Resting Our Cortices by Going DOWN to Sleep

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In this issue of *Neuron*, Vyazovskiy et al. reports on progressive changes in cortical unit activity within extended wakefulness and within extended sleep paralleling changes in EEG slow-wave sleep activity. Sleep debt may be integrated at the level of individual cortical neurons, providing support for the synaptic homeostasis theory.

In humans (and most mammals), sleep is regulated by the circadian clock and sleep homeostasis (Dijk and Czeisler, 1995). Humans are awake in the morning because sleep pressure is low after a night's rest. Through the day, increasingly strong wake-promoting signals, partially driven by the circadian clock, counteract the mounting sleep debt (or sleep pressure), keeping subjects awake. An opposite interaction occurs during the night. The circadian wake-sleep signal is approximated by body temperature fluctuations under constant conditions, peaking near 9 pm, with a low point at 4 am in humans. Whereas much is known regarding the molecular mechanisms regulating the circadian clock, little is known about what mediates sleep homeostasis.

Dramatic changes in neuronal activity occur across the entire brain between NREM sleep, REM sleep, and wakefulness (Amzica and Steriade, 1998; Huguenard and McCormick, 2007; Ji and Wilson, 2007; Marshall and Born, 2007; Mignot, 2008). This phenomenon is most obvious in the cortex, where deep non-REM (NREM) sleep manifests with low-frequency variations in surface potential that characterize slow-wave activity (SWA) on the electroencephalogram (EEG). At the neuronal unit level, these events reflect synchronization (<1 Hz) of cortical neuronal units between sustained firing (ON periods, which likely correspond to conditions of persistent membrane depolarization—"UP" states) and silent states (OFF periods, corresponding to membrane hyperpolarizations and "DOWN" states). Of special interest is the fact that SWA on the EEG is the best-known correlate of sleep homeostasis, or "sleep pressure." Indeed, prior experiments, notably those using the forced desynchrony protocol, have shown that SWA power on the EEG reflects the duration of prior wakefulness almost independently of circadian time (unlike other factors, such as the ability to fall asleep or stay awake) (Dijk and Czeisler, 1995).

Whether or not the occurrence of SWA leads to the feeling of rest after sleep is unknown, although SWA likely reflects a form of restorative process for local cortical circuits. Indeed, SWA in cortical areas that have had increased activity during the daytime, for example after daytime repetitive tasks, generate more SWA locally (Hanlon et al., 2009). Localized decreases in metabolic activity as measured using imaging during sleep at night is also evident more strongly in areas that have been activated during wake. Finally, SWA can occur unihemispherically in some marine mammals who must keep on swimming most of the time, indicating a localized but essential process (Mignot, 2008).

Surprisingly, whereas changes in cortical and thalamic unit activity have been well studied across sleep states, prior to this study (Vyazovskiy et al., 2009) no-one had examined unit activity changes *within* sleep or *within* wake as a function of past sleep history. These authors used multiunit microwire arrays implanted in the rat barrel cortex to study single neuron activities in sleep and wake, and after sleep deprivation in long-term EEG recording studies. This study fills an important gap, studying whether cortical activity changes across wakefulness as it is extended (and thus subjects are more tired), or across sleep when SWA accumulates (and thus subjects are increasingly rested). Its major findings are the observation of progressive increases in neuronal activity during wakefulness, and of changes of the occurrence of DOWN/UP state distribution as sleep is prolonged. In SWS, DOWN states were found to become progressively shorter with less unit synchronization, a process paralleling decreased SWA on the EEG (Vyazovskiy et al., 2009). Higher levels of firing may thus be needed to counterbalance increased sleep pressure when staying awake for long periods of time, while the opposite happens when sleeping.

Based on simple energetics, and considering the fact that the cortex is a large portion of the human brain, these findings indicates that staying awake for longer and longer periods of time is more and more costly. Interestingly, based on these data, the increase in neuronal activity during extended wakefulness seems to continue for up to 3 hr of sleep deprivation, after which it saturates. It is tempting to speculate that with longer periods of time, unit activity does not increase further because of the occurrence of microsleep and/or increased difficulty of maintaining animals awake during extended sleep deprivation. In this context, 3 hr of continuous wakefulness may represent the reserve capacity a rat needs to face its ecological needs without wasting extra energy (robustness) (Mignot, 2008). In sleep, DOWN states (with associated overall decreased unit activity) are frequent and long lasting early in sleep, a phenomenon that should be associated with energy savings. As sleep debt decreases, the prevalence of UP states increases and eventually leads to wakefulness. Energy saving by the brain during

NREM sleep has long been one of the leading hypothesis explaining the selection pressure of NREM sleep (Mignot, 2008).

Whereas this hypothesis is in line with the data, it does not explain why neurons must still fire in synchrony during sleep as opposed to simply being silent, with the former presumably having a higher energy cost. One possibility may be the need to transfer memory back and forth from the neocortex to other brain areas, as shown for the hippocampus and visual cortex (Ji and Wilson, 2007; Marshall and Born, 2007). It is important to note that this study primarily examined the barrel cortex, and thus the conclusions especially regarding synchronization will need to be generalized to other cortical areas and between areas. The authors propose an elegant "synaptic homeostasis model," which builds on their earlier ideas regarding increases and decreases in synaptic strength during wakefulness and sleep (Tononi and Cirelli, 2006). In this model, wake is associated with learning, leading to long-term potentiation (LTP) and strengthening of glutamatergic synapses, a process that eventually becomes unsustainable as the energy requirement for maintaining connections and associated firing increases. Sleep then occurs, leading to a proportional synaptic downscaling, leaving only the most robust connections intact and reducing energetic requirements to those required only for the maintenance of crucial learned circuits. Synaptic downscaling during sleep would increase signal-to-noise ratio for remaining connections, improving performance. The fact that molecular and electrophysiological markers of LTP track homeostatic sleep needs in animals supports this hypothesis. For example, a large number of transcripts upregulated in concert with sleep debt independently of circadian phase include markers of glutamatergic transmission, such as homer1a, Arc/Agr3.1, and nptx2 (Vyazovskiy et al., 2008). In this model, SWA, a measure that decreases with decreased sleep debt (especially as measured by the ascending slope of individual slow waves) tracks unit synchronization, which is shown in this study to decrease with extended sleep. Whether or not SWA is a correlate or somehow needed for the downscaling process of glutamatergic synapses is however still unclear. Possibly, unit synchronization is needed to enhance neural representation (Miller and Wilson, 2008), reducing redundant local synaptic connectivity while keeping longer-range connectivity more intact.

Interestingly, and rather unexpectedly, waveform analysis of units in this study now suggests that the neuronal activity changes observed with sleep debt occurred in all three known types of cortical neuronal units, regular spiking, intrinsically bursting, and fast spiking (Vyazovskiy et al., 2009). As these units are believed to be both excitatory and inhibitory, the downscaling process may apply not only to glutamatergic but also to GABAergic neurons. This finding is surprising, as modeling work to date favored a shift in the balance of excitatory and inhibition toward inhibition as the major mechanism explaining the generation of localized SWA and associated reduced long-range corticocortical connectivity during NREM sleep (Esser et al., 2009). Note however that his finding is in line with the view that UP/DOWN state transitions are associated with balanced changes in excitation and inhibition (Haider et al., 2006). It may thus be that synaptic downscaling of these various neuronal types produces slight changes in activity balance between inhibitory and excitatory input that leads to the formation of synchronized activity. Recent studies in *Drosophila*, where glutamatergic transmission is not dominant, also suggest that the process might be general to other chemical subtypes (Miller, 2009).

The authors elegantly argue that the dramatic firing changes observed in this study occur largely independently of changes in the neurochemical balance of established sleep-regulating neurotransmitter, such as acetylcholine, adenosine, dopamine, histamine, norpinephrine, or hypocretin. As pointed out, however, careful studies of neurotransmitter release at the onset versus later stage of each sleep state remain to be studied to fully address this issue. The model is however more consistent with local homeostatic changes, possibly even at the single-neuron level, modulated by rather than driven by external neurochemical inputs. The fact that cortical reactivation induced by artificial local transcranial magnetic stimulation (as measured by SWA ascending slope) also tracks prior sleep homeostasis is also in line with the concept of local changes in architecture and synaptic organizations as mediators of SWA (Massimini et al., 2009).

Although this exciting study is a major step forward in our understanding of SWA and sleep homeostasis, much remains to be done to understand the complexities of sleep at the molecular and anatomical level. Whether or not the occurrence of SWA is responsible for the restorative feeling one feels after sleeping is unknown. Restoration can be induced without SWA, for example with the administration of benzodiazepines, drugs which primarily increase spindling activity, a form of synchronized thalamic activity (Huguenard and McCormick, 2007) that also reverberates in the cortex. Spindling is nonetheless also associated with synchronized and decreased cortical neuronal activity and thus could also be restorative through a similar process. Similarly, REM sleep, a state associated with a desynchronized, wake-like EEG, and hippocampal theta is likely needed for restoration (Mignot, 2008) and has a role in learning and memory consolidation (Marshall and Born, 2007). Other evidence suggests that decreased thalamic activity is the first event leading to sleep onset and associated light sleep prior to the occurrence of widespread SWA (Amzica and Steriade, 1998). Further, part of cortical SWA has been suggested to be of thalamic origin (Amzica and Steriade, 1998). Gating of cortical input by the thalamus has traditionally been suggested as a major feature of sleep onset and needed for the subsequent generation of SWA (Huguenard and McCormick, 2007).

To resolve these discrepancies, it has been argued that various sleep states reflect coordinated recovery of various parts of the brain, a phenomenon that could be deleterious if occurring all at once (Mignot, 2008). Like for circadian regulation, sleep may be grounded at the molecular, cellular, and network levels. Sleep would occur in all parts of the brain, providing some form of restoration for prior activity, but possibly with slightly different electrophysiological correlates. In REM sleep, more primitive and ancient networks, especially those located in the brainstem and the hypothalamus, would undergo neuronal

silencing, also explaining loss of thermoregulatory and locomotor control during this state. Cortical activation during REM sleep would have emerged later to sustain other functions, most likely for cognitive processing.

Based on this study and others, it is increasingly likely that SWA involves some form of local restoration through synaptic plasticity changes at least for cortical circuits, a major feature of human brain architecture. As one of the major functions of the cortex is learning and memory, much of its synaptic organization may be more influenced by prior activity than by circadian modulation. In this model, circadian modulation of synaptic organization may be more essential to the regulation of other, noncortical, non-memory-forming circuits. The finding that cortical unit activity changes with sleep debt independently of sleep and wake suggests that extended wakefulness has a cost for individual cortical neurons, in support of the synaptic homeostasis theory proposed by the authors.

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Conceptual Representation and the Making of New Decisions

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A key feature of an adaptive decision making mechanism is its ability to guide behavior even in new situations. In this issue of *Neuron*, Kumaran et al. report that conceptual representations, which allow generalization from one situation to another through their shared features, can guide decisions even when new problems are encountered via the hippocampus.

Everyone has an intuitive sense of what it means to make a decision, and it is perhaps for this reason that some scientists' careful investigations into decision making appear to some to lack a critical component—an account of how decisions are made in novel situations. According to the new findings presented by Kumaran and colleagues (2009) in this issue of *Neuron*, the ability to exploit information gained in one context when making decisions in a new context may depend on the hippocampus and on the way that it interacts with the ventromedial prefrontal cortex (vmPFC).

Recent years have seen a great blossoming of interest in the brain mechanisms of decision making. It has been suggested that a "standard model" of decision making is beginning to emerge from the abundance of data, much of it from functional magnetic resonance imaging (fMRI) studies of the human brain (Kable and Glimcher, 2009). In such models the vmPFC is assigned a preeminent role because activity in this region is often correlated with the *value* of the choice that is being taken by a subject (Tanaka et al., 2004). Some of the progress is due to the widespread adoption of computational accounts of reinforcement based learning that make quantitative predictions about values of choices on a trial-by-trial basis. It is just such quantitative predictions about value that have been correlated with vmPFC fMRI signals.

Typically, decision-making experiments ask subjects to choose between a limited number of responses, normally just two, again and again, sometimes for more