Brain Plasticity, Sleep and Aging

Chiara Cirelli

Department of Psychiatry, University of Wisconsin-Madison, Madison, Wisc., USA

This viewpoint discusses two concepts, namely that sleep quality and quantity can affect life span, as recent studies in flies seem to suggest, and, in turn, that impoverished wake experience in the elderly could contribute to poor sleep quality and quantity (fig. 1).

Sleep Duration and Mortality Risk

The relationship between duration of sleep and mortality risk was described in 1964 [1] and 1979 [2], and the findings have been replicated in over a dozen studies [for example, 3–12]. While the link between extremes of reported sleep duration and mortality risk is well documented [13], whether sleep duration per se affects longevity remains a highly controversial topic. Doubters have argued, for instance, that epidemiological studies can never fully control for comorbidities [14], while supporters have noted that epidemiological studies tend to control for comorbidities even when they should not [4]. More recently, it was pointed out that since reported sleep duration is not a reliable measure, extreme responses to the question ‘how many hours do you sleep at night’ may simply be indicative of overall poor health [15]. Moreover, most epidemiological studies that rely on self-reported sleep duration (without all-night EEG sleep recordings) suffer from another limitation, namely they cannot determine whether sleep fragmentation, with or without
changes in sleep duration, can also affect life span. This is important because individuals with disturbed sleep (i.e. who report either difficulties in falling asleep or regular use of hypnotics) have an increased risk of cardiovascular disease [7, 16], diabetes [17] and overall mortality [4, 8, 18]. One study that specifically tested only individuals with the same total sleep time (approx. 6.5 h/night), for instance, found that fragmented sleep per se is associated with increased levels of lipids, cortisol and blood pressure [19].

Even if one assumes that the association between sleep duration and mortality reflects a real effect of sleep, the big question that still needs to be addressed is about the underlying mechanisms and whether they are the same for short and long sleep. In many studies, long sleep has been associated with mortality even more strongly than short sleep, although the association between long sleep and mortality may be especially confounded by factors such as socioeconomic status or depressed mood [20, 21]. A recent epidemiological study in Japanese men and women found that sleep duration was associated with cardiovascular deaths and noncardiovascular, noncancer deaths but not with cancer deaths [12]. An increase in inflammation was suggested as a potential mechanism linking both short and long sleep to increased mortality risk in this study, while increased catecholaminergic tone and disrupted energy metabolism were suggested to account for the association between short sleep and increased mortality [12, 21]. However, these hypotheses remain speculative and rely on two major assumptions. The first assumption is that reported short sleep does indeed reflect a chronic decrease in sleep duration. The second (perhaps even greater) assumption is that a chronic decrease in sleep duration impairs health by causing changes similar to those known to occur during acute sleep deprivation and short sleep restriction, including decreased glucose sensitivity and increased insulin resistance [22, 23], increased blood pressure and heart rate [for example, 22, 24], blunted nocturnal decline in blood pressure [25] or increased metabolic rate [26, 27]. However, there is no direct evidence that either of these assumptions is correct.

The fruit fly *Drosophila melanogaster* has been used successfully to study life span and aging [28, 29]. Flies were used to prove for the first time that life span is an inherited trait [28], to test evolutionary and mechanistic theories of aging [30], to clarify how dietary restriction affects life span [31] and to identify genes that increase longevity [28]. Flies are also good models to study sleep [32, 33]. Indeed, an extensive analysis has shown that fly sleep shows most of the fundamental features that characterize mammalian sleep. Specifically, fly sleep (1) consists of sustained periods of quiescence associated with an increased arousal threshold; (2) is tightly regulated in a circadian and homeostatic manner; (3) is decreased by stimulants such as caffeine and increased by hypnotics; (4) is most abundant early during development and shows remarkable interindividual variability; (5) is characterized by changes in brain activity; (6) is accompanied by changes in the expression of genes involved in energy metabolism, synaptic plasticity and the response to cellular stress, and (7) is longer and deeper after sleep deprivation. Moreover, in mammals and flies, sleep deprivation impairs vigilance and performance as well as learning and memory. Fly mutations that decrease sleep duration also impair memory. Because of these similarities, *Drosophila* is now used as a model system for the genetic dissection of sleep [34].

Using forward and reverse genetics, several genes that affect sleep duration in flies have been identified [for a detailed list, see 35]. Forward genetics is an especially powerful method because it is unbiased, allowing novel genes to be discovered [34]. This approach first identified a short-sleeping line carrying minisleep, a loss of function mutation in *Shaker*, a gene coding the α subunit of a voltage-dependent potassium channel [36]. Subsequent studies found that loss of *Hyperkinetic (Hk)*, which encodes the β (regulatory) subunit of the Shaker channel, also results in a short-sleeping phenotype [37], although not as pronounced as that seen in Shaker mutants. Another forward genetic screen identified *Sleepless*, a muta-
tion in the *quiver* locus, which shows significantly reduced sleep time similar to *Shaker* mutations. In fact, *quiver* codes a ly-6/neurotoxin family member that has been shown to interact directly with the Shaker channel, and its loss reduces Shaker localization, kinetics and current density [references in 38]. Thus, two independent genetic screens identified a major role for the Shaker current in sleep regulation.

To shed light on the link between sleep duration and life span, we measured sleep and mortality risk in 3 short-sleeping mutant lines carrying a mutation in *Hk* (*Hk*¹, *Hk*² and *Hk*³) and in their wild-type siblings [38]. In previous studies, we and others had shown that *Hk* mutants have both short sleep and reduced life span [references in 38]. However, those studies could not determine whether the short sleep/mortality association is also present in wild-type (nonmutant) flies, which show large interindividual variability in sleep duration. Moreover, those studies could not tease apart the role of sleep amount from that of other factors, such as waking activity. This is an important point because most mutant short-sleeping lines tend to be hyperactive. Using Cox regression analysis, we found that in *Hk*¹ and *Hk*³ mutants and their control lines, there was a negative relationship between total sleep amount and hazard (individual risk of death) during the first 2 weeks and at 4 weeks of age, while no association was found in *Hk*² flies and their wild-type controls. *Hk*¹ and *Hk*³ mutants and their control lines also showed an association between total daily wake locomotor activity over the first 2 and 4 weeks of age and hazard. However, when both sleep duration and wake locomotor activity were used in the same regression, the effects of activity were much reduced, while most of the sleep effects remained significant. Overall, these data confirm the idea that life span is affected by many factors, including environment and genetic background, but also suggest that sleep may in some cases affect longevity. Of course, whether the link between sleep and life span is causal remains to be determined. However, these results suggest that if there is a causal relationship with life span, the causal variable is most likely sleep, not motor activity. Of note, we found that *Hk*¹ and *Hk*³ flies were short sleepers especially early in life, while *Hk*² flies only became short sleepers starting 2 weeks after eclosure. This suggests that the effects of sleep on mortality risk may be especially prominent early in life. In this study, we could not assess the effects of fragmented sleep independently of those of short sleep, because all parameters related to sleep quantity and quality were strongly correlated in all fly lines.

**Sleep and Aging**

In humans, aging is often associated with a decrease in total sleep duration, an increase in the time it takes to fall asleep and, most significantly, a decrease in sleep efficiency [39]. In other words, the percentage of time in bed spent asleep decreases progressively with age, from more than 90–95% in adolescents to less than 80% in 70-year-old subjects. Sleep composition also changes, with a relative increase in superficial sleep stages (stages N1 and N2) and a decrease in deeper stages rich in slow waves (N3, slow-wave sleep [39]). In fact, one of the most prominent sleep changes associated with aging is the decrease in slow-wave activity (SWA), which is already obvious in middle age [40, 41]. SWA, defined as the EEG power between 0.5 and 4 Hz during non-rapid eye movement sleep, is a convenient and quantitative way of measuring the number and amplitude of non-rapid eye movement sleep slow waves. More crucially, SWA is the best established marker of sleep need and sleep intensity, because it peaks at sleep onset and decreases with the time spent asleep. Moreover, staying awake from approximately 3 to approximately 24 h results in progressively higher SWA levels at sleep onset, and naps during the day reduce SWA the following night.

The slow waves are generated by the cerebral cortex, one every second or so, are especially prominent over frontal regions and travel along the cortical surface. Intracellular recordings have shown that SWA in the EEG is generated by virtually all cortical neurons engaging in a slow (<1-Hz) oscillation, consisting of a depolarized up state, when neurons show sustained firing, and a hyperpolarized down state, characterized by neuronal silence [42]. Theoretical considerations [43], large-scale simulations [44] and empirical studies [45, 46] indicate that the amplitude and slope of EEG slow waves is related to the number of neurons that enter an up state or a down state near synchronously and that synchrony is directly related to the number, strength and efficacy of synaptic connections among them. Converging evidence also shows that the more synapses that are potentiated during wake, because of learning, the more we need to sleep [reviewed in 47]. Thus, we have suggested that SWA can serve both as a marker of sleep need as well as a proxy for synaptic density/strength/efficacy [48]. Indeed, recent findings in both humans and animals suggest that rapid increases and decreases in synaptic strength (within the 24-hour cycle) due to synaptic plasticity during wake are reflected in similarly rapid increases and decreases in sleep SWA. In particular, there is compelling evidence that SWA can
reflect synaptic strength at a local level. For instance, in humans, SWA increases locally over the parietal cortex following learning of a visuomotor task, while arm immobilization during the day, which leads to a decrease in motor performance and sensory evoked responses, consistent with synaptic depression, is followed by reduced SWA over the contralateral sensorimotor cortex. Cortical potentiation and depression triggered in humans by paired-associative stimulation also result in an increase and decrease in SWA, respectively. In rats, training on a reaching task known to induce long-term potentiation results in a local increase in SWA in the activated motor region. Overall, these studies show that the need to sleep, assessed by SWA, is strongly affected by the amount of synaptic potentiation occurring during prior wake and can be regulated to some extent at the local level.

If sleep SWA reflects the density, strength and/or efficacy of cortical synapses, one should expect that long-lasting changes in synapse density, which occur across weeks, months or even years, are reflected in chronic changes in SWA. For instance, during the massive pruning of synapses occurring during adolescence, the absolute levels of SWA should decrease, and recent studies in adolescents confirm that this is the case [reviewed in 49]. Moreover, new data obtained using high-density EEG also indicate that the location of maximal SWA undergoes a shift in topography, from a peak in posterior regions to a peak in frontal regions, which seems to parallel brain maturation. Most importantly, these longitudinal SWA data obtained with EEG are consistent with data on synaptic density obtained from postmortem human brain tissues [50].

Do the low levels of SWA in the elderly reflect a decrease in synaptic density, strength and/or efficacy? There is no comprehensive analysis that has tried to correlate long-lasting absolute SWA changes in middle and old age with synaptic density data. Also, while it is known that the age-related decrease in SWA is prominent in frontal areas [51], the extent to which this reflects a more severe synaptic decline in frontal cortex relative to other cortical regions remains unclear. More crucially, the ability of the aging brain to show rapid (within the 24-hour sleep/wake cycle) homeostatic changes in relative SWA in response to learning during wake has not been studied. A few reports have analyzed the SWA homeostatic response after sleep deprivation, but with inconsistent results, some concluding that the SWA increase after sleep loss is similar in young and old age, others reaching opposite conclusions [40, 51, 52]. More experiments are needed, especially to test whether in the elderly, as in young subjects, learning and exposure to enriched, novel experiences can trigger strong homeostatic increases in sleep need and thus in SWA. If so, a richer wake, because of its effects on sleep pressure and intensity, may be at least one of the ways to ameliorate sleep quality in the elderly.

References


