fast spindles and the emergence of regular spindles during preschool ages [80]. These changes in oscillation in early childhood, particularly in those of delta and spindle may reflect maturation of the thalamocortical system [81].

Cortical structural changes in the brains of infants and young children

The human brain undergoes rapid expansion in early childhood [5]. The volume of gray matter (brain cells) peaks at approximately six years of age and then decreases slowly. In contrast, the volume of white matter (brain connections) increases rapidly throughout early childhood and peaks in adulthood. Similarly, the cortex continues to show development through late childhood and adolescence [6]. The timing and rates of change differ among cortical regions; for example, sensory regions develop early and quickly, whereas

associative regions develop later and more slowly. Below we describe changes in cortical structure (thickness, surface area), cortical myelination, and circuit refinement during childhood which can potentially interfere with sleep-dependent memory consolidation.

Total cortical thickness increases from birth to early childhood after which it starts to thin [82–85]. The timing and rate of cortical thinning varies across the cortical sheet. Whereas the sensory motor cortex starts to thin early (middle childhood) [86], with minimal thinning in adolescence [85], thinning of the prefrontal cortex and other association cortices (cingulate, inferior parietal, precuneal, and middle temporal) occurs from early childhood and continues until early adulthood (early twenties) [85,87,88].

Previous studies suggest that cortical surface area increases rapidly after birth [89] and peaks at approximately 9–12 years of age [86]. Additionally, cortical myelination [90,91] and circuit refinement continue during childhood when, excitatory pyramidal neurons of the prefrontal cortex exhibit a larger increase in basal dendritic tree size, spine density, and synapse number [92]. In this context, Herring and coworkers [93] examined human prefrontal cortex gene expression throughout childhood and suggested that pyramidal neuron maturation occurs in a stepwise manner and in three phases: infancy, childhood, and adolescence.

Sleep-dependent memory consolidation in middle-aged and elderly individuals

Sleep-dependent memory consolidation diminishes with age. A *meta*-analysis suggested that impairments in sleep-dependent consolidation may be responsible for deficits in declarative memory (procedural memory remains intact) in older individuals [94]. Subjects aged between 25 and 55 do not show detectable differences in learning a declarative memory (word pair association) task, indicating that the memory encoding process is undisturbed in this age range. However, as compared to ~ 55-year olds, ~25-year olds showed significantly higher amounts of slow wave sleep (SWS); recall of word pairs was also greater in the younger group. This result indicates a decline in sleep-associated declarative memory consolidation that starts from the fifth decade of life, coincident with decreased SWS [95]. While there are excellent reviews that explain how aging affects sleep-dependent memory consolidation [96,97], we here focus only on the similarities in sleep characteristics of older subjects and young children, in an attempt to understand the importance of sleep-dependent memory consolidation.

Sleep characteristics of middle-aged and elderly individuals

Daytime napping

The prevalence of napping is high among older individuals, although this varies according to local climatic and cultural factors. Afternoon napping is less common in countries with cooler climates and more common in countries in Asia, Africa, and Latin America where afternoon temperatures are high. According to a Japanese study, 14.4 % of middle-aged individuals (40–59 years old) and 25.8 % of older individuals (60 years and above) take daytime naps regularly [98]. In China, daytime napping is more common in middle-aged (50 %) and older (55 %) individuals than in other age groups [99,100]. Similarly, a study on a Korean-based population (sample 5427) reported that 35.7–42.3 % of middle- to older-aged participants (40–69 years) took a daytime nap [101]. Furthermore, a American cohort comprised of 97,890 women and 110,647 men (age 50–71 years) revealed that 40.3 to 52.6 % of the participants regularly napped during the day [102]. Naps among older adults are dominated by a light NREM stage, a short bout of SWS and, less often, REM sleep [103]. Older adults are prone to take naps during the day to compensate for their nighttime sleep deficits [104]. Some authors also suggest that afternoon napping can improve memory in the elderly. Importantly, however, a link between frequent day time napping and progression of Alzheimer's dementia has also been proposed [105,106].

Fragmented nighttime sleep

Shorter sleep duration and sleep fragmentation are common in older adults [107]. The impact of age on various measures of sleep supports this view, exemplified by the results of a study of 211 women aged 22–71 years who underwent ambulatory polysomnography examined the impact of age on various sleep measures [108]. Sleep staging was conducted according to the classification criteria of the American Academy of Sleep Medicine (AASM). In this study, total sleep time (TST), time spent in different sleep stages (N1, N2, N3, and REM sleep), sleep fragmentation using wake within total sleep period (WTSP), time in consolidated wake after sleep onset, the arousal index (number of arousals per hour TST), the awakening index (number of awakenings per hour TST), and stage shift index (number of stage shifts per hour TST) were measured. It was found that older age was significantly associated with decreased TST, time spent in N3 and REM sleep, whereas N1 sleep increased with age. Age was also loosely associated with a decrease in N2 sleep. Older age was significantly associated with increased wake after sleep onset, longer time spent in consolidated wake after sleep onset and increased number of stage shifts per hour. Additionally, the number of awakenings per hour increased, albeit non-significantly, and age did not significantly associate with the number of arousals per hour [108].

In another study in men, Moares et al., reported an age-related decrease in TST and an increase in the occurrence of wake-after-sleep onset as well as arousal. The authors also observed an increase in sleep latency and the percentage of N1 and N2 with age, and an age-dependent reduction in N3 [109]. A reduction in N3 likely impacts on memory consolidation, as reported by previous research [95,110].

Instability in sleep-dependent oscillations

Aging is associated with a significant alteration in brain oscillatory activity [111–113] that may be associated with cognitive

decline. Here, we mainly focus on sleep-dependent oscillations that change as a function of age. For example, there is a decrease in the duration of sleep spindles as individual age. The latter was demonstrated in a study of 114 healthy volunteers aged 20–73 years; specifically, the authors reported that spindle density, amplitude, and duration was higher in younger, compared to middle-aged and elderly subjects [114]. Further, two other studies observed age-dependent decreases in absolute slow wave power, NREM theta [115] as well as progressive reduced NREM sigma spectral power during aging [108]. And, yet other work suggests that aging is accompanied by a decrease in lower-frequency activities and an increase in higher-frequency activities during REM sleep. Here, it is pertinent to add that the sleep EEG of older subjects is consistently characterized by a reduction in slow waves and slow wave activity [116].

A recent longitudinal study conducted by Gao and Scullin [117] in 2202 participants aged 39–86 years used polysomnography to monitor EEG and other sleep parameters on two occasions separated by 4–7 years; the recording was made in the participants' home environment. Analysis of the data involved spectral power density calculations for each 0.5 Hz bin for 0.5 Hz–25 Hz and for slow

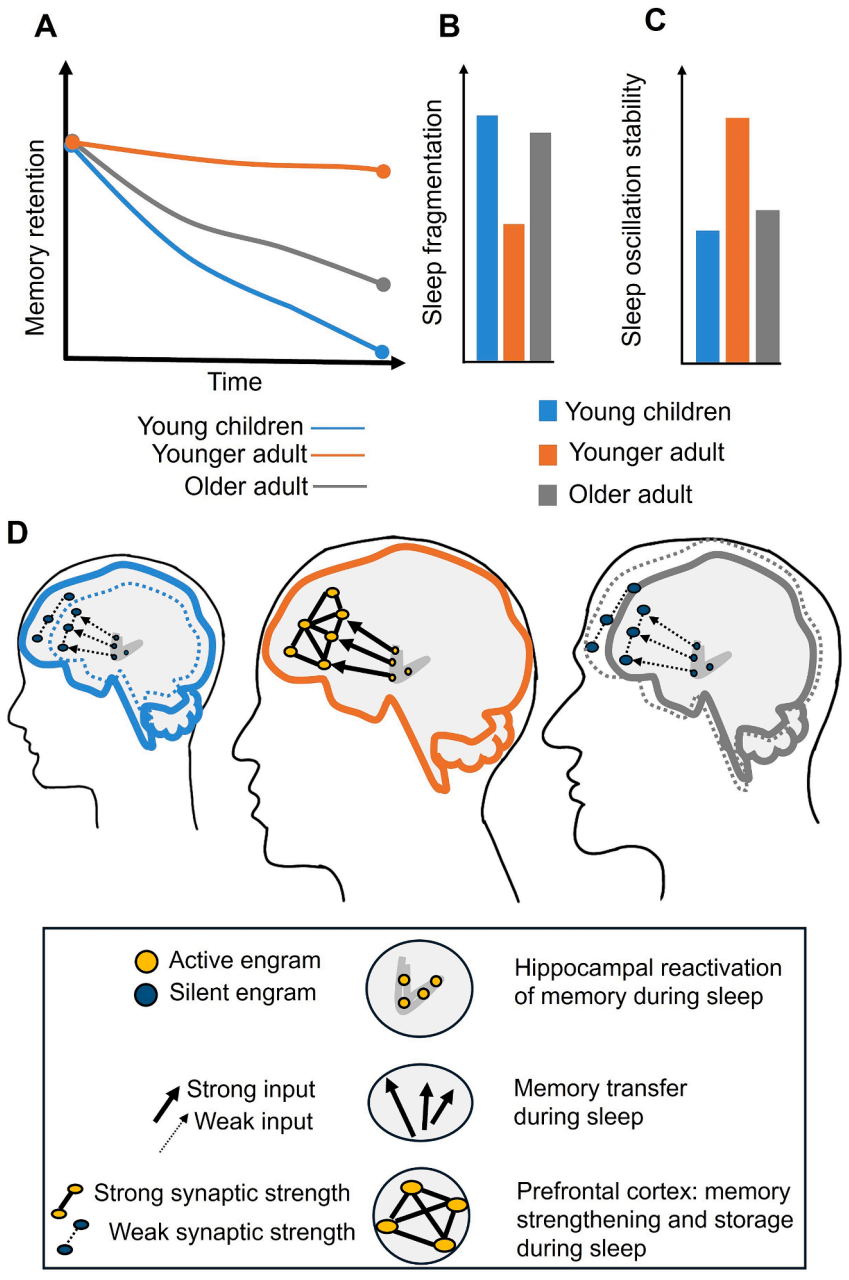

Fig. 1. Low memory retention in young and aged adult brains, compared with younger adult brains (a). Young and older adult brains show greater sleep fragmentation (b), and decreased stability of sleep-dependent oscillations (c) than young adult brains. Together, these features may affect hippocampal memory reactivation and transfer to long-term storage in the cortex (d).

oscillation (0.5–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), and beta-1 (15–20 Hz) waves, separated by REM and NREM sleep stages. The investigators found that, on average, NREM power density significantly decreased in the delta and sigma bands between the first and second recordings a result that aligns with other cross-sectional studies that demonstrated age-related declines in slow wave activity and spindles [108]. Extending earlier studies, Gao and Scullin [117] however found that NREM theta power density significantly increases over time; importantly, they also observed that, whereas NREM alpha power density increases longitudinally in middle-aged individuals, this parameter gradually decreases in older individuals. The latter finding suggests that a nonlinear change was also reported in a cross-sectional study. In the same study by Gao and Scullin [117], a different longitudinal pattern was found for REM sleep as the REM power density for all frequency bands increased. In contrast, a cross-sectional study suggested an age-related decrease in lower frequency activity during REM [118].

Cortical structural changes in the brains of middle-aged and elderly individuals

The cortex undergoes morphological changes as it ages. These included alterations in volume, area and thickness. Age-related cortical thinning is a well-established phenomenon [119–123] Based on a total of 1376 MRI scans, to follow cortical aging throughout the eighth decade of life in an aging cohort at ages 73, 76, and 79 years, Cox and colleagues [124] reported a significant decline (0.87 % per year) in cortical volume, although this was not consistent across regions. This may be due to the fact that different regions have distinct genetic signatures, as demonstrable after decomposing volumes into surface area and thickness [125]. Using such analysis, Cox et al., found that the volumes of the frontal and temporal lobes reduce by $>$ 1.30 % per year [124]. Such changes have been ascribed to changes in synaptic number and spines as well as cell body shrinkage [126–128]. It is important to note that reduced cortical volume and thinning during aging will compromise, intrinsic and long-range anatomical connectivity of the prefrontal cortex with distributed structures [129,130].

Previous studies of aging have suggested changes in gene expression in the aged cortex. A *meta*-analysis based on a brain tissue transcriptome dataset revealed that a significant decline in the expression of genes responsible for synaptic transmission in the aging prefrontal cortex [131]. Gene ontologies revealed that downregulated genes are associated with axon development, nervous system development, generation of neurons, glutamate signaling pathways, and neuronal cell morphogenesis and differentiation [131]. Further, assessment of the transcriptomes of specific neuron types in the human cortex revealed an age-dependent decline in the relative proportion of inhibitory neuron types, particularly in cells expressing somatostatin and vasoactive intestinal peptide [132].

Commonalities between young and aged brains

Both young children and aged individuals exhibit sleep patterns that lack important parameters for memory consolidation, such as sustained sleep and sleep-dependent brain oscillations. Hence, memory loss in young and elderly brains may be due to incomplete consolidation steps during sleep. Which stage of memory consolidation is incomplete? Memory at recent time points was the same across age groups but was lost at remote times in young and aged brains (Fig. 1a), suggesting that memory loss may have occurred from brain regions involved in long-term storage.

Memory is initially encoded in the hippocampus and later transferred to the cerebral cortex for long-term storage. The transfer of information from the hippocampus to the neocortex may bring memory into a labile state, especially when sleep fragmentation is high in young and aged brains (Fig. 1b). Results of an early optogenetic study in which orexinergic neurons in mice were activated to result in interrupted sleep without affecting overall sleep amount or intensity, demonstrated that uninterrupted sleep is crucial for memory consolidation, regardless of the amount or intensity of sleep [133]. This view was further supported by the authors' observation that recall is significantly disrupted by fragmented sleep after acquisition of a novel object recognition task.

Decreased hippocampal reactivation and replay during sleep

The rapid memory loss observed at the two ends of the aging spectrum (young children and older persons) may be likely caused by fragmented sleep which results in decreased hippocampal reactivation and replay. In addition, the unstable strength of sleep oscillations (Fig. 1c) and phase-amplitude decoupling of oscillations plausibly affects the replay phenomenon in these age groups since studies suggest that spindles become uncoupled from slow waves in very young [134] and aging [49,135] brains, leading to degrading memory. Investigating hippocampal replays in the human brain presents considerable challenges, the above findings justify the assumption (at least at this time) that the fading of memories in young and aged individuals results from reduced replay activity (Fig. 1d). Indeed, research in rodents has provided evidence of impaired hippocampal replay in the aged brain [136] as well as underdeveloped replay in the rodent postnatal (days P17-P32) brain [137].

Silent engrams

Engrams (memory traces) are believed to be encoded within neurons (neuronal ensembles) activated during learning and recalled by reactivation of the same population of cells [138]. Sleep-associated reactivation of engrams has been hypothesized as an important mechanism for memory consolidation [29,139–141]. This notion was supported by work showing that hippocampal engram input is necessary for the gradual maturation of the prefrontal cortex (PFC) engram and remote memory recall [142]. It therefore follows that reduced hippocampal reactivation, and therefore weak engram input in young and aged brains represents poor maturation of the PFC engram, i.e., the PFC engram remains in an immature or silent state in young and aged brains (Fig. 1d).

Interestingly, previous studies on infantile forgetfulness in rodents showed that reminders, drugs, and optogenetic interventions can successfully recover lost memories [58,59]. Further, there are reports of memory regain in aged mice, which exhibit amnesia in long-term memory tests, after optogenetic activation [143,144]. Such findings indicate that the memory engram in both young and aged brains is not completely erased but may rather exist in a labile (inaccessible and silent) state that can be recovered by activation. Finally, it is noteworthy that changes in cortical structure in young and aged brains, can alter engram properties and connections, leading to the transformation of active engrams into silent engrams that account for retrograde amnesia [145].

Conclusion

This review compares sleep patterns of young children and older individuals in order to identify similarities that may explain memory loss in the two age groups. We conclude that naturally occurring maturational and aging processes of the brain underpin age-related sleep fragmentation and instability in oscillatory activity, as well as changes in brain regions involved in memory processing, ultimately affect sleep-dependent memory consolidation. We suggest that gaps in our empirical knowledge must be filled by strengthening the links between sleep and memory research. Better understanding of the sleep-dependent memory consolidation process in young and aged individuals can have important implications for the development of new therapeutic strategies to combat forgetfulness as individuals age.

Author contributions

All the authors listed made substantial, direct and indirect intellectual contributions to the work and approved it for publication.

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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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