Mission statement
INSomnia and its Optimized Management
INSOM aims to provide practitioners with the best information on insomnia and its management from the world’s sleep specialists.

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Editor-in-Chief
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Jessica D. Payne, Matthew P. Walker

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Welcome to the tenth issue of INSOM. Dedicated to keeping primary care physicians and sleep specialists updated on key developments in the field of insomnia, INSOM delivers reviews and case studies of experts working in sleep medicine and the management of sleep disorders.

In this issue of INSOM, Jessica Payne and Matthew Walker examine the functional significance of delta sleep. Potentially playing a part in homeostasis, thermoregulation, immune functions, tissue repair and memory consolidation, the full role of delta sleep is not yet clear. Payne and Walker review the current research with a view to answer the question: Does delta sleep matter?

For many years insomnia was considered to be a symptom rather than a disorder and Sara Matteson-Rusby and colleagues address the issue of why we should treat insomnia. With insomnia still regularly undiagnosed and untreated, their article examines the costly and unrelenting nature of insomnia.

The link between insomnia and depressive disorders or anxiety is now firmly established and Paul Doghamji reviews two articles on the relationship between insomnia and anxiety and the impact of this association on patients.

Marie-Françoise Vecchierini reports on the 21st Annual Meeting of the Associated Professional Sleep Societies, held in Minneapolis in June, 2007. This congress report gives an account of the presentations covering the evidence for synaptic modification during wake and sleep, the effects of total versus partial sleep deprivation, how the deleterious effects of partial sleep deprivation vary among individuals, and the physiological manifestations of sleep fragmentation.

I am pleased to introduce a new feature – Ask the Editorial Board. In each issue a question will be picked from those submitted to us and will be answered by a member of the Editorial Board or other selected specialist. In this issue, David Neubauer responds to a question about how much change needs to be seen in traditional measures of a patient’s sleep for the change to be considered clinically significant.

I hope the diverse mix of articles in this issue will prove stimulating and educational. Any feedback that you may have regarding INSOM is most welcome, as are any suggestions for topics related to insomnia that could be examined in future issues.

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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 role(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. 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). In our understanding has developed, electrophysiological interest and characterization has also focused on the especially slow oscillatory range of <1 Hz, which may play an important orchestrating role in modulating many of the neurophysiological signatures of nonREM 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 less than one stage 1 and 2 sleep being regained). 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. In support of this idea, the level of delta activity in the first half of a night’s sleep occurs most prolifically during stages 3 and 4 of nonrapid eye movement sleep.
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’). 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. While some consider this tight

Figure 1. Relationships between the non-rapid eye movement (nonREM) oscillatory waveforms proposed by Steriade. (A) Combined intracell (intracellular) 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 spindle (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.

Figure 2. The relationship between sleep-stage architecture and circulating levels of growth hormone and cortisol. Figure adapted with permission from Lavie P. The Enchanted World of Sleep. Copyright © 1996 Yale University Press.
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 – 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.13 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.13

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. 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).16 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, caused by some species falling asleep, challenges the sleep-specific aspects of this theory. 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 activity14 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.

Sleep may function to enforce rest and limit metabolic requirements.

When infectious agents are administered to animals, the probability of survival increases in those who sleep more.
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 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). Furthermore, experimentally impairing the amount of experience-dependent learning during the day produces the opposite effect – reduced amounts of delta activity in associated cortical areas.

**Figure 3.** Overnight improvement of memory by experimental stimulation of slow oscillations. (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 (F). (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.

**Figure 4.** Delta sleep and motor-skill memory. (A) 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.
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 (NREM) 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.

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 unfunctional. 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 relevant functions, that perhaps for the first time, appears to be a scientifically realistic possibility.

References


After reading this article you will be able to:

1) Recognize how unremitting, disabling and harmful insomnia can be for patients
2) Understand that insomnia continues to be under diagnosed and untreated but should be a primary focus for treatment
3) Value the therapy options that are available for this disorder and know that they can be safely and effectively implemented

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Insomnia, when chronic, tends to be unremitting, disabling, costly, pervasive and harmful. These factors, in combination with the existence of effective treatments, provide more than sufficient justification for the perspective that insomnia should be a primary focus for treatment.

Insomnia is unremitting

There are very few studies on the natural history of insomnia. To our knowledge, there are a handful of such investigations. In general, these studies find that chronic insomnia does not spontaneously resolve and the presenting form of insomnia (i.e. initial, middle or late) tends to be unstable or variable over time. With respect to spontaneous remission, Mendelson and colleagues concluded that patients who reported difficulty sleeping at their initial assessment (average chronicity of 10 years) continued to report insomnia at two follow-up intervals (70% at 40 months and 88% at 64 months) (fig. 1). Insomnia is disabling

To date there are a number of investigations that suggest that individuals with chronic insomnia, compared with those without or occasional insomnia, have more difficulty with intellectual, social and/or vocational functioning (fig. 2). With respect to intellectual functioning, there are numerous studies documenting patients with chronic insomnia reporting impaired cognitive performance. In fact, this type of daytime complaint constitutes one of the defining attributes of insomnia as it is...