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Review article

Does delta sleep matter?

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After reading this article you will be able to:

1) Understand the defining characteristics of delta wave sleep and its importance in regulating various body processes
2) Appreciate that delta wave sleep has a number of important prospective functions in both the body and the brain

The functional significance of nearly all major biological systems, such as respiration, metabolism and circulation, are largely understood. Yet the functional reason(s) for why we sleep remains an elusive mystery. A multitude of diverse hypotheses have been proposed, including homeostatic restoration, thermoregulation, tissue repair, immune control, memory processing and, most recently, emotional regulation.[1] Many of these proposed hypotheses place emphasis on the deepest stages of human sleep, and, when viewed together, may provide meaningful insights into the question: does 'delta' sleep matter?

Delta sleep is characterized by high-voltage, low frequency (<4 Hz) electroencephalography (EEG) oscillations occurring most prolifically during stages 3 and 4 of nonrapid eye movement (nonREM) sleep, and represent the surface expression of underlying network synchrony between the thalamus and cerebral cortex (fig. 1).[2] As our understanding has developed, electrophysiological interest and characterization has also focused on the especially slow oscillatory range of <1 Hz,[3] which may play an import orchestrating role in modulating many of the neurophysiological signatures of nonREM sleep.

Delta sleep occurs most prolifically during stages 3 and 4 of nonrapid eye movement sleep.

The basic necessity for delta sleep has been elegantly illustrated by studies focusing on recovery sleep following total deprivation across numerous species including humans. These experiments demonstrate that it is delta sleep which rebounds most dramatically and dominantly in the hours that follow deprivation; indicating a particularly high homeostatic (and possibly evolutionary) demand for, and preservation of, delta sleep. Indeed, while only about 30% of the sleep lost during total deprivation is ultimately regained, *all* of the missed stage 4 sleep is recovered (with only half the lost REM sleep and little of stage 1 and 2 sleep being regained).[4] Such findings indicate a potentially obligatory need for delta sleep and signal a strong functional value.

The question, then, becomes what function(s) might delta sleep serve? Numerous hypotheses have been offered, and here we will first focus on those that are not specific to the brain (homeostatic regulation, tissue repair, thermoregulation and immune function), and second, turn our attention specifically to those involving cerebral function; where we highlight the role of delta sleep in learning and memory.

Delta sleep and the body

One proposed function of delta sleep involves homeostatic restoration: after a day of 'use', sleep restores chemical and physiological processes that have become depleted during wakefulness.[4] In support of this idea, the level of delta activity in the first half of a night's sleep

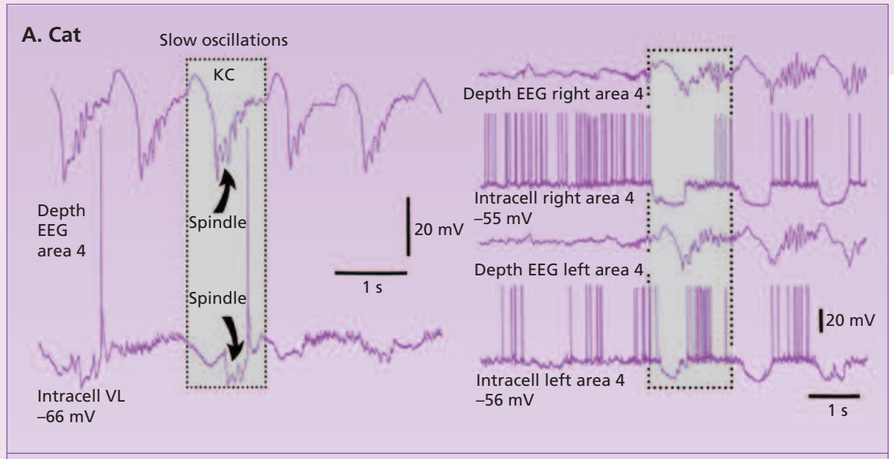

Figure 1. Relationships between the nonrapid eye movement (nonREM) oscillatory waveforms proposed by Steriade.[2]
(A) Combined intracellular (intracell) and depth recordings during nonREM sleep in the cat (VL, ventral lateral thalamocortical neuron).
(B) Scalp electroencephalography (EEG) in human stage 2 and delta (stage 3 and 4) nonREM sleep (A, reference electrode placed over mastoid process or auricle of ear; C, central scalp electrode; P, parietal scalp electrode). In the cat, the depolarized (excitatory) phase of the cortically generated slow oscillation (gray box in right panel of A) is believed to trigger and synchronize the characteristic nonREM thalamic combined spindle/K-complex (KC) waveform (gray box in left panel of A). In the human, a similar KC (left panel of B), as well as a similar temporal relationship between slow (S), delta (D) and spindle (s) oscillations (right panel of B), is seen during stage 2 nonREM. Reprinted from Neuroscience, Vol 101, Steriade M. Corticothalamic resonance, states of vigilance and mentation, p243–276, Copyright © 2000, with permission from Elsevier.

The more hours of wakefulness one accumulates, the more intense subsequent delta sleep will be.

appears to be strongly related to the relative amounts of prior sleep and waking, and thereby represents a marker of homeostatic sleep regulation (termed 'Process S').[5] Thus, the more hours of wakefulness one accumulates during the day (or the more sleep one has lost on previous nights), the more intense subsequent delta sleep will be. This rebounding effect has led to the suggestion that delta sleep provides a mandatory period of recovery or restoration for many organism systems. Indeed, some believe that delta sleep reflects general tissue repair following the 'wear and tear' of waking activities, a concept that is supported by the surge in growth hormone (GH) that corresponds with delta sleep early in the night, and the increase in delta sleep observed following daytime exercise.

A critical factor in development, GH is responsible for stimulating cell division and multiplication during early life stages, most crucially in bone formation, but it is also responsible for continued growth and maintenance of tissues throughout life. It is released from the anterior pituitary in a pulsatile fashion, and it varies in peripheral concentration throughout the day. However, GH reaches its highest levels during the first half of a night's sleep, in parallel with delta sleep predominance (fig. 2), with 50–70% of GH released during the early period of nocturnal sleep.[6] While some consider this tight

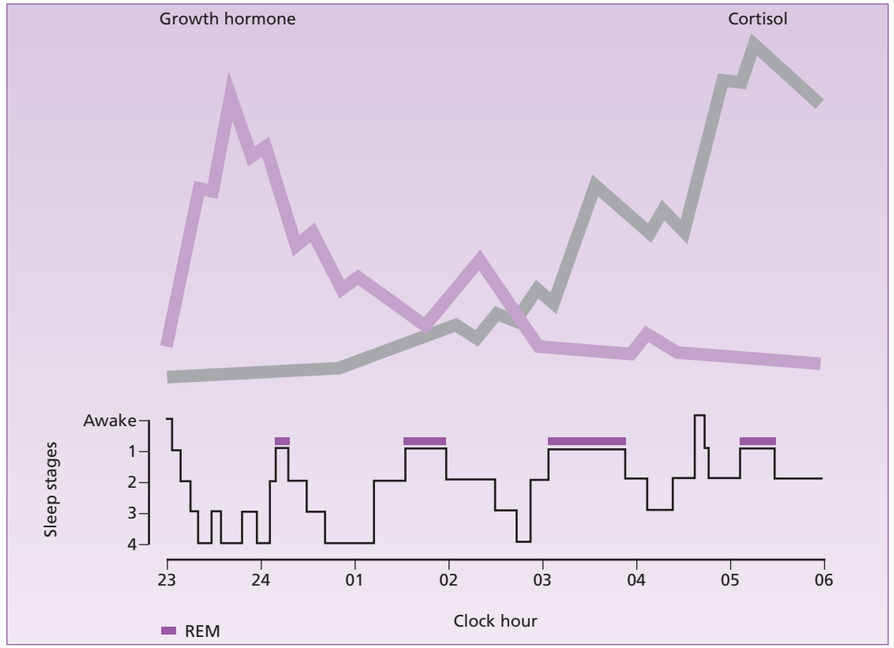

Figure 2. The relationship between sleep-stage architecture and circulating levels of growth hormone and cortisol.[7] Figure adapted with permission from Lavie P, The Enchanted World of Sleep. Copyright © 1996 Yale University Press.

Sleep may function to enforce rest and limit metabolic requirements.

relationship indicative of delta sleep function, others believe the correlation is better explained by the fact that sleep is a state of fasting, and as a consequence, GH is released as protection against catabolism rather than to enhance tissue repair and growth.

Delta sleep also increases in a responsive manner following exercise, particularly taken late in the day.[8] However, the sleep-enhancing effects are dependent upon an accompanying increase in body temperature. For example, if an individual is prevented from body temperature increases by being cooled with a fan during exercise, the sleep-promoting effects of exercise are prevented. Thus, metabolic expenditure in association with, or directly caused by, increased core body temperature may be a homeostatic trigger for delta sleep.

Indeed, thermoregulation itself may turn out to be an important function of delta sleep due to its role in energy conservation.[8] Body temperature significantly drops during delta sleep and it seems that achieving the proper (lowered) temperature potentiates delta sleep and thus results in energy conservation. This relationship appears to be consistent across phylogeny: a strong positive correlation has been demonstrated between total sleep time and metabolic rate in approximately 30 species of animals,[9] which suggests that sleep may function to enforce rest and limit metabolic requirements. Some even believe that delta sleep may have evolved in parallel with temperature regulation as an active mechanism for periodically forcing mammals and birds – with their relative high body temperature – to conserve energy. However, the energy-saving difference between quiet resting wakefulness and sleep, which is minimal relative to the environmental dangers caused by some species falling asleep, challenges the sleep-specific aspects of this theory.

When infectious agents are administered to animals, the probability of survival increases in those who sleep more.

Delta sleep has also been hypothesized to regulate immune function.[10] Rats deprived of sleep will die within approximately 3 weeks, and although it is not entirely clear whether death results from sleep deprivation per se, or from stress and other factors associated with deprivation techniques, dense infection is a strong factor in the mortality.[11] Consonant with this theory, when infectious agents are administered to animals, the probability of survival increases in those who sleep more, particularly in those who have enhanced delta activity,[12] which in turn is associated with an increase in white blood cell (immune participating) production. These data would suggest that delta sleep participates beneficially in regulating immune function and, as a consequence, promotes survival.

Interestingly, this relationship appears to be bi-directional: sleep not only regulates immunity, but immune function can also regulate sleep. Pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) all vary with the sleep–wake cycle and can directly influence sleep quality and structure.[13] For example, IL-1β and TNF-α play a modulatory role in sleep production and particularly in enhancing slow-wave activity[13] and when these pro-inflammatory cytokines are inhibited, so are the sleep inducing and delta-enhancing effects. In fact, when IL-1β and TNF-α are blocked, the normal delta sleep rebound that occurs following sleep deprivation is inhibited. These immune markers are thus believed to be important factors governing physiological sleep regulation. It therefore appears that delta sleep and immune function are tightly linked in a potentially causal and reciprocal partnership.

The early part of the night, dominated by delta sleep, may offer a selective consolidation benefit for memory.

Delta sleep and the brain

Given the broad evidence in support of these multiple theories, it seems unlikely that delta sleep serves a single function. Rather, delta sleep probably evolved to serve a variety of functions, and there is now good evidence that these extend beyond the body and include critical brain functions. In the remaining section, we focus on one of the most exciting and recently emerging of these cognitive faculties – memory processing; and its underlying neural basis – brain plasticity.[14,15]

In an effort to avoid confounds associated with sleep deprivation studies, experiments beginning in the 1970s investigated the benefit of normal sleep on memory function. These studies strongly implicated delta sleep in solidifying or 'consolidating' memory. Some of the earliest evidence involved participants learning a list of facts (pairs of words) and then, after a time delay, attempting to recall the words.[16] Participants who learned the words and were tested after the first half of a night of sleep (rich in delta sleep) demonstrated significant memory benefits. Yet, participants who were tested after obtaining sleep in the second half of the night (lacking in delta sleep) expressed no memory advantage, suggesting that this early part of the night, dominated by delta sleep, may offer a selective consolidation benefit. This result has since been replicated many times, with different types of memory stimuli and with efforts made to control for confounds such as interference effects and circadian influences, confirming the role of delta sleep in stabilizing newly learned facts.[17]

The increase in hippocampal reactivation during delta sleep is proportional to the amount of improvement seen on the task the next day.

Evidence from neuroimaging experiments (e.g. functional magnetic resonance imaging and positron emission tomography) provide additional support for the relationship between delta sleep and memory. For instance, initial daytime learning of a virtual-maze task is typically associated with signature activity in the hippocampus – a structure that is critical for normal memory function.[18] During subsequent delta sleep, there is a re-emergence or 'replay' of this hippocampal activation, as if the brain is reprocessing recently learned information. The most compelling finding, however, is that this increase in hippocampal reactivation during delta sleep is proportional to the amount of improvement seen on the task the next day. This suggests that the re-expression of hippocampal activation during sleep reflects the off-line processing of memory traces, which in turn leads to the strengthening of brain network connections and resulting in improved memory performance.

In addition to classically defined slow delta waves (1–4 Hz), the very slow cortical oscillation (<1 Hz) also appears to be important for memory consolidation. Marshall and colleagues showed that experimentally boosting human slow oscillations in the prefrontal cortex results in improved memory performance the following day (fig. 3).[19] Following learning of a word-pair list, a technique called direct current stimulation (DCS) was used to induce these slow (in this case, 0.75 Hz) oscillation-like field potentials during early delta-rich sleep. The DCS not only increased the amount of delta sleep during the simulation period (and for some time after), but also enhanced the retention of these hippocampal-dependent factual memories, suggesting a causal benefit of delta sleep neurophysiology.

In recent years, an orthogonal memory theory of delta sleep has emerged, called the 'synaptic homeostasis model'.[20] This model considers delta sleep a neurobiological state that actively promotes the *decrease* of synaptic connections,

not their increase. Accordingly, plastic processes, such as learning and memory occurring during wakefulness, result in a net increase in synaptic strength in numerous brain circuits. The role of delta sleep, and the slow oscillation in particular, is to selectively downscale or 'depotentiate' synaptic strength back to baseline levels, but in doing so, also

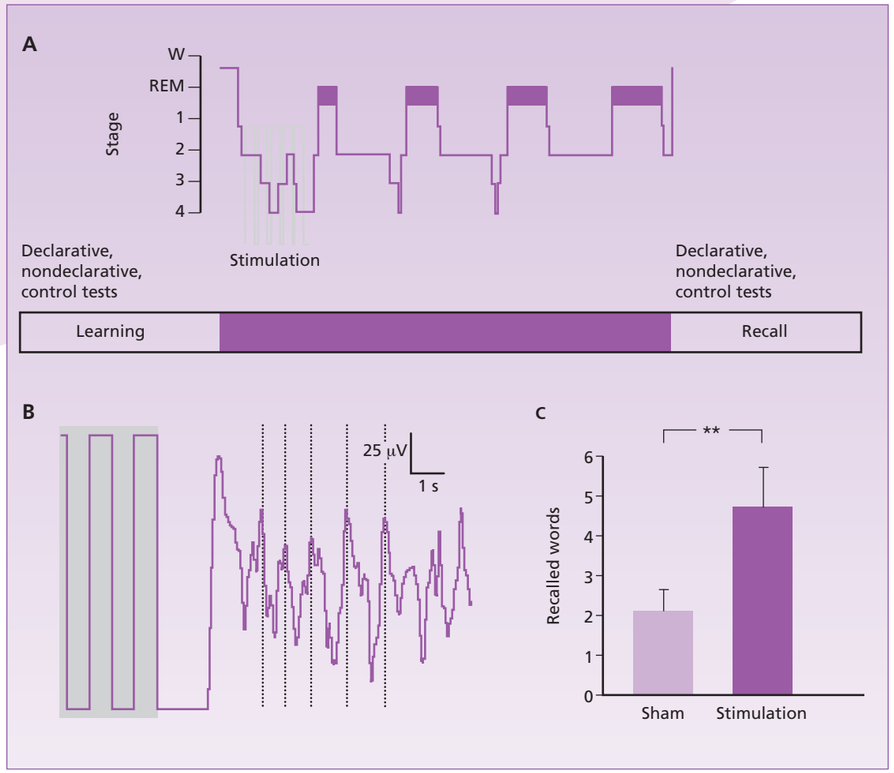

Figure 3. Overnight improvement of memory by experimental stimulation of slow oscillations.[19]
(A) Time-course of experiment. Indicated are time points of learning and recall of memory tasks, psychometric control tests, stimulation intervals, period of lights off (horizontal gray bar), and sleep represented by a hypnogram. W, wake; 1–4, sleep stages 1–4.
(B) Slow oscillatory electroencephalography (EEG) activity following a 5-min period of 'direct current stimulation' (DCS; shaded areas), demonstrating post-stimulation synchronization of slow EEG activity at prefrontal sites (Fz).
(C) Performance on the declarative paired-associate memory task across the retention period of nocturnal sleep following DCS and sham stimulation. Performance is expressed as difference between the number of correct words reported at recall testing and learning. (***P*<0.01). Reprinted by permission from Macmillan Publishers Ltd: Nature 444: 610–613, copyright © 2006.

sculpt and leave behind a more efficient and lean memory trace. This model predicts both a more refined and relatively strengthened memory (the basis of consolidation), but also the prevention of synaptic over-potentiation, resulting in saturated brain plasticity which would effectively negate new learning the next day. A number of human studies have provided evidence supporting this model. For example, it has been shown that the learning of motor skills during the day subsequently triggers locally specific increases in cortical delta sleep activity at night, the extent of which is proportional to both the amount of initial daytime learning and the extent of next-day improvement (fig. 4).[21] Furthermore, experimentally impairing the amount of experience-dependent learning during the day produces the opposite effect – reduced amounts of delta activity in associated cortical

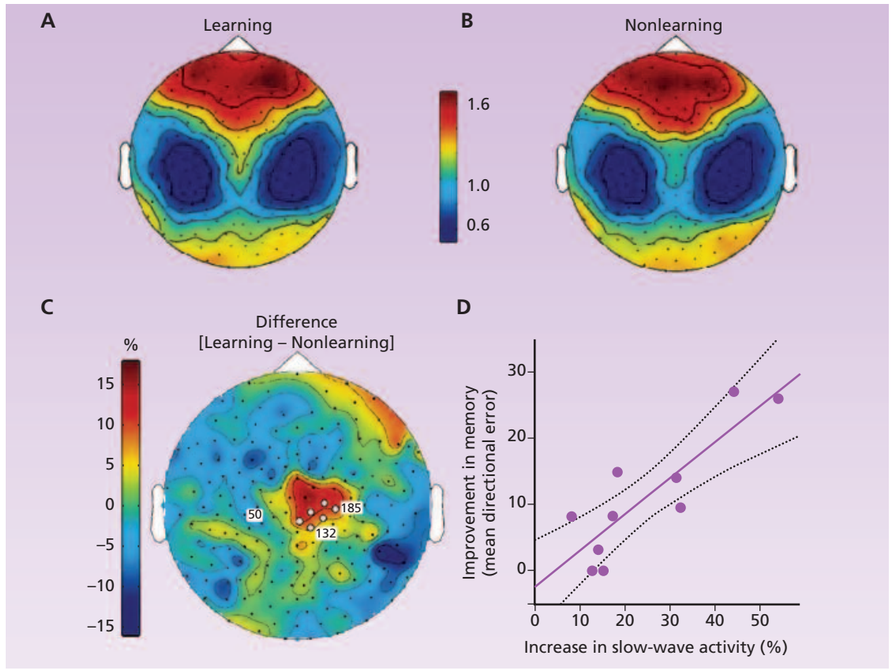

Figure 4. Delta sleep and motor-skill memory.[21] Topographical high-density electroencephalography (EEG) maps of delta frequency activity (average power in the 1–4 Hz range) during nonrapid eye movement (nonREM) sleep following either (A) motor-skill learning or (B) a nonlearning control condition, together with (C) the subtracted difference between nonREM delta activity in the learning versus nonlearning condition, demonstrating a local homeostatic increase above the learning-related central-parietal brain region. (D) the correlation between the amount of overnight improvement on the task (measured the next day) and the extent of increase in delta activity across subjects. Reprinted by permission from Macmillan Publishers Ltd: Nature 430, 78–81, copyright © 2004.

regions.[22] These findings offer support to the concept of sleep-dependent neural pruning by delta sleep, the goal of which may be to regulate the neural architecture of the brain at a highly anatomically specific (rather than global) level, mapping onto the corresponding location of the memory trace in the brain.

Our knowledge of the molecular, cellular, network and whole-brain mechanisms generating delta sleep, and its biological consequence played out in the body, has increased exponentially over the last decade. With such advances have come increasingly sophisticated models attempting to explain the functional significance of delta sleep. These hypotheses include the regulation of immune function, body temperature, metabolic status, and, more centrally, learning, memory and brain plasticity. While a consensus on which of these functions delta sleep is a) necessary for, b) permissive too, or c) simply correlated with, is currently lacking, it is clear that the purpose will be multifunctional, not unifunctional. With the resolution of these questions will come the most important next-steps: 1) understanding the consequence of impaired and abnormal delta sleep that a vast array of clinical disorders can cause, and 2) most significantly, the challenge to restore delta sleep and its reliant functions, that perhaps for the first time, appears to be a scientifically realistic possibility.

Key messages

- Delta sleep is characterized by high-voltage, low frequency (<4 Hz) EEG oscillations occurring during stages 3 and 4 of nonrapid eye movement (nonREM) sleep.
- In the body, delta sleep appears to be strongly associated with the regulation of temperature control, metabolism and immune function.
- In the brain, delta sleep has most commonly been associated with memory processing, allowing the consolidation of newly learned facts, and in promoting the associated underlying neural mechanisms of brain plasticity.
- Together, these findings signify a critical role for delta sleep in both basic and complex life processes.

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