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Essay

"Deep Sleep": A Comparative Approach to Defining Meaningful Rest

Matt Gaidica

Department of Psychology, University of Michigan, Ann Arbor, 530 Church St, Michigan 48109, USA
mgaidica@umich.edu

Abstract: A modern definition of "deep sleep" is elusive despite being ubiquitously appreciated as an important physiological state supporting health and homeostasis. In modern times, human deep sleep is identified by specific bioelectric signatures in the electroencephalogram (EEG) emerging somewhere between periods of wakefulness. However, deep sleep has been used to describe states of quiescence well before the first electrical brain recordings in the late 1800s, highlighting its own evolution in both lay and medical literature. Furthermore, EEG states are not only ill-defined in most mammals outside of humans and laboratory rodents, but non-existent in some invertebrates. Given that all organisms rest and do so with seemingly well-defined utility, it remains a challenge linguistically, scientifically, and comparatively define what "deep sleep" means—or what it *should*—in a research context. Here, I explore standard definitions of deep sleep from a modern, comparative perspective, and discuss potential problems of using a strict and narrow definition of such a fleeting concept that has historically undergone significant updates. Finally, I suggest a path towards resolving inconsistencies around the meaning of "deep sleep" and consider whether it is truly reflected by any one measure.

Keywords: deep sleep; slow-wave activity; evolution; comparative; physiology; homeostasis

1. Introduction

There is not any one thing in the constitution of animals which is more to be wonder'd at than sleep. –Universal Journal, 1738

"Deep sleep" was a common term in pre-enlightenment literature, found among other sleep adjectives like "sound" and "quiet". Nineteenth-century physician Constantine Hering used "deep sleep" to describe sleep filled with snoring or the recollection of rich dreams (Hering, 1873) and around the same time, the French Jesuit Louis Richeome described the prolonged unfeeling and unconscious qualities of deep sleep as, *la mort petite*, or "short death" (see Ekirch, 2006). The Italian proverb rang true that "bed is medicine," and deep sleep strengthened the body, mind, and spirit. Even without rigorous investigation, it is clear that throughout history deep sleep was desirable, as opposed to what was sometimes called "hare sleep," referring to slumber that is broken, light, restless, anxious, or frightened.

What is deep sleep? Based not only on history (Figure 1), but building on qualities synonymous with depth, deep sleep should be a natural state poised somewhere between waking episodes that is (1) less prone to interruption (i.e. increased arousal threshold), (2) results in being rested, as indicated subjectively or through motor or cognitive performance tasks, and (3) contributes to objective measures of resiliency, health, or fitness. Assessing these three tenants from a comparative perspective appreciates their evolutionary origins and introspects from a first-principles approach. This approach also highlights that although many animals sleep "deeply", they also sleep differently, such that specific biophysical states may play different roles for, and paradoxically affect an organism (Affanni et al., 2001).

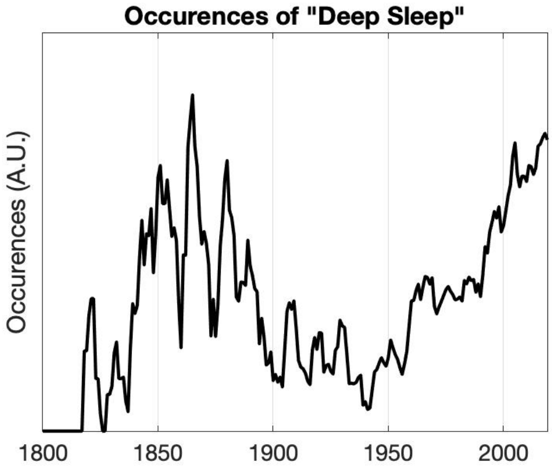
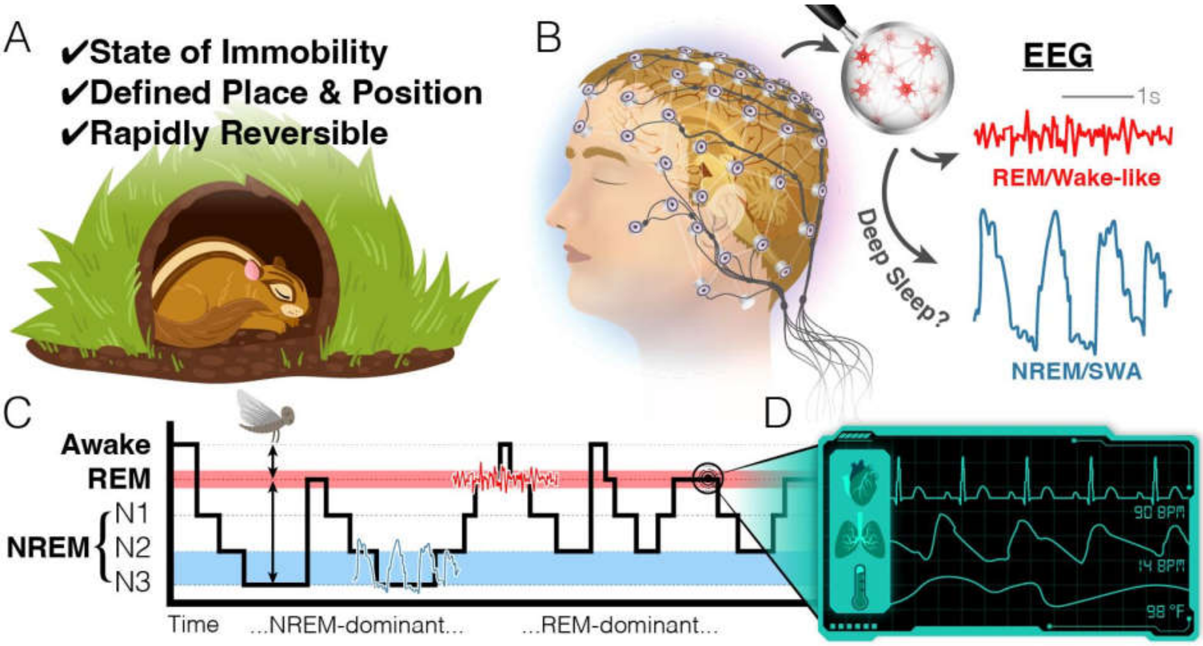


Figure 1. Occurrences of "Deep Sleep" in the English Corpus. Occurrences (y-axis) are given as arbitrary units (A.U.) representing the occurrence of the bigram "deep sleep" between years 1800-2019 (*Google Books Ngram Viewer*, 2022).

2. Deep Sleep Across Species

The fruit fly (*Drosophila melanogaster*) is from whom the basic mechanisms of the 24-hour circadian clock were first discovered (Konopka & Benzer, 1971). With only 100,000 neurons in their nervous system, fruit flies manage to engage in complex behaviors and have stereotyped, light-dependent sleep cycles (Xu et al., 2021). The fruit fly also exhibits a robust homeostatic response to sleep deprivation, consistent with the two-process model of sleep regulation whereby wakefulness accrues sleep pressure (Borbély, 1982). Sleep deprivation in fruit flies not only impairs vigilance and performance but results in longer and less fragmented 'recovery' sleep where the arousal threshold is increased (Cirelli & Bushey, 2008). Sleep intensity or "depth" in fruit flies was, for many years, equated to total sleep time. However, van Alphen et al. have identified a distinct "deep sleep" state in the fruit fly that serves synaptic homeostasis (2013) and functional waste clearance with electrophysiological correlates (2021; see also Iyengar & Wu, 2021). Therefore, it appears that sleep depth is well conserved and even in the most basic of organisms exhibits a complex relationship within and between other sleep states.

Although sleep states have been identified in fish, reptiles, and birds (Libourel et al., 2018), the most significant departure from understanding deep sleep in the fruit fly is the advent of the large and layered cortex in mammals (see Box 1). Physiological data indicate that mammals sleep in cycles that can have a relatively complex architecture, switching between REM and NREM many times between periods of wakefulness (Dimanico et al., 2021). What determines sleep architecture is a continuing source of scientific debate and inquiry. For example, it has long been thought that slow-wave activity (SWA) present during NREM sleep indicates the "deepest" form of sleep because it is positively correlated with previous waking time. That is, SWA "rebounds" after sleep deprivation, suggesting a causal contribution to homeostasis (Vyazovskiy et al., 2007; Yamazaki et al., 2020). Stressed rats also engage in more subsequent SWA during sleep which has been interpreted as a marker of resilience (Hargis et al., 2018; but see Yu et al., 2022). An apparent increase in arousal threshold in rats (*Rattus norvegicus*) during NREM, and specifically, SWA epochs, also seems to support the notion that NREM has qualities consistent with a deeper state of sleep (Neckelmann & Ursin, 1993; and in humans Bonnet & Moore, 1982) in the same sense that Richeome appreciated it (i.e. towards death). It has been questioned whether or not hibernation is a natural extension of "deep" NREM sleep (see Box 2). On the contrary, evolutionary theory predicts that predator-induced enhancement of REM sleep in wild-caught rats is an adaptation towards more time spent in a 'lighter' vigilant state (Lesku et al., 2008). More broadly, the trophic position in mammals has a significant correlation with the percent time spent in NREM sleep, which predicts apex predators are the privileged beneficiaries of more "deep" sleep (Lesku et al., 2006).



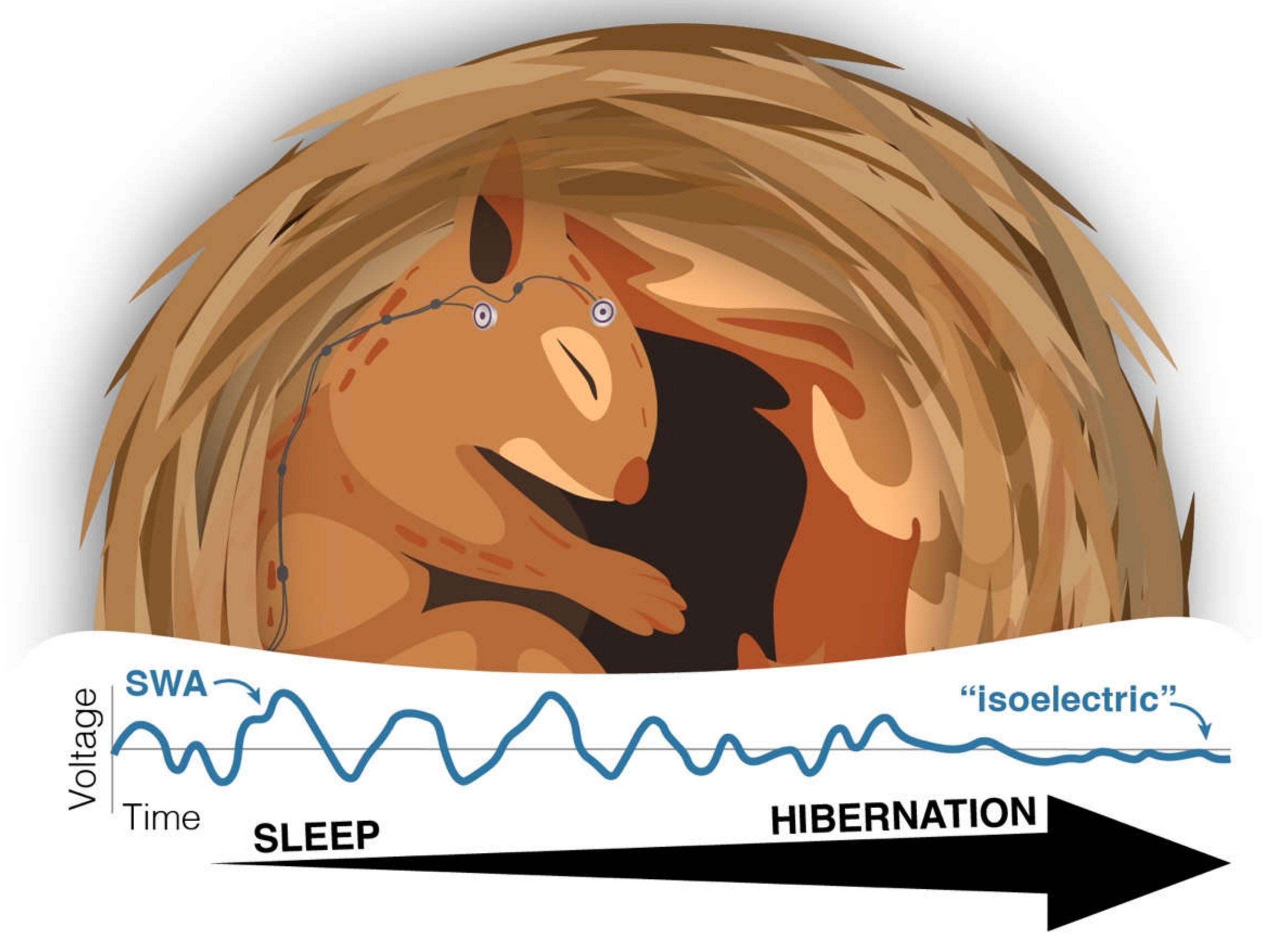
Box 1. The evolving definition of sleep from behavior to physiology. **(A)** The once behavioral definition of sleep, as an immobile state encountered in a defined place and position which is rapidly reversible, has evolved to require physiological (e.g., serving homeostasis) and neurologic criteria (Siegel, 2008). **(B)** Sleep "states" are now more strictly defined by extracellular fields and currents that emerge as brain rhythms from a diversity of neuronal cell types and their organization into distinct, hierarchical brain networks (Buzsáki et al., 2012). Brain rhythms are measured as a voltage via extracellular field potential (within the brain) or electroencephalogram (EEG, outside the brain). These brain rhythms tend to show up in patterns. Subtle, high-frequency rhythms—indicative of local brain computation and also typical of wakefulness—correlate with a fluttering of the eyes during sleep, giving it the name rapid eye movement (REM) sleep. High-amplitude, low-frequency rhythms—indicative of global brain communication—are also known as slow-wave activity (SWA) and are a signature of late stages of non-REM (NREM) sleep. In most, but not all literature, NREM/SWA is considered "deep sleep". **(C)** In humans and some other mammals, SWA is most prominent in the latter of the NREM states (N1-N3), but in smaller organisms like the fruit fly, this may be restricted to simpler substates (see Gottesmann, 1992; Lacroix et al., 2018). In many, but not all animals, sleep states will progress from NREM- to REM-dominant through a major sleep period. **(D)** Future sleep state classifications may rely upon an amalgam of physiological signals such as heart rate, respiratory rate, and internal body temperature to better represent the status and relationship of the brain and body at a particular point in time (Guo et al., 2022).

Humans have been integral in our understanding of deep sleep through its relation to psychomotor, cognitive, and memory domains. Changes in vigilance and sleepiness seem to be tightly linked with NREM-SWA sleep (Neu et al., 2015). For example, sleep "inertia" typical of early mornings and marked by impaired performance, reduced vigilance, and a desire to return to sleep, is worse when awakened from NREM versus REM sleep (Burke et al., 2015; Scheer et al., 2008; Trotti, 2017). NREM-SWA enhancement has led to improvements in memory consolidation (Bellesi et al., 2014; Diep et al., 2019; Leminen et al., 2017; Papalambros et al., 2017; Tononi et al., 2010) and sustained attention (Krugliakova et al., 2022), consistent with observational study analytics that positively correlate the amount of NREM to the degree of learning and memory performance in both overnight sleep episodes and naps (Alger et al., 2012; Niknazar et al., 2022; Schabus et al., 2005; Whitmore et al., 2022). In fact, SWA may not only be use-dependent, but have localized effects ("local sleep") on involved brain regions following motor and memory tasks (Geva-Sagiv & Nir, 2019; and in rodents Vyazovskiy et al., 2006). Intense, whole-body exercise will also boost subsequent SWA suggesting it either aids in recovery or at least reflects some homeostatic process (Park et al., 2021). One way of measuring coordinated brain-body states is to use heart rate variability (HRV), or the relative spacing between heart beats, as a surrogate for parasympathetic activation; HRV increases during states of rest-and-digest (Gaidica & Dantzer, 2020). Not only are SWA and HRV broadly coordinated, but enhancing SWA through external audio stimulation increases HRV (Diep et al., 2022) and decreases morning cortisol (Grimaldi et al., 2019). Remarkably, tactile peripheral stimulation can modify HRV and presumably alter SWA through the bidirectional autonomic pathways (Choi et al., 2020). Subjective sleep quality is also greater when HRV is high (Werner et al., 2015). Finally, SWA seems to be enhanced in states of fragility—injury, fatigue, and disease—which can be interpreted as a disaster response urging the nervous system to normalize (Gaidica & Clem, 2017). More "deep sleep," which many consider to be synonymous with SWA, is also associated with greater sleep efficiency (less awakenings) and mental toughness (Brand et al., 2014).

To summarize, most complex organisms exhibit periods of sustained quiescence with altered neural-physiological characteristics that reflect graded sleep depth. SWA has been a major focus of study because it appears to be well-conserved and has notable demonstrations of cause-and-effect on homeostasis and the regulation of stress and performance. However, the relatively straightforward identification of SWA relative to other sleep states may lead us to believe that it is unequivocally what matters most.

3. Emerging Inconsistencies

What is typically lost from the first total sleep deprivation (24 hours) studies in rats is the "massive" enhancement of REM sleep after sleep deprivation—nearly 200% above baseline (Borbély et al., 1984). Rechtschaffen (1999) later argued that the field has been "lulled" into believing SWA is critical for recovery, when in fact, total sleep deprivation results in huge and prolonged increases in REM sleep. Depriving rats of REM sleep required an increasing number of arousing stimuli over time which far exceed the relatively fixed arousal threshold for NREM, suggesting that REM sleep has an intensity dimension. The arousal threshold study discussed in the previous section also hides a critical confound in the details: spontaneous awakenings occur more frequently during REM, complicating the statistics in determining a latency to arousal (Neckelmann & Ursin, 1993). Surely, SWA within NREM has homeostatic correlates, but it may not be "worth more" in the grand scheme, as some authors propose (Dement & Greenberg, 1966).



Box 2. Is hibernation deep sleep? The narrative that hibernation and SWA are linked is plausible on the basis that both states are metabolically efficient (Franzini, 1992; Lyman, 2014; Madsen et al., 1991). Hibernation in ground squirrels (*Spermophilus lateralis*) is also entered through (or, preceded by) SWA-dominant sleep suggesting it might be an extension of "deep" sleep (Larkin & Heller, 1999). In ground squirrels, SWA is also increased after emerging from hibernation suggesting that hibernation does not fulfill an SWA-associated quota (Larkin & Heller, 1999; see also Walker et al., 1979). Brain activity during hibernation becomes isoelectric (i.e., no electric potential) and preemptive dietary changes engender physiological resilience to extreme cold (Sonntag & Arendt, 2019). Intermittent euthermic arousals during hibernation are mostly spent sleeping, periodically engaging SWA, such that this effect has been called "waking up to sleep" (Daan et al., 1991). One hypothesis suggests that SWA debt serves as a trigger to arouse from hibernation (Larkin & Heller, 1996). The effects of torpor—a lighter form of hibernation—on subsequent SWA are also dissimilar from sleep deprivation, suggesting that torpid states are not a deeper form of sleep (Strijkstra & Daan, 1998).

"Deep sleep" (as in, elevated SWA) is widely appreciated to promote neural consolidation due to SWA-dependent neural binding and restructuring (Bliss & Collingridge, 1993; Buzsáki, 1989; Diekelmann & Born, 2010). From this viewpoint, SWA-associated sleep is not a quiescent brain state, but rather an active one, restoring microwake-like neural activity and interactions (Dang-Vu et al., 2008). Interestingly, Kim et al. (2019) found that within the typical SWA band, specific oscillations preserved memories while others weakened them, a phenomenon also dependent on the nesting of higher frequency sleep spindles. Since most SWA enhancing protocols do not isolate these pro-memory forming slow oscillations, it is not surprising that many studies fail to show an effect of SWA on memory (Henin et al., 2019). Furthermore, when SWA is pharmacologically enhanced (e.g., ketamine anesthesia) short- and long-term memory suffers suggesting, at the very least, SWA must accompany a suite of other neural dynamics to produce an effect (Yang et al., 2021). On the other hand, the relative complexity of REM sleep—which approximates wakefulness—is akin to a moving target with respect to probing (or enhancing) its function (see Clawson et al., 2021; Harrington et al., 2021), but resolving this issue may be aided by investigating patterns of neuronal activity. For example, mulitneuronal activity presents as mnemonics (long and structured) when rats engage in a navigation task and replays with a similar temporal structure during REM sleep (Louie & Wilson, 2001). REM-specific memory consolidation may also be fundamentally different from the types of memories carried by short spindle bursts embedded in slow waves. This theory is consistent with the observation that REM sleep encodes procedural memories (i.e., containing order or structure) and NREM sleep encodes declarative memories (i.e., facts and events) (Plihal & Born, 1997). These results can also be appreciated through the precarious state of dreaming—mostly occurring in REM sleep (Crick & Mitchison, 1983; but see Domhoff, 2022)—which is story-like and contextual, potentially offering an opportunity to rehearse motor sequences or experience emotional states while offline (Stickgold & Wamsley, 2011). Although common REM-suppressing drugs (e.g., benzodiazepines, anticholinergics) were once leaned on as evidence that individuals can function normally without REM sleep (Wyatt et al., 1971), more recently this issue has been appreciated as an epidemic affecting mental, physical, and emotional well-being (Baglioni et al., 2016; Naiman, 2017; Neu et al., 2015). Even subjective measures of sleep quality have best correlated with REM sleep duration (della Monica et al., 2018). Taken together, it is unclear that "depth," as measured by restoration, health, or even memory, can be attributed to one sleep state (McCarter et al., 2022).

Albeit abbreviated, the inconsistencies presented here as to what best represents "deep sleep" may be reinterpreted through the hypothesis that NREM and REM sleep serve complementary roles. The first indication of this interplay comes from the observation that rats required entire, undisturbed NREM-REM cycles for the SWA enhancement to present after prolonged waking (Borbély et al., 1984). Hayashi et al. (2015) used a cell fate mapping approach to determine that not only do the regulatory circuits controlling NREM, REM, and wake states in mice share developmental origins, but artificially reducing REM sleep reduces subsequent NREM sleep. In animals such as reptiles, where these specific (and equivalent) cell progenitors are lacking, NREM and REM states are less obvious. However, NREM may also serve a feed-forward function in mammals, consistent with the observation that REM follows NREM in major sleep cycles. In this schema, widescale 'recovery' occurs in NREM sleep through SWA after which the brain transitions to REM sleep where a selection process occurs, effectively eliminating local brain networks that have stabilized (Vyazovskiy & Delogu, 2014). The progressive selection-for-removal of networks that require SWA is therefore reflected in the overall shift from NREM to REM predominance over a major sleep period. The increased ratio of REM to NREM in humans in infancy may reflect the relatively few neural networks established and therefore require synaptic downscaling, a function associated with NREM-SWA sleep (Carskadon & Dement, 2011). This chicken-and-egg predicament leaves the question remaining, which of these processes is "deep sleep"?

4. Conclusion

Casually attributing "deep" to "meaningful" is an error the sleep field continues to make that misconstrues the nuances and salience of sleep states. Whether it be to assess the impacts of new drugs or neuromodulatory therapies on sleep, it appears that more rigor in what is meant by depth or intensity should be defined in sleep research. This problem is in part complicated by the need to present science in lay, relatable, and impactful terms (e.g., 'more deep sleep matters most') that perhaps make the world seem simpler than the data actually suggests. It is notable that in the earliest handbook of standardized terminology for sleep state classification by Rechtschaffen and Kales (1968), the only two mentions of “deep sleep” attribute it both to NREM and REM states.

What is sleep depth, anyways? I proposed three tenants that seem to capture the instinctual, historical, and physiological qualities of deep sleep: [deep sleep is] (1) less prone to interruption, (2) results in being rested, and (3) contributes to resiliency, health, or fitness. These qualities are seemingly *not* associated with only one sleep state, and furthermore, there is emerging evidence that other biophysical processes, subjective measures, or long-term outcomes are critical to determining when sleep was, in fact, deep. The arbitrary definitions of “deep sleep” also fail to adjust for context: developmental and aging timelines that make it difficult to apply across individuals (McConnell et al., 2022) and clearly there are differences between the slow-wave states induced by anesthesia or even waking tasks (Kirmizi-Alsan et al., 2006) than those that naturally arise in the late NREM period.

The seemingly important relationship between sleep states, or the idea that sleep architecture as a whole has both a progressive and optimal form, makes applying importance to only fragments of this behavioral gestalt—that we call *sleep*—tenuous, at best. The relative heterogeneity of neural activity in REM sleep and “lighter” stages of NREM (e.g., N1, N2) may also guide research towards the more tractable states identified by SWA (Guo et al., 2022), such that there emerges an artificially reinforced focus on the latter. Just as we have found that there is far less “junk” DNA than we originally thought, it is unlikely that any sleep state is superfluous.

The field of endocrinology provides a model of the “deep sleep” predicament: the labeling of testosterone as a “male hormone” or cortisol as a “stress hormone” (MacDougall-Shackleton et al., 2019) is dubious and has caused a rift between working scientists, their funders, and public beneficiaries. To avoid a similar back-stepping in sleep research, “deep sleep” should be spoken of in terms of tenets that are historically and contextually accurate. In sum, sleep is a vibrant behavioral state with many outstanding questions that will continue to be pursued in diverse model systems. Surely, adjectivizing sleep (e.g., “deep”) will remain an urge we have, but it should be stated with careful thought and exceptional clarity.

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