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Sleep deprivation and neurobehavioral dynamics

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Lifestyles involving sleep deprivation are common, despite mounting evidence that both acute total sleep deprivation and chronically restricted sleep degrade neurobehavioral functions associated with arousal, attention, memory and state stability. Current research suggests dynamic differences in the way the central nervous system responds to acute versus chronic sleep restriction, which is reflected in new models of sleep–wake regulation. Chronic sleep restriction likely induces long-term neuromodulatory changes in brain physiology that could explain why recovery from it may require more time than from acute sleep loss. High intraclass correlations in neurobehavioral responses to sleep loss suggest that these trait-like differences are phenotypic and may include genetic components. Sleep deprivation induces changes in brain metabolism and neural activation that involve distributed networks and connectivity.

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Introduction

Sleep as an adaptive state of dormancy is found widely throughout the animal kingdom [1]. Although its biological and behavioral functions have not been fully understood, there is substantial evidence that human sleep must be of sufficient duration and physiological continuity to ensure coherent levels of waking alertness, attention, cognitive performance and neurobehavioral effectiveness [2–4], and to avoid predisposing humans to adverse health outcomes [5]. Epidemiological evidence has linked habitually short sleep duration to excessive sleepiness, accidents, cognitive deficits, and more recently to increased risk of obesity [6], diabetes [7], hypertension [8], and all-cause mortality. Despite growing awareness of these risks, current surveys indicate that 35–40% of the adult US population chronically restrict their sleep to less than 7 hours on weekday nights [9], primarily for lifestyle reasons [10]. This makes chronic sleep restriction more common in modern cultures than acute total sleep deprivation, and it highlights the need to understand the dynamics of neurobehavioral changes induced by chronic sleep restriction intermittently followed by extended sleep for recovery [3]. Below we focus on recent scientific evidence on human neurobehavioral differences in response to acute total versus chronic partial sleep deprivation and the implications for the two-process model of sleep–wake regulation; phenotypic and genotypic factors related to responses to sleep deprivation; and neuroimaging evidence for the neural basis of the behavioral effects of sleep deprivation.

Chronic sleep restriction induces cumulative neurobehavioral deficits

Increased scientific focus on dynamic changes in sleep physiology and waking neurobehavioral functions during sleep restriction and recovery has revealed that the results of decades of experiments on acute total sleep deprivation cannot be used to precisely predict the effects of chronic partial sleep restriction. Although the former experiments are more cost-effective to perform than the latter, and hence more common, experiments on chronic sleep restriction have revealed the importance of much longer time constants in the biology of sleep homeostasis and waking functions.

A decade ago, well-controlled sleep-dose–response experiments found that chronic restriction of sleep to between 3 hours and 7 hours time in bed per 24 hours, for a period of 1–2 weeks, resulted in near-linear declines across days in behavioral alertness and cognitive performance [11,12]. The rate of these cumulative changes varied systematically with the degree of sleep restriction. The experiments also revealed that no matter what psychometric scales were used, participants subjectively underestimated the growing degradation of their neurobehavioral functions across days of sleep restriction [12]. Since then, the effects of chronic sleep restriction on human biology and behavior have been extensively replicated and expanded [4,13••,14•,15–18,19•,20–22]. This has included experiments confirming that the neurobehavioral effects of chronic sleep restriction are modulated by endogenous circadian phase — manifesting most severely at times of circadian 'night' [23–25].

Remarkably, the cumulative deficits in vigilant attention performance that developed over 14 nights of sleep

restricted to 4 hours per night were comparable to those recorded after 3 nights (64–88 hours) of total sleep deprivation [12], indicating that chronic partial sleep loss has the potential to induce waking brain deficits equivalent to even the most severe total sleep deprivation. These findings also suggested that the neurobiology underlying the behavioral effects of chronic sleep debt could continue to undergo long-term changes. Further evidence of such long time constants in homeostatic sleep pressure manifesting in waking neurobehavioral functions comes from an experiment by Rupp and colleagues [26••] in which the amount of baseline nightly sleep obtained before chronic sleep restriction affected both the rate at which behavioral and physiological alertness was degraded and the rate at which these deficits were reversed by repeated nights of recovery sleep.

Neurobehavioral consequences of sleep loss

Both acute total and chronic partial sleep deprivation induce neurobehavioral changes in humans beyond subjective sleepiness, despite motivation to prevent these effects. The most reliable changes include increased lapses of sustained attention (i.e., errors of omission) and compensatory response disinhibition (i.e., errors of commission); psychomotor and cognitive slowing; working memory deficits; slow eyelid closures; and reduced physiological latency to sleep, even when it is being resisted [3,4]. A recent experiment by Lo and colleagues [14•], and a meta-analysis [27••], have called into question the claim that sleep loss primarily degrades executive functions and reasoning. High-order cognitive functions can be diminished by sleep loss, but when this occurs, it is likely mediated by deficits in the ability to sustain wakefulness, alertness, attention, and to respond accurately in a timely manner. Moreover, sleep deprivation may prevent the now well-documented benefits of sleep for memory consolidation [28].

The most sensitive measures of sleep loss appear to be those that precisely track moment-to-moment changes in neural indicators of state (especially EEG, EOG, and functional magnetic resonance imaging (fMRI)), or behavioral indicators of the stability of sustained attention, such as the psychomotor vigilance test (PVT). The latter has proven to be among the most sensitive measures of acute and chronic sleep loss [2,29] in part because it prevents compensatory stimulation and lacks the aptitude and learning affects that confound other cognitive measures. It also has the advantages of reflecting performance that has ecological validity (i.e., vigilant attention is required for learning, safe driving, etc.). These characteristics and performance parameter optimizations make the new brief PVT-B a rapid assay for tracking the dynamic interaction of sleep homeostatic drive and circadian phase relative to sleep loss [30]. As importantly, rodent versions of the PVT have recently been developed and validated to be sensitive to both acute total sleep deprivation [31] and chronic partial sleep loss [32], enhancing feasibility of translational studies.

Sleep deprivation and the two-process model

According to the two-process model [33] sleep–wake behavior is regulated by a homeostatic process S (integrating pressure for sleep during wakefulness that dissipates during sleep) and a circadian process C (modulating sleep pressure depending on time of day). The two-process model is a theoretical and mathematical description of sleep–wake dynamics [34]. It predicts that the homeostatic drive for sleep decays during sleep at a much faster exponential rate than its build-up during wakefulness, as putatively reflected in the intensification of sleep EEG slow wave activity (SWA). The accelerated recovery is evident in sleep SWA increasing well above pre-deprivation (baseline) levels after acute total sleep deprivation. A recent study by Banks and colleagues [13••] revealed that this SWA response was much less dramatic following chronic partial sleep deprivation, accumulating modestly as sleep duration increased, exceeding pre-deprivation (baseline) levels only when sleep duration was increased to approximately 9–10 hours. This finding is supported by recent experiments on recovery responses in chronically sleep-deprived rats [35,36], and humans [21,37–39]. Thus, both recovery sleep duration and elevated SWA are correlated with essential neurobiological elements of sleep homeostatic response and recovery. Critical questions that remain to be answered include: first, why some neurobehavioral functions (e.g., subjective sleepiness) recover much faster than others (e.g., PVT performance stability) and second, whether 'recovery' actually 'resets' the sleep homeostatic drive, or whether it harbors underlying neurobehavioral vulnerability to further sleep loss. Both of these issues are major gaps in our current understanding of the meaning of 'recovery.'

While the neurobiology underlying escalating behavioral deficits induced by chronic partial sleep deprivation remains to be discovered, a promising advance recently has been made on the neurobiology of the two-process model prediction of a nonlinear interaction between process S and process C, which produces the dynamic modulation of neurobehavioral functions during acute total and partial sleep deprivation [23,24•]. A new report from Paul Franken's laboratory [40••] provides evidence that forebrain expression of the clock gene *PER2* responds to both sleep loss and time of day, making it a prime candidate for integrating C and S processes in the expression of neurobehavioral profiles during sleep loss.

Mathematical modeling of neurobehavioral dynamics

Modifications of the mathematical models based on the two-process model have been underway for two decades,