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Review

The aging brain: sleep, the circadian clock and exercise

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ABSTRACT

Aging is a multifactorial process likely stemming from damage accumulation and/or a decline in maintenance and repair mechanisms in the organisms that eventually determine their lifespan. In our review, we focus on the morphological and functional alterations that the aging brain undergoes affecting sleep and the circadian clock in both human and rodent models. Although both species share mammalian features, differences have been identified on several experimental levels, which we outline in this review. Additionally, we delineate some challenges on the preferred analysis and we suggest that a uniform route is followed so that findings can be smoothly compared. We conclude by discussing potential interventions and highlight the influence of physical exercise as a beneficial lifestyle intervention, and its effect on healthy aging and longevity. We emphasize that even moderate age-matched exercise is able to ameliorate several aging characteristics as far as sleep and circadian rhythms are concerned, independent of the species studied.

1. Aging theories and the aging brain

The previous century was associated with great scientific advances in the fields of medicine and biology leading to a significant increase of our life expectancy [1] however these advances were accompanied by significant open questions which remain an enigma even nowadays and are still under investigation. One such enigma is the process of aging. As it is shared in the current review, aging can be viewed as a point in life closer to the end where the variations in biological functions exceed the physiological range. Owing thus to this complicated nature of aging, several theories have been proposed over the years to shed light upon this matter.

According to the *error theories* environmental factors affect the organisms at various levels, inducing damage that eventually leads to death [2–5] the *free radical theory* supporting the accumulation of damage due to the augmented release of active free radicals comprises one of the protagonists of this group of theories. Furthermore, it is believed that aging is in a sense genetically programmed such as morphogenesis leading to another cluster of theories, the programmed ones [2–5]. In contrast to the other two blocks of theories, the *evolutionary aging theories* have been developed, suggesting that following the reproductive age there is a decline in maintenance and repair mechanisms in the organisms that ultimately leads them into their end [2–5].

During the last decades, experiments on the fruit fly Drosophila melanogaster have been extensively performed in several fields, including aging research, and it was proposed for the first time that life span may also be an inherited trait [6–7]. The heritability of human longevity has been estimated to be interestingly low (~15–30%), since life span generally integrates several aspects of health but also environment [8].

Irrespective to which aging theory is the prevailing one, aging is characterized by an age-dependent functional deterioration of cells and their products and pathways, tissues and whole organ systems which contributes to the end of life.

Like all organs, our brain is also not spared from the effects of aging even though it has a remarkable resilience and plasticity. During the normal aging process across species, brain alterations are found at several organizational levels, starting from single molecules and extending up to brain morphology and size. These alterations reflect the normal aging process and are not necessarily associated with any pathological issues.

In this review, in addition to human studies, we pay particular attention to rodent studies, since rodents have been extensively used as animal models in neuroscientific research contributing to remarkable advances. However, this facilitation comes at a cost, namely the translation process from animals to humans. One evident difference between the rodent and human brain is the increased cortical dimension as well as the formation of a more elaborate cortical architecture in primates as compared to rodents [9]. It should be therefore noted that data from rodent studies ought to be treated with caution and albeit being helpful

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they are not always sufficient to decipher the aging process in the human brain.

In humans, it has been demonstrated that total brain volume declines as a function of age [10] at a rate of approximately 5% per decade following the age of 40 [11]. Likewise, albeit having simpler cortical structure as aforementioned, reduced cortical grey matter volume and enlargement of the brain ventricles has been observed in the mouse brain [12]. Aging likely affects white matter density, as findings across species including humans have indicated great reductions in the prefrontal cortex as well as the anterior corpus callosum [13–14]. Notably, white matter volume changes in aging have been shown to be nonlinear, with a more rapid change with advancing age in humans, whereas gray matter has shown a smaller and more linear decrease [15]. In addition to the prefrontal cortex, one of the mostly affected areas in healthy aging, the hippocampus comprises another greatly affected area [16–18]. Advanced age has been additionally associated with widespread thinning of the cerebral cortex [19]. During the last decades it became apparent that in both rodents and humans, the age-related cognitive decline [20–21] is not a result of a loss of neurons, but most likely a diminishment in functional synapses in areas such as the cerebral cortex and hippocampus [16,22]. The aging brain is additionally characterized by a selective disruption of myelinated fibers that connect neurons in different cortical regions, which suggests a disruption of integrated function correlating with poor cognitive performance [23].

Overall, we see that even during healthy aging the brain does not come out unscathed and this is not pertaining to humans. In the following section, we delve into the sleep process and the brain mechanisms that contribute to age-related sleep alterations in both humans and animal models.

2. Sleep and the aging brain

2.1. Universal sleep: Brain mechanisms

Sleep, albeit being an almost universal component throughout the animal kingdom, remains one of the most puzzling behaviors and involves several pathways linked to brain activity. As several of these pathways together with their components and the brain itself begin to degenerate with time, the most logical view is that sleep will be also altered as a function of age likely due to this damage accumulation.

Sleep in the course of aging is associated with a disrupted physiology possibly due to interrupted pathways and brain atrophy [24]. Elaborating, sleep quality gradually decreases in older humans, owing to reduced capacity to initiate and/or maintain sleep. Studies have shown that the amount of sleep is reduced in the elderly, with sleep complaints, frequent awakenings and superficial stage 1 sleep being common as a function of age [25–27]. Regarding the sleep electroencephalogram (EEG) lower slow-wave activity (SWA, EEG power density between ~ 0.75–4.0 Hz) in non-rapid eye movement (NREM) sleep is found, reflecting a less deep sleep, and reduced sigma activity (around 13 Hz) during NREM sleep, beginning as early as the middle age [28–30].

Although sleep and its function are highly affected with age, the brain mechanisms contributing to age-related sleep alterations are not fully understood to date. The prefrontal cortex has been demonstrated to be impaired with age, possibly intervening with the sleep process [24]. In the medial prefrontal cortex, which is an area where NREM sleep slow waves show a dominance in origin and density over EEG derivations, gray matter is reduced in older subjects [24,31]. Notably, older subjects show lower slow-wave amplitude and density, as compared to young adults specifically in prefrontal and frontal brain areas [32].

The brain mechanisms that regulate sleep and wakefulness have been extensively discussed throughout literature [33]. Many brain areas involved in sleep-wake regulation can be found in the pons and the hypothalamus [34–36]. Two ascending pathways promote waking. The first pathway is active during waking and REM sleep, but less during NREM sleep [37] and runs from the pons to the thalamus and activates thalamic relay neurons. This pathway mainly consists of acetylcholine-producing neurons from the pedunculopontine and laterodorsal techmental nucleus [38]. The second pathway originates from multiple groups of monoaminergic neurons, including the serotonergic raphe nucleus, the noradrenergic locus coeruleus, the histaminergic tuberomammillary neurons and the dopaminergic ventral periaqueductal grey matter [34–36]. These monoaminergic pathways project to the lateral hypothalamus as well as the entire cortex [39] and are most active during waking, less active during NREM sleep and virtually silent during REM sleep [19,40–41]. Together the two pathways are called the ascending reticular arousal system (ARAS). On the opposite side is the ventrolateral preoptic area (VLPO) which is thought to induce NREM sleep [42]. The VLPO is mainly active during sleep inhibiting ARAS by GABAergic projections with galanin as neuropeptide co-transmitter, the latter can also act as a neurotrophic factor. Besides the VLPO, additional sleep-inducing brain centers have been unveiled, such as the NREM and REM sleep promotion through the control of inhibitory reticular nucleus neurons by melanin concentrating hormone (MCH) neurons of the lateral hypothalamus [43–44].

Notably, alterations in the output of these pathways may contribute to age-related cognitive impairments. Increased concentrations of neurotrophic factors are able to restore cognitive function in aged animals [45], whereas the decreased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus may contribute to age-related cognitive impairments [46]. Both BDNF and serotonin, likely acting in concert, in order to regulate aspects of neural plasticity in several brain regions, have been shown to be compromised in aging and age-related neurodegenerative disorders [47]. Moreover, recent research in both rats and humans points towards an imbalance in the cerebral dopaminergic neuronal system in aging [48–49]. The cholinergic and monoaminergic systems have also been demonstrated to be functionally impaired in the course of aging, with the metabolites of acetylcholine, dopamine, and noradrenaline being generally depleted in the cerebral cortex of aged rats and monkeys and humans [50–54]. Serotonin also plays an important role in several neural functions together with sleep regulation [55] diminished populations of serotonin receptors with age have been demonstrated in rat and human brains, therefore serotonin is also likely to contribute to age-related sleep alterations [56]. Although the translational aspect of the plethora of existing animal research studies is significant, additional future human studies, that are scarce regarding the aforementioned sleep and wake brain pathways and associated neurotransmitters, are needed to have a more complete picture.

We can, therefore, conclude that several age-related changes occur, affecting brain pathways implicated in sleep. Future research based on human subjects will likely clarify this notion.

2.2. Rodent as an aging model for sleep

Mouse models have been proven to be an important laboratory tool into the investigation of fundamental research questions that concern humans. Although both species share mammalian features, differences have been identified on several experimental levels. Regarding the field of sleep, an overall different pattern has notably been observed between mice and humans.

In particular, it is not until recently that the whole spectrum of age-related sleep alterations, including EEG spectral changes and cortical electrophysiology was fully documented [57–59]. It was found that older mice differed in their sleep architecture and the sleep EEG characteristics compared to young mice. We demonstrated that during the night, the older mice were less awake and showed an increase in NREM sleep due to elevated numbers of long NREM sleep episodes as well as fewer long waking episodes. At the end of their rest period the older mice also showed decreased REM sleep [57]. These findings were in agreement with other studies conducted in mice [58,60–64]. Regarding

the sleep EEG features, older mice showed higher EEG SWA in NREM sleep (see text box) in addition to a generally altered slow-wave morphology compared to young mice, including altered slow-wave slopes, decreased sigma activity (activity between 9 and 13 Hz) during the down state of the slow-wave, and a decrease in the number of multipeak waves [57]. The finding on SWA in NREM sleep suggests that elderly mice are likely to live under higher sleep pressure conditions, while the ensemble of the morphological differences in slow-wave attributes indicates altered brain network properties in the elderly mice. Augmented SWA in the NREM sleep EEG was also found in older mice in two subsequent studies [58–59]. Interestingly, it was shown that the local cortical neural dynamics and local sleep homeostatic mechanisms were not impaired during healthy senescence in mice [58].

Summarizing the existing data, we can conclude that aging affects sleep in humans and mice in different, somewhat opposing ways. More specifically, regarding aged humans, in addition to complaints falling asleep, their sleep is characterized by fragmentation, being overall attenuated in its amount and less efficient together with a decrease in the SWA in NREM sleep [28,65–67]. In contrast, older mice sleep more and show higher EEG SWA in NREM sleep [57–59].

Although these differences remarkably emerge in sleep, aged circadian rhythms coincide between humans and mice, both showing a clear attenuated fashion as it is discussed in the following paragraphs.

2.3. Aging and the circadian clock

Virtually all organisms have developed a biological circadian clock to adapt the daily scheduling of physiological processes in the body to daily environmental changes caused by the rotation of the earth. In mammals the central circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [68]. The SCN generates a circadian rhythm in electrical activity which is controlled by the action of molecular oscillations. Changes in the SCN, as well as other parts of the circadian timing system are thought to underlie sleep disturbances in elderly people [69–70]. Even in healthy aging the signal of this endogenous clock seems to weaken, resulting in (among others) altered timing of sleep and less consolidated sleep phases, diminished rhythms of body temperature and hormones [71]. This attenuation of the central timing signal leads to increased variability in the phases of peripheral oscillators controlling physiological functions outside the SCN. It has been suggested that this can cause or aggravate health problems, like metabolic syndrome, neurodegenerative disorders and cardiovascular disease [72]. Recently several age-related changes in physiology in the SCN in mammals have been identified.

2.4. Circadian rhythms in aging

With aging the daily timing of processes in our body changes. The most noticeable change is a phase advance in several rhythms, such as the daily decrease in body temperature and the onset of sleep in the evening [73], which has also been described in nonhuman primates [74] and rodents [75], and the reduction in circadian amplitude of physiological and behavioral rhythms [60,71]. However, the effect of age on the intrinsic circadian period length seems to depend on species and genetic background. The endogenous circadian period of locomotor activity shortens in aging hamsters [76–77], primates [74] and rats [78], whereas the period lengthens in inbred mice [60,79]. In contrast in humans no significant change in period was found [80].

The SCN consists of a network of approximately 20.000 neurons in mice. Molecular clocks in each SCN neuron interact to accomplish a circadian modulation in cell physiology as they control a variety of ionic conductances. This results in circadian changes in neuronal excitability and a circadian rhythm in electrical activity which peaks in the middle of the day [81]. In individual SCN neurons the peak in activity lasts for approximately 4 h and a major task of the SCN network is to construct an ensemble waveform that encodes dusk, dawn and daylength [82–83]. Many age-related deficits in the circadian system are likely based on changes in physiology and function within the SCN neuronal network [84].

For the SCN to function as a reliable circadian parameter, it needs to synchronize to the environmental light–dark cycles. For this, non-visual light information is processed by photosensitive retinal ganglion cells and relayed to the SCN through retinal hypothalamic fibers containing glutamate as their main neurotransmitter [85]. Most retinorecipient SCN neurons are then activated through their glutamate receptors, which leads to an increase in intracellular calcium and a subsequent change in the expression of clock genes initiating phase shifts [86–87]. The possibility of phase shifting by light is relatively reduced during the day and resets the SCN to correct for differences between the phase of the internal clock with the phase of the external light–dark cycle. In the course of aging, the ability to synchronize or reset the internal clock phase is hampered in humans [88] and in rodents [60,89–91]. This reduction is reflected in the increased light intensities required to achieve similar entrainment in the elderly compared to young subjects [92] and in non-human primates [93]. This can be caused by a reduction in light transmission of lens and pupil [92], and an aging induced decline in photosensitive ganglion cells as was observed in rodents [94]. Also in the SCN age-associated changes occur in glutamate receptor function [95] and modulation [96] that can contribute to this.

As mentioned, one of the clearest features in aged circadian rhythms is the reduction in circadian amplitude. Recordings in the SCN of aged mice found that this feature is reflected in a significant reduction in amplitude of the electrical activity rhythm [60,97]. This is probably not due to a loss of SCN neurons in the course of aging, as cell counts of SCN neurons in aged mice and rats did not find a significant change with age [98–99]. Aging does lead to a decrease in SCN neurons expressing VIP and AVP [99–102]. Also GABA-ergic signaling is reduced in aged animals [60,103–104]. Together the data suggest that the reduction in SCN output amplitude may be caused by age-dependent changes in neurotransmitter signaling, which then results in reduced synchronization between SCN neurons causing a reduction in amplitude [105].

Analogous to this, the reduction in phase resetting capacity in the course of aging may also be related to the reduction in SCN amplitude. This decrease in amplitude is probably caused by an increase in phase dispersal of the individual neurons. This situation is very similar to animals adapted to a long photoperiod where the increase in phase dispersal is paralleled by a decrease in phase shifting capacity [106–107].

Both the decrease in peak activity in single neurons and the activity of neurons at the wrong time of day (i.e. more active neurons during the night) result in a dampened amplitude in the whole SCN ensemble. Remarkably, this age depended dampening in neuronal activity rhythm was greater on the cellular level compared to the whole SCN [60,97] suggesting compensation of SCN functioning on the network level. Nevertheless, some of the changes seen in sleep in the course of aging are probably caused by changes in circadian regulation. In particular the fragmentation of waking in the dark period observed in aged mice [57] and the fragmentation of sleep in the same circadian phase in humans [71] can be a consequence of the increase in improper night time electrical activity of SCN neurons.

Considering the effects of aging, from the circadian SCN mechanistics perspective (from light input information to SCN behavioral output) mice and humans are strikingly similar, but when taking into account their sleep and sleep EEG, striking differences emerge. In addition, most laboratory rodent models used to date are nocturnal and mostly devoid of melatonin, a key signal of the circadian system [108]. Generally, melatonin can produce phase shifts when applied at pharmacological doses, so it is used as a chronotherapeutic “drug”. More importantly, endogenous melatonin seems to stabilize synchronization and enhance light-induced entrainment in old hamsters [109–110]. However, despite the fact that melatonin-deficient nocturnal animals are used in research, they are able to phase shift after melatonin application and interestingly

the response curve is almost identical to the day-active animal [111]. Indeed, the grass rat that can be either nocturnal or diurnal has the same melatonin profile in both behavioral subtypes, even though the activity of the paraventricular nucleus of the hypothalamus (PVN) is 180 degrees out of phase [112]. Discussing, therefore, the nocturnal laboratory rodent models, tt is not surprising that differences in sleep patterns are found and future studies including diurnal animal models may show more similarities to human studies. However, exploring through various environmental factors that are shown to influence both human and mice, we are able to test whether despite the prior differences these factors converge into any improvements in sleep. For example, physical activity, known already for it beneficial effects, including cognition, mood, general body and brain health across ages, is able to ameliorate sleep as well in both humans and mice, as it will be discussed in the following section.

3. Exercise and brain age

Aging is a physiological process that occurs asynchronously in different brain areas while the rate of that process is dependent on the lifestyle of the individuals. As stated in the beginning of the current review, life span largely depends on environmental factors in addition to having a small hereditary component [8]. Many factors are likely to intervene in aging, leading to either detrimental or beneficial effects, which in turn could accelerate or decelerate parts or the whole aging process.

Two salient lifestyle interventions, able to promote healthy aging and longevity, are caloric restriction (e.g. intermittent fasting) and physical activity [113–114]. Extensive studies on the cellular and molecular hallmarks of aging and lifestyle interventions have been reported earlier [84,115–116]. In the present review we focus on exercise which constitutes a factor that has gained a lot of attention the last decades regarding general health. Specifically aerobic exercise has been shown to improve cognition, memory and mental health, as well as to promote structural and functional plasticity in the brain, mimicking the action of antidepressants [114,117–121]. Physical activity, such as wheel running, is able to phase shift and entrain the circadian rhythms in rodent species [122–124] and it has been assessed as a phase-resetting cue in humans, especially useful for totally blind and elderly people [125–127]. As far as the elderly are concerned, even moderate exercise can still be beneficial, since cognitive functioning is particularly enhanced [128–129]. Hippocampal volume loss commonly found in aged humans has been shown to be restored after solely one-year walking training [130]. Notably, exercise has been proposed as an alternative treatment in order to ameliorate potential sleep disturbances in both young and aged humans [117,131–134].

The effect of prolonged physical activity has recently been profoundly investigated on sleep, the sleep EEG and circadian behavior in mice [135]. Elaborating, in that study, a running wheel was available in the cages of the mice for up to three months for voluntary use on a daily basis. This was followed by sleep recordings, which were performed with an absence of the running wheel [135]. It was demonstrated that aging reduced significantly the strength of the 24-h rhythm. Furthermore, young mice provided with a wheel were more awake and slept less in the dark period compared to young controls, resembling sleep patterns from mice recorded concomitantly with a running wheel [136–137]. This effect was attenuated in the aged mice [135]. However, the aforementioned age-related increase in the EEG SWA levels in NREM sleep in mice [57–59], was markedly counteracted by long-term exercise in mice towards levels similar to young sedentary mice [135]. The running wheel was introduced much later in the life of the aged mice, and these aged mice ran overall less compared to the young ones; however even this moderate exercise was able to induce significant changes towards a younger brain phenotype [135]. Additionally, by conducting machine-learning analysis based merely on the SWA in NREM sleep, the different groups could be classified and accurately distinguished, showing that characteristic information regarding age and exercise was actually enclosed in SWA, pointing towards a younger brain age after exercise [135]. In a similar way, it was demonstrated that in the elderly, after short- and long-term exercise, SWA levels and slow-wave-sleep were altered, reaching levels closer to younger subjects [132,138,139,140].

As it has been discussed across literature, individuals having the same chronological age may vary in health, disease and disability, and hence, although coeval they may differ in biological age, which in turn can be influenced by parameters such as genetic background, disease and lifestyle [141–145]. Several EEG features have been successfully used in brain age prediction, and age group classifications, since they are found to be altered in the course of aging [146–147]. There is mounting evidence that also the sleep EEG could provide information to successfully predict brain age and therefore to be a very useful tool for research and medicine [132,135,138–140].

A prominent role of physical activity in general body and brain health enhancement has therefore emerged, which may improve the quality of life even in advanced age. Concluding, we suggest that, first, even moderate age-matched exercise is likely to ameliorate several aging characteristics while attenuating the effects of sedentary behaviors, such as the elevated sleep slow waves that we portrayed and second, that it could be prescribed as a first-order “medication” for general body as well as brain health augmentation throughout the whole age spectrum.

4. Textbox

4.1. EEG slow-wave activity: Plots and challenges

The result of an EEG spectral analysis or power density analysis and in particular the hourly time course of slow-wave activity (SWA), also called delta power or delta activity, is usually plotted in relative values. The advantage of using relative values is that the interindividual differences in (baseline) power are eliminated. This approach is appropriate in cases where an analysis is performed on a particular experimental intervention within the same animal. It is also more needed in animal research as there is less standardisation of the recording conditions when it comes to electrode placement and electrical properties of the recording conditions, like for instance a standard impedance over the electrode. However, when different groups of animals need to be compared, as is for instance the case in aging, this choice can be challenging. In human sleep and aging research, when comparing EEG variables like power density or slow-wave amplitudes, this is done by expressing these in absolute μV’s instead of relative values [28,28,66,71]. Here, the general conclusion in human research is that in the course of aging SWA in NREM sleep is decreasing. However, a different approach has been used in animal research, where mainly relative values have been chosen to compare SWA between age groups [63,148] with the results obtained suggesting that also in mice SWA decreases in the course of aging. As described in the main text, this is not exactly the case [57–59]. Below, we discuss the ways that the daily time course of SWA values have been plotted across literature.

First, in Fig. 1A every 2 h-data point is plotted relative to the average SWA over the 24 h baseline day. This 24-h reference is used in many animal sleep publications analysing the time course of SWA over time. Differences between the two age groups are not very large, but during the baseline day, particularly in the middle part it seems as if the older group has a higher SWA compared to the younger group. Second, in Fig. 1B the data are plotted relative to the level of SWA in the first hour, a method less often used. Here the differences between young and old become a little larger and again we find that the older group shows a higher slow-wave activity compared to the young. Third, Fig. 1C shows a relatively new way of plotting SWA [149]. The idea is that during the last 4 h of the baseline rest period (here in the mice the end of the light period) animals are producing the lowest SWA over the entire day. It is

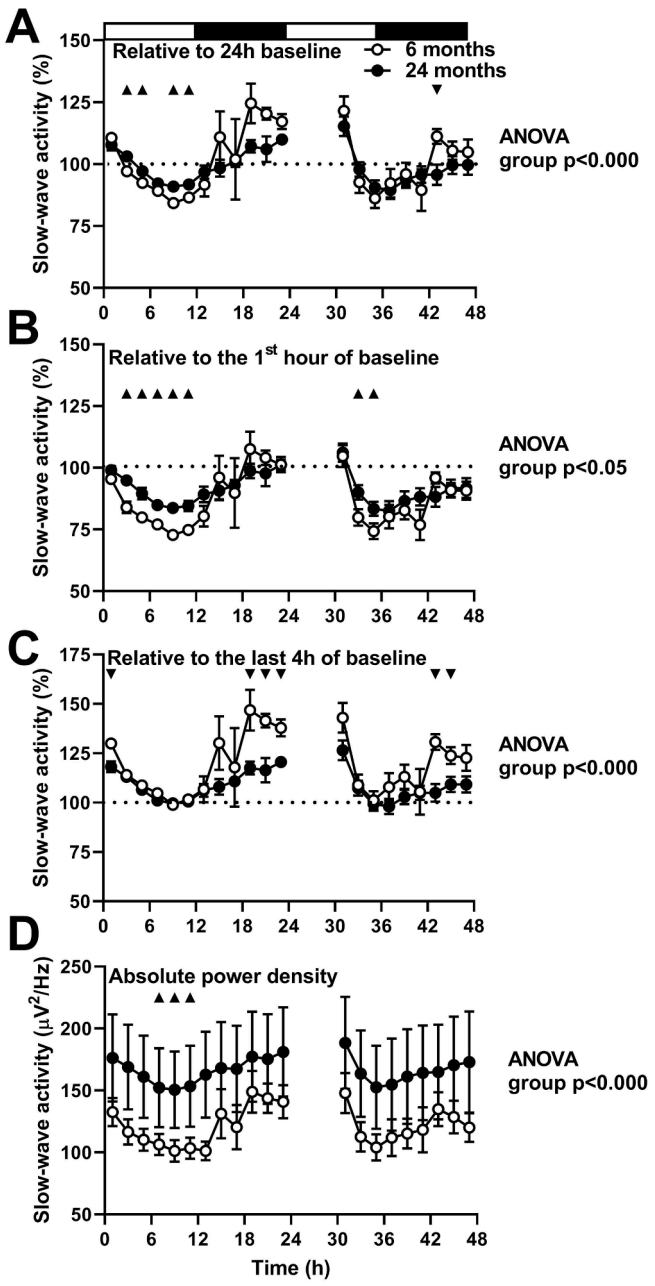

Fig. 1. Time course of hourly values of EEG SWA during NREM sleep (mean ± SEM) over 48 h in young (6 months, n = 11) and old (24 months, n = 9) male C57BL/6JOlaHsd mice that were housed under controlled conditions (12:12 h light:dark cycle; lights on at 09:00). The first 24 h consist of a baseline recording, which is followed by a 6 h sleep deprivation (gap in the data) and an 18 h recovery period. Triangles denote significant differences between age groups ($p < 0.05$, unpaired *t*-test) after significant ANOVA factor 'age group' (indicated next to each graph). The direction of the triangle indicates the direction of deviation of the old group compared to the young. The data in panel A-C are plotted relative to a different reference (A 100% is the 24-h baseline average, B 100% is the first hour of baseline, C 100% are the last 4 h of the light period of baseline). The data in panel D are plotted as absolute μV^2. Further explanation can be found in the text box. *The data were originally produced and published at an earlier study* [135].

assumed that this is for all groups compared a similar condition and therefore plotting SWA relative to the SWA produced during this period should allow a fair comparison between different groups of animals. When plotted like this, we see the opposite result compared to the methods in Fig. 1A and B. Particularly during the first part of the rest phase and the end of the active phase the older group has a lower SWA compared to the young group (See also [63,148]). These three types of standardization therefore result in two opposite conclusions.

In Fig. 1D, SWA is plotted in μV^2's, as is done in human sleep research on aging. This is possible here because the EEG recording system used is regularly calibrated by sending a known signal (here 10 Hz, 300 μV peak-to-peak) through the system, so it is known what signal enters the setup on the side of the animal and what amplitude and frequency comes out on the side of the recording system. The variability in SWA increases here, and in the older group this increase is even rather large. However, what is clear is that the older group shows levels of absolute SWA which are higher compared to the young and in some intervals this difference is significant. We have shown previously that this increase is specific for SWA in NREM sleep and that the difference over 24 h is significant [57] and [135], and this result was confirmed independently by two other groups [58–59]. The first conclusion is that in the course of aging in mice the change in absolute SWA shows an opposite direction (increase) compared to humans (decrease). Second, without forcing a specific methodological approach, we suggest that a uniform route is cautiously followed so that findings can be smoothly compared.

CRediT authorship contribution statement

M. Panagiotou: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **S. Michel:** Conceptualization, Methodology, Writing - review & editing. **J. H. Meijer:** Conceptualization, Methodology, Writing - review & editing. **T. Deboer:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

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

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