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# Sleep and memory consolidation in aging: a neuroimaging perspective

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## **Abstract**

Recently acquired information is strengthened and consolidated during sleep. For hippocampus-dependent memory, this process is assumed to occur mainly during slow-wave sleep. Changes in sleep patterns in older adults can contribute to the disruption of the consolidation process during sleep and thus lead to cognitive impairment. Current findings suggest that reduced gray matter volume, particularly in frontal areas, A $\beta$  and tau accumulation in combination with age-related changes of specific oscillations during sleep may contribute to memory deficits. This non-exhaustive review aims at providing a comprehensive picture of the associations between sleep changes and memory consolidation in aging, mainly based on neuroimaging studies. Overall, data confirm the utmost importance of sleep for healthy aging and the need to develop interventions aiming at improving sleep to reduce cognitive decline observed with advancing age.

Keys words: Aging; Sleep; Neuroimaging; Brain integrity; Episodic memory

## **1. Introduction**

Aging is associated with changes in sleep quality and physiology. With advancing age, sleep complaint is frequent and sleep architecture is substantially modified, leading to poor restorative sleep [1]. Sleep is essential for cognitive functioning, especially attention, executive functions, and memory, playing in particular a key role in memory consolidation [2]. Moreover, growing evidence suggests that age-related sleep changes could be a risk factor of cognitive decline and dementia such as Alzheimer's disease (AD) [3]. A better understanding of the impact of age-related changes in sleep on memory is needed to develop interventions aiming at improving sleep to reduce the risk of cognitive decline and dementia. The aim of this non-exhaustive review is to provide a comprehensive picture of the associations between sleep changes and memory consolidation in aging, mainly based on neuroimaging studies.

## **2. Sleep changes in aging**

Sleep complaint is common in older adults, with almost 50% of adults older than 60 years complaining about their sleep [1]. Older adults report advanced sleep timing (i.e. earlier bedtimes and rise times), difficulties falling asleep, frequent nocturnal awakenings fragmenting sleep, and ultimately poorly refreshing sleep [1,4].

Self-reported questionnaires are commonly used to assess sleep quality and identify any sleep-related issues older adults may be experiencing. One of the most widely used questionnaires in the literature is the Pittsburgh Sleep Quality Index (PSQI; [5]), assessing subjective sleep quality and sleep disturbances over the past month. Using this questionnaire, it has been shown that aging is associated with a decrease in self-reported sleep quality, with up to 64% of older individuals categorized as poor sleepers [6,7]. Several parameters are particularly affected by aging, including sleep efficiency, which is reduced, and sleep latency,

which is longer, especially in older women [7,8]. Moreover, some sleep disorders are frequent in aging. These include obstructive sleep apnea, whose prevalence varies, according to studies, from 30 to 80% [9].

Polysomnography studies revealed significant changes in sleep architecture (Fig. 1), including an increase in sleep latency, number of arousals (reflecting sleep fragmentation), and time spent awake throughout the night. In contrast, total sleep time and sleep efficiency (defined as the ratio between time asleep and time in bed) decrease [10,11]. Sleep stages are also affected by aging, the most significant change is a decrease in the deepest NREM sleep stage known as Slow Wave Sleep (SWS or N3) contrasting with an increase in lighter sleep (N1) [11,12]. In contrast, sleep stage N2 remains relatively stable and the amount of Rapid Eye Movement (REM) sleep is less affected by aging with a decrease of less than 1% per decade [13]. Regarding sleep microstructure, NREM sleep oscillations are modified with aging. Slow waves (0.5-4.0 Hz) are high-amplitude neocortical oscillations prominent during SWS [14], generated in anterior neocortical regions and propagating along an anterior-posterior axis. Slow waves can be divided into slow oscillations (SO, 0.5-1Hz) and delta waves (1-4Hz) [15]. Older adults have lower amplitude, slope and spectral power of slow oscillations and delta waves, particularly in frontal regions [15]. Sleep spindles are transient 0.5-2s oscillations in the 11-15 Hz frequency band, mainly observed during N2 sleep and originating from coordinated thalamo-cortical loops [16]. Based on their frequency and topographical distribution on the scalp, two types of spindles have been distinguished: slow spindles (~11-13 Hz) which have an anterior distribution, and fast spindles (~13-15 Hz) which are more prominent in posterior cortical areas [17]. In aging, there is a progressive decrease in the density, amplitude, and duration of slow and fast spindles [12,18]. In addition, age-related reductions in spindle duration are most pronounced in posterior regions, while changes in spindle density and amplitude are more noticeable over frontal areas [19].

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Insert Figure 1 about here

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### **3. Memory consolidation during sleep**

Consolidation of declarative/episodic memories would mainly occur during NREM sleep and is subserved by neuronal reactivations during sleep (a phenomenon also called neuronal replay), NREM sleep oscillations and a specific neurochemical environment.

#### 3.1. Neuronal reactivations

During sleep, brain plasticity processes enable newly encoded memories to be consolidated by strengthening the connections between memory-related brain areas. One key mechanism subserving sleep-dependent memory consolidation is neuronal reactivations which refer to specific patterns of neural activity observed during a memory experience that are replayed during subsequent sleep. Wilson and McNaughton demonstrated, in rats, that hippocampal place cells activated during a spatial navigation task were reactivated during post-training sleep [20]. Studies in Humans, using neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), have also provided evidence of neuronal reactivations during sleep. Thus, Peigneux et al. were the first to show that hippocampal areas activated during a spatial navigation task were reactivated during subsequent SWS. In addition, the magnitude of hippocampal activity during SWS was positively correlated to spatial memory performance on the next day [21]. Memory can be spontaneously reactivated during sleep, but reactivations can also be triggered in “targeted memory reactivation” paradigms. In a seminal study, Rasch et al. exposed participants to an

odor during the learning of a visuospatial object-location task. Re-exposure to the odor during SWS acted as a contextual cue that reactivated new memories, increasing hippocampal activation and improving memory performance [22]. Similar memory improvements were observed after targeting memory reactivations with sounds for instance [23].

### 3.2. NREM sleep oscillations

Neuronal reactivations and reorganization of memory traces within neocortical areas during SWS are supported by a precise temporal coordination of sleep oscillations, including slow oscillations, sleep spindles and sharp-wave ripples (SPW-Rs) [24]. SPW-Rs are brief, high-frequency neuronal oscillations (100–200 Hz) which occur in the hippocampus during quiet wakefulness and NREM sleep and promote hippocampal reactivations [25]. Under the influence of slow oscillations, the synchronization between sleep spindles and SPW-Rs enables information to be transferred to neocortical areas. Studies using non-invasive brain stimulation showed that slow oscillations contribute to memory consolidation. Thus, in order to increase during SWS spectral power in the 0.5–4.5 Hz frequency band, also known as slow wave activity (SWA), Marshall and colleagues used transcranial direct current stimulation (tDCS) applied over frontal areas, at 0.75Hz, during early SWS. This stimulation improved the retention of hippocampus-dependent memories, but not performance on a procedural task [26]. This stimulation induced an increase in slow oscillations and slow spindle activity in the frontal cortex. Another study reported that non-invasive auditory stimulation finely applied to the ascending phase of slow oscillations increased SWA and improved consolidation of declarative memories [27]. These results indicate that slow oscillations have a causal role in sleep-dependent memory consolidation.

Sleep spindles may also play a crucial role in memory consolidation [28]. Ji and Wilson reported that spindles observed in rats were closely linked to the firing of hippocampal neurons, which are essential for memory consolidation [29]. In another study, Clemens et al.

reported that disrupting spindle activity impaired spatial memory consolidation [30]. In Humans, Gais and colleagues showed that performance on a word-pair association task was positively correlated with spindle density during NREM sleep [31]. When distinguishing slow and fast spindles, several studies suggest that fast spindles are more involved than slow spindles in the consolidation of declarative memories [32,33].

SPW-Rs oscillations also appear to be essential for memory consolidation [29]. In rats trained on a spatial memory task, Girardeau et al. suppressed SPW-Rs using commissural stimulation during post-training sleep, which resulted in impaired spatial memory performance [34].

### 3.3. Neurochemical environment of SWS

The neurochemical environment of SWS involves the modulation of multiple neurotransmitters, hormones, and neuromodulators that may influence sleep-dependent memory consolidation. During SWS, acetylcholine levels are considerably decreased particularly within the hippocampus. Acetylcholine levels drop to a minimum during early night, a period rich in SWS that favors the consolidation of declarative memory by contributing to slow wave generation, hippocampal reactivations and transfer of information to the neocortex [35,36]. Increasing acetylcholine levels by pharmacological manipulations during SWS alters memory consolidation of a hippocampus-dependent word-pair task but not the consolidation of a nondeclarative mirror tracing task [37]. Conversely, high levels of acetylcholine during wakefulness are necessary for successful encoding. Administration of drugs blocking acetylcholine receptors during learning impaired the encoding of a word-pair memory task [38]. These findings indicate that memory processes benefit from the alternation between periods with high cholinergic levels during wakefulness favoring encoding, and periods with low cholinergic tone during SWS to promote memory consolidation.



Cortisol concentration follows a circadian rhythm, fluctuating between low levels during the day and early night, and rising in the late night to reach a maximum level on awakening [39]. This hormone, involved in stress response, is known to modulate memory processes during SWS by regulating the activity of the hippocampus and the prefrontal cortex (PFC). Plihal and Born performed several pharmacological manipulations of cortisol levels and investigated their impact on sleep-dependent memory consolidation. Enhancing cortisol concentration during early sleep impaired declarative memory retrieval and induced a forgetting of an associative word-pair task but had no effect on a mirror tracing task [40]. In another study, increasing glucocorticoid levels pharmacologically during early sleep blocked the beneficial effect of sleep on paired-associate lists task but did not impair visuomotor skills [41]. Interestingly, a study in rats found that increasing cortisol by infusion of intrahippocampal glucocorticoids disrupted the consolidation of an object place recognition task during sleep, but promoted its consolidation during wakefulness [42]. Together, these studies demonstrate the critical role of the neurochemical environment and especially low levels of acetylcholine and cortisol during SWS to promote declarative memory consolidation.

#### 3.4. Synaptic homeostasis hypothesis and active system consolidation

Based on existing studies, some of which have been detailed above, two main theories, mutually non-exclusive, have been proposed to explain the mechanisms underpinning the consolidation of memories during sleep.

According to the synaptic homeostasis hypothesis proposed by Tononi & Cirelli, global homeostatic regulation of synaptic activation promotes memory consolidation during sleep at a cellular level [43]. More precisely, encoding of new information during wakefulness results in synaptic potentiation, which strengthens the connections between neurons in cortical and subcortical networks and is accompanied by an increase in the strength and size of the synapses, the creation of new synapses and a general increase in neuronal activity. Synaptic

potentiation during wakefulness reduces space and energy available in the brain and therefore saturates our ability for new learning. Sleep, and especially SWS, would result in a global decrease in synaptic strength allowing a reduction of neuronal activity, energy consumption, a restoration of the homeostasis of the neuronal circuits, and would avoid saturation of our learning abilities [44]. Synaptic depotentiation during SWS proportionally decreases the strength of each synapse, which helps to maintain a trace in the neuronal networks associated to the learning experience. Supporting this theory, Human studies showed an increase in cortical excitability during a period of sustained wakefulness followed by a decrease after sleep [45,46] and a local use-dependent increase in SWA in cortical regions active during learning which was associated with improved memory consolidation [47].

The second theory, called the hippocampo-neocortical dialogue or the active system consolidation hypothesis, implies a coordinated set of neural mechanisms operating over time to transform newly acquired information into a stable and potentially improved form [48]. During wakefulness, information is initially encoded within hippocampal and neocortical networks. The active system consolidation hypothesis posits that during SWS, the synchronized activity of thalamic sleep spindles and hippocampal SPW-Rs during the depolarizing up-states of neocortical slow oscillations reactivates the memory trace in the hippocampus and drives the transfer of information toward neocortical regions [49,50]. The memory is repeatedly reactivated in associated brain regions. Thus, recent memory traces become gradually redistributed into long-term memory stores and integrated into preexisting knowledge. This hypothesis is supported by neuroimaging studies revealing a progressive disengagement of the hippocampus during the retrieval of memories, contrasting with increased activity in neocortical areas, especially the ventromedial prefrontal cortex [51,52].

#### **4. Sleep, memory and aging**

Based on the studies described above and the hippocampo-neocortical dialogue model, several changes occurring during aging may disrupt sleep-dependent memory consolidation (see Fig. 2). Aging is associated with changes in the neurochemical environment. It has been observed a decrease in the diurnal variations of the cortisol rhythm and an increase in cortisol levels during the evening and nocturnal sleep with aging. These changes are hypothesized to affect hippocampal networks and consequently inhibit long-term potentiation and transfer of information to the neocortex [53]. Age-related degeneration of cholinergic neurons result in cholinergic hypofunction, which could be associated with memory impairment. High acetylcholine levels are necessary to enable efficient encoding [54]. However, we do not know whether the global age-related decrease in cholinergic tone has an impact on sleep-dependent consolidation of episodic memories.

Numerous studies have examined the impact of age-related structural and functional brain changes on sleep quality and memory consolidation (for reviews see [10,55]). In a recent review, Muehlroth et al. highlighted that changes in gray matter volume in frontal and temporal areas, in the neurochemical environment, and alterations of NREM rhythms may hinder sleep-dependent memory consolidation in aging [56]. However, the literature is not totally consistent, especially for behavioral studies.

#### 4.1. Results from behavioral studies

Behavioral studies on the relationship between memory and sleep during aging have provided conflicting results. Several studies revealed that sleep-dependent memory consolidation process is impaired during aging. More precisely, it has been shown that the proportion of SWS, which is reduced in aging, is positively associated with memory performance on a word-pair task [57] and on an object-location task [58] in young adults but not in older ones. Deficits in memory retention for a word-pair task in middle-age adults were associated to a decrease in the proportion of SWS during the first part of the night [59]. In the same vein,

Sonni and Spencer showed that early NREM sleep was positively associated with performance on an object-location memory task in young but not in older adults [60].

In contrast, other studies suggest that sleep-dependent memory consolidation is preserved during aging. Using a task consisting in memorizing unrelated word-pairs in young, middle-aged and older adults, Wilson et al. reported no effect of age on memory performance after sleep [61]. In a study by Aly and Moscovitch, memories of stories and personal events were assessed following a night of sleep or an equivalent period of wakefulness in young and older adults. Following a period of sleep, older and young adults showed better memory performance for both types of material [62]. The authors concluded that the consolidation process is preserved when the material to learn is emotionally engaging or personally relevant. Overall, these studies suggest that the type of material used may influence declarative memory consolidation processes during sleep in aging, and may explain some inconsistent findings in the literature.

#### 4.2. Impact of age-related changes in NREM sleep oscillations on memory consolidation: insight from neuroimaging studies

Using a task consisting in learning word-nonsense word pairs, Mander et al. investigated the association between brain atrophy, reduced SWA and the retention of episodic memories [63]. They found that atrophy of the medial prefrontal cortex (mPFC) was associated with reduced SWA during NREM sleep, which in turn predicted the impairment of overnight memory retention. In addition, this memory impairment was associated with persistent hippocampal activation and reduced functional connectivity between the hippocampus and the prefrontal cortex during retrieval. According to the hippocampo-neocortical dialogue model, sleep-dependent memory consolidation is supposed to be associated with decreased activity in the hippocampus contrasting with greater recruitment of neocortical areas. In this context, persistent hippocampal activation may reflect impaired memory consolidation [63].

Aging is also associated with changes in sleep spindles, known to support memory consolidation in young adults. Recent studies suggest that age-related alterations in spindle activity may also contribute to memory impairment. In aging, impaired episodic performance was predicted by reduced prefrontal fast spindles during the pre-learning night. Interestingly, prefrontal spindles also significantly predicted the magnitude of impaired hippocampal activation on the next day [64]. In a recent study analyzing the temporal distribution of sleep spindles (i.e. isolated or in clusters), Champetier et al. showed that the proportion of fast spindles organized in clusters decreased after 50 years old. Moreover, the mean size of fast spindle clusters was positively associated with performance on a visuospatial memory task [65].

In aging, cortical accumulation of  $\beta$ -amyloid ( $A\beta$ ) occurs insidiously during several years and has been associated with disruption of the sleep-wake cycle [66]. Increased  $A\beta$  deposition has been related to variables reflecting poor sleep quality, measured objectively or using self-reports, such as reduced sleep duration and sleep efficiency, increased sleep latency and sleep fragmentation [67,68]. In addition, the microstructure of sleep, notably SWA, has also been associated to  $A\beta$  burden [69]. An interesting hypothesis proposes that sleep, and especially SWS, may play an important role in the clearance of the toxic metabolites that accumulates in the brain during active wakefulness through the glymphatic system [70]. Aging is accompanied by a dramatic decrease in SWS, which could disrupt the functioning of the glymphatic system, contributing to the accumulation of toxic proteins such as  $A\beta$  and increasing the risk of neurodegenerative diseases [71]. It has been shown that early cortical  $A\beta$  accumulation in frontal regions [72] is associated with impaired generation of SWA and therefore negatively correlated with hippocampus-dependent memory consolidation [72]. To conclude, these studies show that the increase in  $A\beta$  burden and lower brain volume, mostly

in prefrontal areas, are associated with poor sleep quality and impaired memory consolidation in aging.

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Insert Figure 2 about here

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#### 4.3. Desynchronization of NREM sleep oscillations coupling as a potential mediator of the effect of brain atrophy on memory consolidation

Hippocampal reactivations and synaptic plasticity in the neocortex are dependent on a very precise coupling of slow oscillations, sleep spindles, and SPW-Rs to support consolidation processes [28]. Changes in the temporal association between spindles and slow oscillations have been observed in aging. Using a scene-word association task, Muehlroth et al. showed that accurate coupling of slow oscillations-fast spindles was associated with enhanced memory retention while desynchronization of this coupling predicted memory impairment in aging [74]. In the same way, Helfrich et al. demonstrated that a decrease in the accuracy of slow oscillations-spindle coupling predict greater overnight forgetting in a sleep-dependent word-pair task [75].

Several studies showed that brain atrophy during aging may have an impact on the generation of slow oscillations and on slow oscillations-spindles coupling [63,74–76]. Raz et al. found that age-related decrease in gray matter volume is not uniform, and that frontal regions are particularly sensitive to the effects of age [77]. Moreover, longitudinal changes in white

matter integrity in prefrontal regions have also been highlighted in older adults [77]. Age-related atrophy of the mPFC has been related to poor sleep quality [78] and a decrease in slow oscillations generation [63,76]. Empirical evidence supports that mPFC atrophy predicts higher power in the fast-spindles range during the slow oscillation upstate [74] and the desynchronization of slow oscillation-spindle coupling [75]. Both increased fast spindle power during the slow oscillation up-state and higher global EEG activity during the slow oscillation upstate were correlated with hippocampal and entorhinal volumes. Higher spindle activity during the slow oscillations upstate was related to greater thalamus volume [74], a region involved in spindles generation [15]. Together, these studies suggest that the integrity of the hippocampus, entorhinal cortex, thalamus and frontal areas (in particular the mPFC) is essential to support slow oscillation-spindle coupling, and thereby enable efficient hippocampal-neocortical dialogue in aging. Besides brain atrophy, a recent study investigated the role of markers of AD such as A $\beta$  and tau accumulation on slow oscillation-spindle coupling. Winer et al. reported an association between impaired slow oscillation-spindle coupling and greater tau burden in the medial temporal lobe. A $\beta$  burden was not associated with impaired coupling, but rather predicted the diminished amplitude of <1 Hz SWA [79]. The authors hypothesized that altered slow oscillations-spindle coupling underlies the association between tau pathology and impaired hippocampal-related memory performance [79].

Although several studies showed that age-related disruption of NREM sleep oscillations contributes to impaired memory consolidation, other authors reported discrepant results. According to a recent study by Frase et al., aging has a significant impact on both brain integrity and memory consolidation. Thus, smaller hippocampal, parahippocampal, and mPFC volumes were associated with poorer overnight declarative memory consolidation. However, neither polysomnographic variables nor spectral power variables (e.g., SWA) mediated this

association [80]. As well, Baran et al. compared the association between EEG activity during a nap and consolidation of a word-pair task in young and older adults. Although older adults showed lower delta power than younger adults, a negative correlation between hippocampal activity during retrieval and delta power was observed only in young adults [81]. Further studies are required to better understand the associations between SWS oscillations, brain integrity and memory during aging.

## **5. Conclusion**

Aging is associated with changes in sleep architecture, particularly during SWS which plays a crucial role in episodic memory, but the impact of these changes on memory impairment in aging is not fully understood. Recent research has shed light on the potential mechanisms underlying this relationship, including the accumulation of A $\beta$  and tau proteins, brain atrophy and changes in neurotransmitter systems. Age has an impact on slow oscillations, sleep spindles and their temporal coupling which are important for declarative memory consolidation during sleep, facilitating a nocturnal dialogue between the hippocampus and neocortical areas where memories will be stored durably. Recent studies are deepening our understanding of the associations between memory, sleep and aging by using increasingly precise measures of neurophysiological oscillatory dynamics such as slow oscillation-spindle coupling. To our knowledge, no study has investigated the association between sleep quality and episodic memory consolidation in cognitively healthy older adults using resting-state functional connectivity measures. Yet, sleep disorders such as obstructive sleep apnea, which is very frequent in older adults, are associated with lower functional connectivity in memory-related areas [82]. Since no association was observed with cognitive performance, these changes in functional connectivity patterns may precede cognitive deficits. Thus, resting-state functional connectivity changes, assessed using fMRI or EEG, deserve further investigations as they could be a very early sign of age-related brain damage. Better understanding sleep



parameters whose alteration with age has a deleterious impact on memory consolidation would help to develop interventions targeting those factors to improve sleep quality and ultimately reduce cognitive decline and promote successful aging.

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## Figure captions

**Figure 1. Age-related changes in sleep architecture** (adapted from [10]). Typical architecture of a night of sleep in a young (top) and an older adult (bottom). Of note, compared to young individuals, older adults show longer sleep latency, a greater number of stage shifts to lighter stages of sleep and wakefulness reflecting more fragmented sleep, more time spent awake after sleep onset, and less time in slow wave sleep. REM: Rapid Eye Movement sleep, NREM: Non Rapid Eye Movement sleep; N1: stage N1, N2: stage N2, N3: stage N3.

**Figure 2. Figure illustrating the hippocampo-neocortical dialogue model in young subjects (left) and the potential dysfunctions in older adults (right).** (A) During wakefulness, information is encoded in neocortical and hippocampal networks (black arrow). During SWS, the repeated reactivation of recently encoded information within the hippocampus is associated with sharp waves-ripples and are driven by a fine-tuned coupling between slow oscillations and sleep spindles (green arrow). The transfer of memory traces to neocortical regions for long-term storage is stimulated by these reactivations (red arrow). These reactivations promote the transfer of memory traces to neocortical regions for long-term storage. Of note, the reorganization of memory traces is favored by low levels of acetylcholine and cortisol during periods of SWS-rich sleep. (B) Age-related structural (reduced gray matter volume) and molecular (amyloid accumulation) alterations in the prefrontal cortex (blue arrow), decreased slow oscillations and sleep spindles, neurochemical changes (lower acetylcholine tone during wake could impair declarative memory encoding, higher cortisol levels during sleep could hinder declaration memory consolidation) and altered memory reactivation in the hippocampus (currently only observed in rats) may explain the alteration of sleep-dependent memory consolidation in aging (adapted from [73]).

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Figure 1

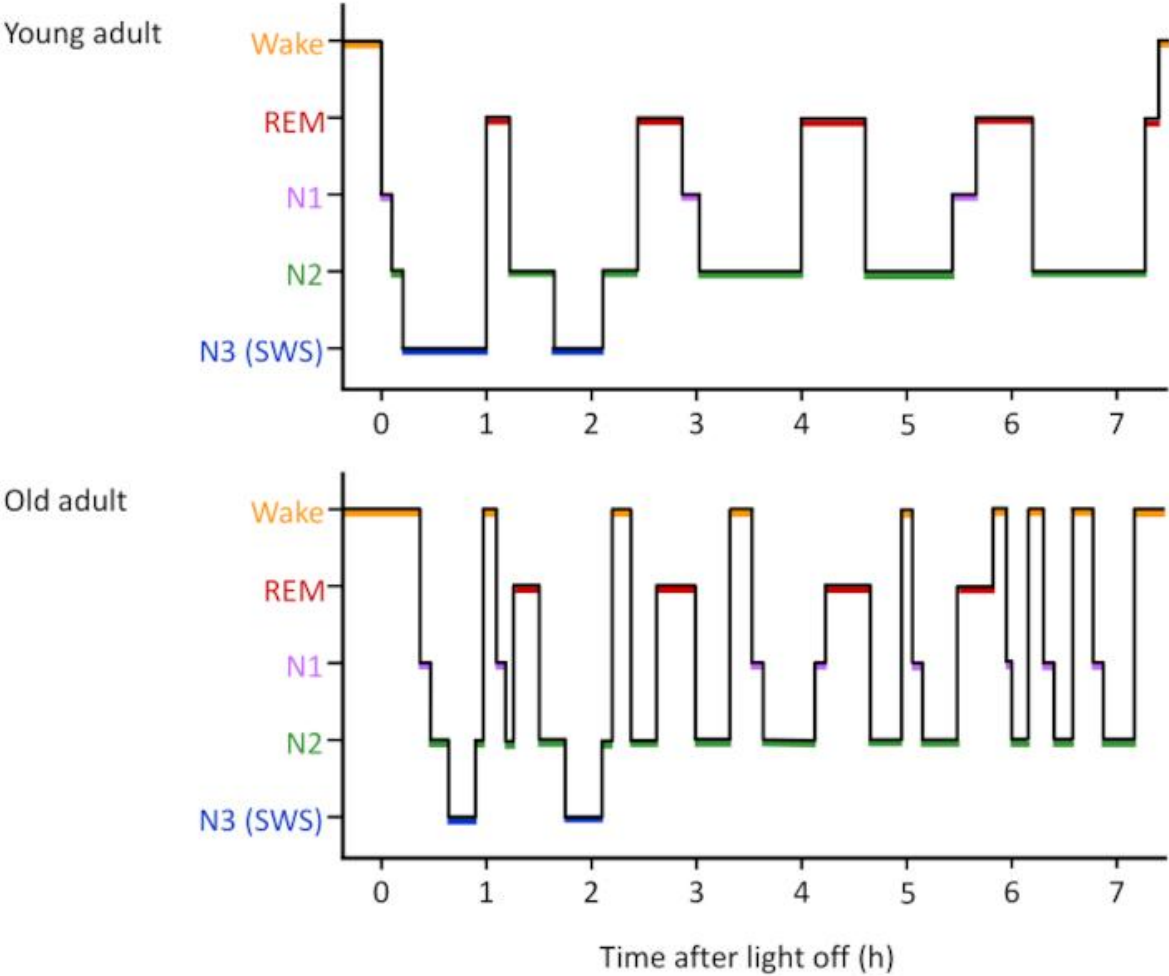


Figure 2

