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Slow wave enhancements

Slow waves in the sleeping brain

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Abstract

The electrical brain activity revealed by the electroencephalogram (EEG) during wakefulness is characterized by a small amplitude and a rapidly changing pattern. During most parts of sleep, in the so-called non-rapid eye movement (NREM) sleep, which accounts for 80% of total sleep, the EEG exhibits a large-amplitude oscillatory pattern with a slow (one-second-long) periodicity. Such slow waves are believed to mediate the restorative function of sleep. Slow wave sleep is homeostatically regulated, i.e., a deficit causes a compensatory increase and an excess reduces its propensity. This paper elaborates on the nature of sleep slow waves, their homeostatic regulation, their influence on behavioral and cognitive function during wakefulness, and emerging methods for peripherally intervening during slow wave sleep to improve sleep quality and/or behavioral/cognitive function during wakefulness.

1. Introduction

Sleep is a state of reversible disconnection from the environment characterized by the quiescence and reduced responsiveness usually associated with immobility. Although the precise function of sleep remains to be elucidated, it appears that sleep primarily benefits the brain [1]. As stated in *Nature*, sleep is of the brain, by the brain, and for the brain [2]. Not surprisingly, the brain activity during sleep undergoes striking changes in comparison to that during wakefulness. In humans, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep cyclically alternate with a periodicity of approximately 90 minutes. REM and NREM sleep occupy approximately 20 and 80 percent of total sleep time, respectively.

NREM sleep includes lighter stages N1 and N2, as well as deep sleep N3 (also known as slow wave sleep). During NREM, cortical neurons are bistable, alternating between “up” and “down” states with an approximate periodicity of one second. Up states are associated with vigorous neural firing, whereas down states are associated with minimal firing [3]. This bistable pattern results in large-amplitude oscillations (slow waves), which are particularly prominent during slow wave sleep (see Figure 1). In humans, N2 sleep is the most prevalent in both the first and second halves of nocturnal sleep. However, the first half is characterized by a higher amount of N3 sleep, while the second half has a higher amount of REM sleep [4].

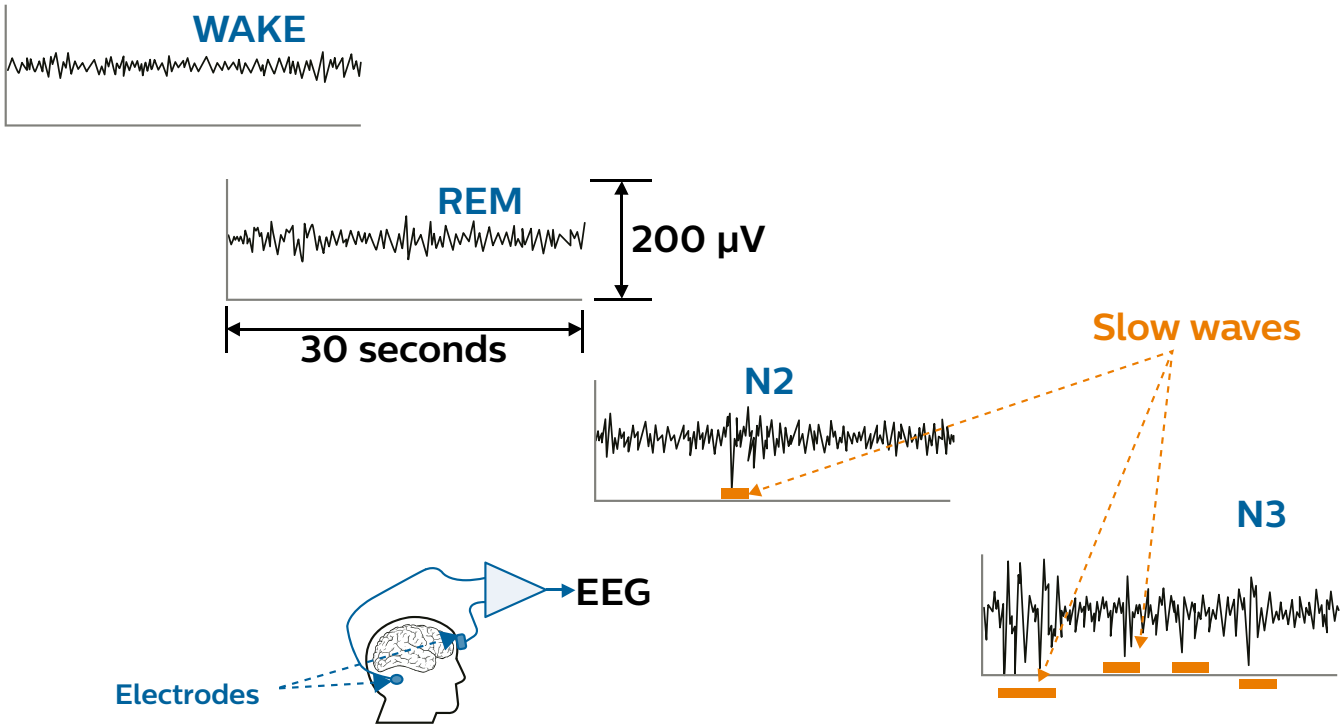

Figure 1: An electroencephalogram of the sleeping brain shows that slow waves characterize NREM sleep and are particularly prominent during N3 sleep.

A comprehensive hypothesis (Synaptic Homeostasis Hypothesis or SHY) about the function of sleep has recently emerged [5, 6]. According to SHY, plastic processes occurring during wakefulness result in a net increase in synaptic strength in many cortical circuits. As a consequence, when cortical neurons begin oscillating at low frequencies during sleep, these oscillations become strongly synchronized, leading to the occurrence of large slow waves in the EEG. The hypothesis also claims that slow waves in sleep do not merely reflect synaptic strength, but also play a functional role. As such, sleep slow waves serve to "renormalize" or downscale synaptic strength to a baseline level that is energetically sustainable and beneficial for performance.

2. Regulation of sleep and wakefulness

Two processes play a dominant role in sleep regulation: a sleep-dependent process (Process S) and a sleep-independent circadian process (Process C). Process S addresses sleep need, which builds up during wakefulness and dissipates during sleep. The longer the period of wakefulness is, the higher the level of sleepiness and the shorter the sleep latency become. The circadian component of sleep is unaffected by the occurrence of waking from sleep, and it appears to be closely related to the circadian rhythms of metabolic and endocrine processes [7].

The dynamics of sleep-need dissipation are linked to the temporal variation of the sleep EEG power in the 0.5-to-4-Hz band, which is referred to as slow wave activity (SWA) [7]. SWA is a quantitative measure of the number and amplitude of slow waves [6]. SWA has a typical behavior throughout the cyclic variations of a sleep night: increasing during NREM sleep, declining before the onset of REM sleep, and remaining low during REM. The level of increase in successive NREM cycles gets progressively lower. Figure 2 illustrates the SWA dynamics along with the corresponding sleep stages.

Sleep restriction causes an SWA increase during the next sleep opportunity following restriction. It is reported in *Human Neurobiology* that an extended waking period of 40.5 hours caused a massive increase of slow wave activity during recovery sleep [7]. Restricting sleep to four hours for four consecutive nights causes an SWA increase of approximately 20% in the first night following sleep restriction [8]. Conversely, a preceding daytime nap causes a reduction in SWA during subsequent nocturnal sleep [8].

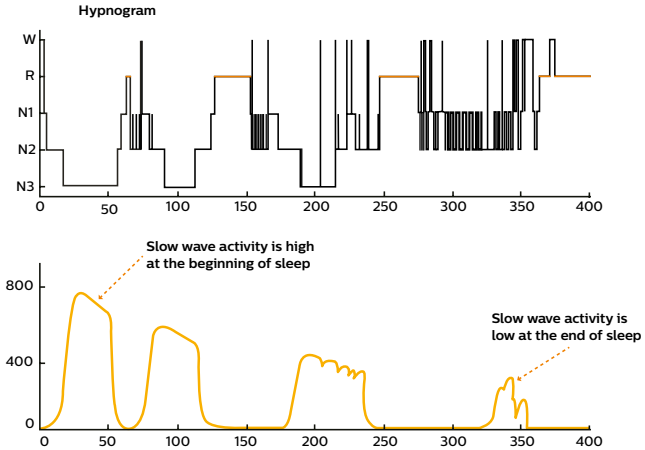

Figure 2: SWA increases during NREM sleep, declines before the onset of REM sleep, and remains low during REM. The level of increase in successive NREM cycles gets progressively lower.

3. Slow wave sleep and its impact on wakefulness behavior and cognition

Sleep plays an important role in the optimization of the memory-consolidation process, which results in quantitative and qualitative changes of memory representations [9, 10, 11]. Slow wave and REM sleep support system and synaptic consolidation by promoting specific patterns of neuromodulatory and electric activities. For instance, *Proceedings of the National Academy of Sciences of the United States of America* found that sleep slow waves are more synchronized following intense declarative learning [12], and according to the *Journal of Cognitive Neuroscience*, there is better retention of declarative memories after slow wave sleep than after a wakefulness control interval [13]. Furthermore, memories that are expected to be relevant in the future appear to be the ones that benefit the most from slow wave sleep [14].

Interestingly, a local increase of SWA can be observed in brain areas previously activated by a learning task during wakefulness. The increase in SWA after learning correlated with improved performance in the task after sleep [15]. Clear evidence of the beneficial role of sleep slow waves comes from studies in which selective slow wave deprivation during the night was carried out in healthy subjects. This manipulation, which did not affect sleep time and efficiency, prevented the improvement in performance after visuomotor and visuoperceptual tasks, and the changes in performance after slow wave deprivation were correlated with SWA changes, suggesting a causal role for slow waves in the sleep-dependent improvement of cognitive performance [15].

Slow wave sleep also plays a role in sleep quality. In a study aimed at finding objective correlates of subjective sleep quality, it is reported that quality relates to continuity (sleep efficiency) and depth of sleep (particularly duration of slow wave sleep) [16, 17]. The importance of deep sleep in explaining subjective sleep quality confirms the results of similar studies [18, 19, 20]. This is also in line with the hypothesis that slow wave sleep is crucial for the restorative value of sleep [5]. The *Journal of Sleep Research* stated that "subjective sleep quality seems to be a matter of slow wave sleep and sleep continuity" [17]. Not surprisingly, stress during wakefulness can have an adverse effect on slow wave sleep. It is reported in *Biological Psychology* that the anticipation of a difficult and stressful day curtails deep sleep and negatively affects subjective sleep quality [21].

4. Slow wave sleep enhancement

Given the importance of slow waves, a variety of methods to enhance slow wave sleep have been studied. Pharmacological GABAergic agents such as tiagabine can increase the time in slow wave sleep, but they fail to benefit memory consolidation [22]. Pharmacological methods can also lead to residual effects, which is why alternative strategies relying on peripheral (electric, magnetic, or sensory) stimulation have been proposed.

As reported in *Nature*, when intermittent transcranial direct-current stimulation (tDCS) was applied at 0.75 Hz for five-minute intervals separated by one-minute off periods after slow wave sleep onset, there was an increase in the EEG power in the slow-oscillation band (< 1 Hz) during the stimulation-free intervals, as well as enhanced retention of hippocampal-dependent declarative memories [23]. *PLoS Computational Biology* also found that tDCS accelerated the SWA homeostatic decay [24].

The precise impact of tDCS is difficult to characterize with EEG due to strong signal interference induced by the stimulation. Also, the complex pattern of activated/deactivated cortical areas following tDCS makes it difficult to predict the effect of the stimulation on sleep slow waves [25]. Transcranial magnetic stimulation (TMS) applied during NREM triggers slow waves that are indistinguishable from naturally occurring ones [26]. However, the long-term effect of repeated exposure to either tDCS or TMS is unknown [27], making it preferable to evoke sleep slow waves in a more natural physiological manner using sensory stimulation.

When the effects of somatosensory and auditory stimulation on SWA were investigated by *Medicamundi* [28], auditory stimulation appeared to be more effective in increasing SWA (see Figure 3). Furthermore, the topography of SWA increase due to auditory stimulation was observed to be very similar to the topography of SWA during natural sleep. High-density EEG analysis of the effect of auditory stimulation shows that the morphology, topography, and propagation patterns of induced slow waves were indistinguishable from those of spontaneous slow waves observed during natural sleep [27]. The slow wave enhancement effect of auditory stimulation is hypothesized to be the result of a "bottom-up" activation of large populations of cortical neurons in response to stimulation from the same mechanism that is responsible for arousing the organism [27].

4. Slow wave sleep enhancement *(continued)*

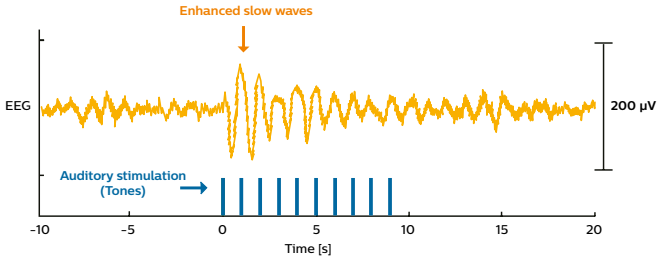

Figure 3: Sleep slow waves are enhanced through auditory stimulation.

In the *Journal of Sleep Research*, study participants were exposed to continuous auditory stimulation in the form of tones presented at a rate of 0.8 Hz, starting during wakefulness just before sleep and continuing for about 90 minutes into sleep [29]. Subsequent staging and EEG analysis showed an increase of power in the 0.5-to-1-Hz band (referred to as "slow oscillation") during the rhythmic stimulation, as compared to a sham condition with no stimulation. A related study [30] from the same author reports that auditory stimulation delivered through tones in phase with the ongoing rhythmic occurrence of slow wave up states substantially enhances slow waves, phase-coupled spindle activity, and consequently, the consolidation of declarative memory. Stimulation out of phase with the ongoing slow waves appeared ineffective. A follow-up study [31] tested the effectiveness of sequences of tones ("driving stimulation") presented in synchrony with slow wave up states versus a "two-click" condition where two tones are likewise presented in synchrony with slow wave up states followed by a pause of 2.5 seconds. Compared with a sham control condition, the driving stimulation prolonged slow waves and enhanced slow wave amplitudes, phase-locked spindle activity, and overnight retention of word pairs. However, the effects of the driving stimulation did not exceed those of the two-click stimulation. Thus, *The Journal of Neuroscience* suggests the presence of a mechanism that prevents the development of hyper-synchronicity during slow wave sleep [31].

In-phase stimulation was applied on older adults (age range of 60-84) in a recent study [32] using the phase-synchronized loop method described in the *Journal of Neuroscience* Methods [33]. Blocks of five tones ("on periods") were followed by equally long blocks without stimulation ("off periods"). SWA increased during on periods in relation to off periods, and the increase correlated with overnight improvement in memory consolidation (recall on word pairs). Based on testing involving four memory tasks (word pairs, serial finger tapping, picture recognition, and face-name association), *Sleep* concluded that the effect of auditory stimulation on memory seems to be specific to verbal associative memory [34].

5. Concluding remarks

The beneficial effects of sleep on the restoration of brain function are thought to be mediated primarily by neuronal slow oscillations that underlie the slow waves of NREM sleep. NREM sleep constitutes 80 percent of normal sleep and often 100 percent of sleep if conditions are stressful. The amplitude and number of slow waves can be quantified by the EEG power in the 0.5-to-4-Hz band, referred to as slow wave activity, which is used in the two-process model of sleep/wake regulation to characterize the dissipation of sleep need.

Enhancing slow waves should boost the restorative value of sleep. Slow wave enhancement can be achieved through transcranial electric/magnetic stimulation, but sensory (particularly auditory) stimulation is preferable because it relies on a more natural physiological effect and is more amenable to practical use. Numerous studies reviewed in this paper report the successful use of auditory stimulation to benefit slow wave sleep and memory consolidation.

Enhancing the restorative value of sleep based on auditory stimulation can be brought into practical use by consumers at home. A closed-loop system would allow for analyzing sleep EEG in real time, detecting ongoing EEG features (slow waves, spindles, microarousals), determining the optimal stimulation parameters, delivering the stimulation, and monitoring the results in order to adjust the next stimulation sequence.

References

1. Chiara Cirelli and Giulio Tononi. Is sleep essential? ***PLoS Biology***, 6(8):e216, aug 2008.
2. J Allan Hobson. Sleep is of the brain, by the brain and for the brain. ***Nature***, 437(7063):1254–1256, 2005.
3. Yuval Nir, Richard J Staba, Thomas Andrillon, Vladyslav V Vyazovskiy, Chiara Cirelli, Itzhak Fried, and Giulio Tononi. Regional slow waves and spindles in human sleep. ***Neuron***, 70(1):153–169, apr 2011.
4. Gary Garcia-Molina, Sreeram Vissapragada, Anandi Mahadevan, Robert Goodpaster, Brady A Riedner, Michele Bellesi, and Giulio Tononi. Probabilistic characterization of sleep architecture: home-based study on healthy volunteers. ***Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society***, EMBS, 2834–2838, 2016.
5. Giulio Tononi and Chiara Cirelli. Sleep function and synaptic homeostasis. ***Sleep Medicine Reviews***, 10(1):49–62, feb 2006.
6. Giulio Tononi and Chiara Cirelli. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. ***Neuron***, 81(1):12–34, jan 2014.
7. Alexander A Borbély. A two-process model of sleep regulation. ***Human Neurobiology***, 1(3):195–204, 1982.
8. Alexander A Borbély and Peter Achermann. Sleep Homeostasis and Models of Sleep Regulation. ***Journal of Biological Rhythms***, 14(6):559–570, dec 1999.
9. Lisa Marshall and Jan Born. The contribution of sleep to hippocampus-dependent memory consolidation. ***Trends in Cognitive Sciences***, 11(10):442–450, 2007.
10. Susanne Diekelmann and Jan Born. The memory function of sleep. ***Nature Reviews Neuroscience***, 11(2):114–126, 2010.
11. Björn Rasch and Jan Born. About sleep's role in memory. ***Physiological Reviews***, 93(2):681–766, 2013.
12. Matthias Mölle, Lisa Marshall, Steffen Gais, and Jan Born. Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. ***Proceedings of the National Academy of Sciences of the United States of America***, 101(38):13963–13968, 2004.
13. Werner Plihal and Jan Born. Effects of early and late nocturnal sleep on declarative and procedural memory. ***Journal of Cognitive Neuroscience***, 9(4):534–547, 1997.
14. Ines Wilhelm, Susanne Diekelmann, Ina Molzow, Amr Ayoub, Matthias Mölle, and Jan Born. Sleep selectively enhances memory expected to be of future relevance. ***The Journal of Neuroscience***, 31(5):1563–1569, 2011.
15. Reto Huber, M Felice Ghilardi, Marcello Massimini, and Giulio Tononi. Local sleep and learning. ***Nature***, 430(July):78–81, 2004.
16. Katherina K Hauner, James D Howard, Christina Zelano, and Jay A Gottfried. Stimulus-specific enhancement of fear extinction during slow-wave sleep. ***Nature Neuroscience***, 16(11):1553–5, 2013.
17. Göran Keklund and Torbjörn Åkerstedt. Objective components of individual differences in subjective sleep quality. ***Journal of Sleep Research***, 6(4):217–220, 1997.
18. Torbjörn Åkerstedt, Ken Hume, David Minors, and Jim Waterhouse. Good sleep—its timing and physiological sleep characteristics. ***Journal of Sleep Research***, (6):221–229, 1997.
19. Carolyn C Hoch, Charles F Reynolds III, David J Kupfer, Susan R Berman, Patricia R Houck, and Jacqueline A Stack. Empirical note: self-report versus recorded sleep in healthy seniors. ***Psychophysiology***, 24(3):293–299, 1987.
20. Meir H Kryger, Darlene Steljes, Zoe Pouliot, Herb Neufeld, and Troy Odynski. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. ***Sleep***, 14(5):399–407, 1991.
21. Göran Kecklund and Torbjörn Åkerstedt. Apprehension of the subsequent working day is associated with a low amount of slow wave sleep. ***Biological Psychology***, 66(2):169–176, 2004.
22. Gordon B Feld, Ines Wilhelm, Ying Ma, Sabine Groch, Ferdinand Binkofski, Matthias Mölle, and Jan Born. Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. ***Sleep***, sep 2013.
23. Lisa Marshall, Halla Helgadóttir, Matthias Mölle, and Jan Born. Boosting slow oscillations during sleep potentiates memory. ***Nature***, 444(7119):610–613, nov 2006.
24. Davide Reato, Fernando Gasca, Abhishek Datta, Marom Bikson, Lisa Marshall, and Lucas C Parra. Transcranial electrical stimulation accelerates human sleep homeostasis. ***PLoS Computational Biology***, 9(2):1–13, 2013.
25. Nicolas Lang, Hartwig R Siebner, Nick S Ward, Lucy Lee, Michael A Nitsche, Walter Paulus, John C Rothwell, Roger N Lemon, and Richard S Frackowiak. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? ***European Journal of Neuroscience***, 22(2):495– 504, 2013.
26. Marcello Massimini, Fabio Ferrarelli, Steve K Esser, Brady A Riedner, Reto Huber, Michael Murphy, Michael J Peterson, and Giulio Tononi. Triggering sleep slow waves by transcranial magnetic stimulation. ***Proceedings of the National Academy of Sciences of the United States of America***, 104(20):8496–8501, may 2007.
27. Michele Bellesi, Brady A Riedner, Gary Garcia-Molina, Chiara Cirelli, and Giulio Tononi. Enhancement of sleep slow waves: underlying mechanisms and practical consequences. ***Frontiers in Systems Neuroscience***, 8(October):1–17, oct 2014.
28. Brady A Riedner, Brad K Hulse, Fabio Ferrarelli, Simone Sarasso, and Giulio Tononi. Enhancing sleep slow waves with natural stimuli. ***Medicamundi***, 45(2):82–88, 2010.
29. Hong-Viet V Ngo, Jens C Claussen, Jan Born, and Matthias Mölle. Induction of slow oscillations by rhythmic acoustic stimulation. ***Journal of Sleep Research***, 10, aug 2012.
30. Hong-Viet V Ngo, Thomas Martinetz, Jan Born, and Matthias Mölle. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. ***Neuron***, 78(May):1–9, 2013.
31. Hong-Viet V Ngo, Arian Miedema, Isabel Faude, Thomas Martinetz, Matthias Mölle, and Jan Born. Driving sleep slow oscillations by auditory closed-loop stimulation—a self-limiting process. ***The Journal of Neuroscience***, 35(17):6630–6638, 2015.
32. Nelly A Papalambros, Giovanni Santostasi, Roneil G Malkani, Rosemary Braun, Sandra Weintraub, Ken A Paller, and Phyllis C Zee. Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. ***Frontiers in Human Neuroscience***, 11(March):1–14, 2017.
33. Giovanni Santostasi, Roneil Malkani, Brady A Riedner, Michele Bellesi, Giulio Tononi, Ken A Paller, and Phyllis C Zee. Phase-locked loop for precisely timed acoustic stimulation during sleep. ***Journal of Neuroscience Methods***, 1–14, 2015.
34. Miika M Leminen, Jussi Virkkala, Emma Saure, Teemu Paajanen, Phyllis C Zee, and Giovanni Santostasi. Enhanced memory consolidation via automatic sound stimulation during non-REM sleep. ***Sleep***, 40(3):1–10, 2017.

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