

Spotlight

Defining slow wave sleep without slow waves

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Recent research by Parks, Schneider, and colleagues demonstrates that brain states during rodent sleep can be predicted from neural activity on millisecond and micrometer scales. These findings contradict the traditional view that defines sleep by brain-wide oscillations. Instead, this work posits that nonoscillatory activity governs different brain states.

A key challenge of neuroscience is to discriminate different brain states, such as wakefulness and sleep, with high spatiotemporal resolution. However, what are the unique characteristics that define sleep [1]? At the behavioral level, sleep is well defined as a periodically recurring and fully reversible state of reduced mobility, decreased arousal, lowered sensory awareness, and reduced responsiveness. At the neurophysiological level, the answer is more complex. Mammalian sleep is typically divided into multiple distinct stages: while rapid eye movement (REM) sleep is mainly defined by indirect electrophysiological markers (eye movements and muscle atonia), non-REM (NREM) sleep is hallmarked by the presence of cardinal sleep oscillations in surface electroencephalography (EEG) recordings, such as slow waves (<4 Hz) or sleep spindles (~11–16 Hz). Specifically, the presence of slow waves is the defining feature of deep NREM sleep, which is therefore also termed ‘slow wave sleep’ (SWS). Typically, sleep is staged in 30-s segments, a practice that dates back to early

EEG recordings when 30 s of EEG were printed per page. Even now, this historical convention prevails, given its convenience for visual inspection and manual sleep staging. Hence, the rich neurophysiological recordings during natural sleep, which often accumulate to millions of individual data points in modern multichannel recordings, are condensed into a highly discretized, low-dimensional trace: the hypnogram (Figure 1, top).

In a recent article, Parks, Schneider *et al.* [2] questioned the classic sleep-stage definitions. By combining high-resolution, large-scale electrophysiological recordings in mice (encompassing spikes and local field potentials up to 7 kHz) from up to ten brain regions with decoding approaches (convolutional neural networks; CNN), they demonstrate that the momentary sleep stage can be correctly predicted from neural activity on the timescale of 1–10 ms (a fraction of the slow wave cycle) and from very small patches of cortex (100 μ m; the fraction of what a typical EEG electrode covers). One key implication of these findings is that slow waves are not even necessary to identify SWS. Critically, classification performance was on par with human expert raters, who typically achieve ~80% inter-rater reliability. In sum, these findings stand in stark contrast to the classic conceptualization of sleep based on brain-wide sleep oscillations. Given that the CNN correctly classified brain states for a very broad range of frequencies that spanned four orders of magnitude, the authors conclude that the embedding of the momentary brain state is inherently nonoscillatory in nature and, hence, does not rely on the presence of cardinal sleep oscillations.

Nonoscillatory activity, also termed aperiodic or scale-free activity (for the lack of a defining periodicity), is the main source of human and rodent EEG background activity, but has often been discarded as ‘noise’, partly because historically, tools and concepts were

lacking to fully grasp its significance [3]. The key characteristic of EEG background activity is that it follows a 1/frequency ($1/f$) scaling law, where spectral power linearly declines as a function of frequency when visualized in log-log space (Figure 1, bottom right). This relationship between frequency and power often remains constant and scales over many orders of magnitude [4]. Given that scaling laws characterize self-organized dynamical systems, concepts from dynamical systems theory may offer valuable tools to understand how brain activity self-organizes during sleep. While scaling laws have long been suspected in the sleeping brain, technical limitations of earlier experimental setups hindered the ability to record sufficient neural activity to test some of the theoretical predictions.

While the relationship to power scaling laws was not made explicit in the article by Parks, Schneider *et al.*, the correct state classification over a broad range of frequencies points toward this intriguing possibility. By establishing these principles that define the spatiotemporal organization of the sleeping rodent brain, the results open new avenues to also study human sleep, for which neural recordings at the same fine-grained spatiotemporal resolution are not (yet) feasible. In fact, several recent studies that capitalize on new tools to quantify nonoscillatory activity [5], demonstrated that 1/f scaling in lower frequencies (up ~50 Hz) reliably discriminates different brain states, irrespective of the presence of sleep oscillations [6] (Figure 1). A key advantage of this approach is that 1/f activity can be quantified for every brain state, which proves beneficial for studying states that are not characterized by oscillations. One such example is human REM sleep, which has also been termed ‘paradoxical sleep’ for its nonoscillatory, wake-like EEG activity. In line with the idea that 1/f scaling reflects neural excitability [7], a recent study demonstrated that human REM sleep contributes to the overnight recalibration of nonoscillatory activity, which

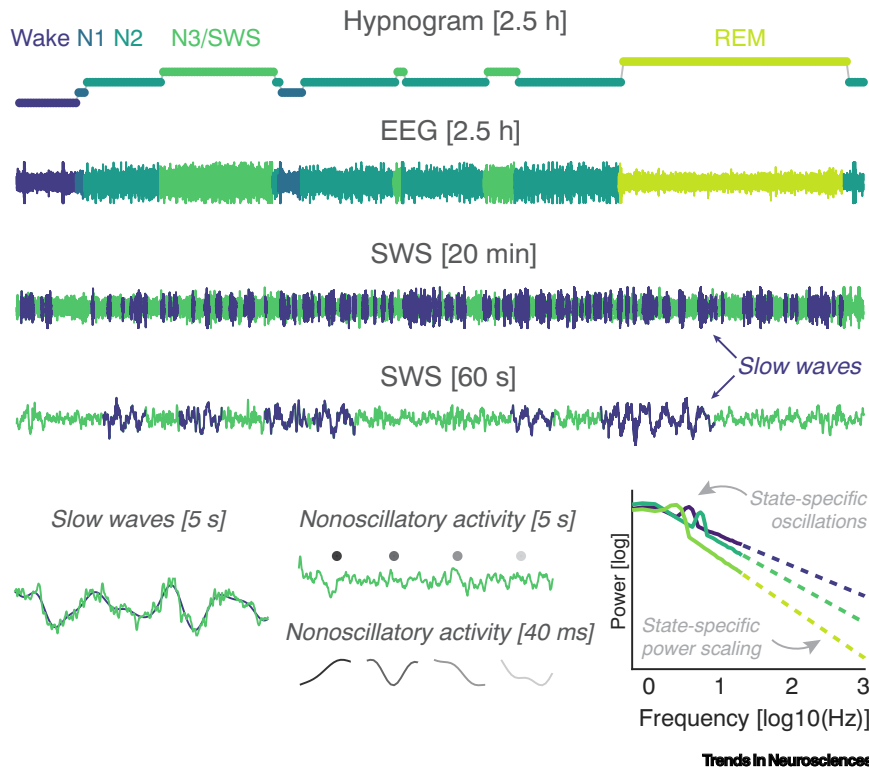


Figure 1. Defining brain states across spatiotemporal scales during sleep. In a recent publication, Parks, Schneider *et al.* [2] combined high-resolution, large-scale electrophysiological recordings in mice with decoding approaches, and examined the ability to predict momentary brain states during sleep based on neural activity at fine spatial and temporal scales. The figure illustrates how these findings might translate to human electroencephalography (EEG). Traditionally, sleep is considered a global brain state and is defined by the hypnogram (top row), which constitutes a low-dimensional abstraction of the underlying scalp EEG activity (second row). Sleep is typically staged in 30-s segments, mainly based on the presence of sleep oscillations, such as slow waves (dark blue, third row). Rows 3–5 zoom in on slow wave sleep (SWS) on increasingly shorter timescales. Parks, Schneider *et al.* examined even higher temporal resolutions. Their findings demonstrate that, in mice, the momentary sleep state can be detected from very short (ms resolution) and local (μm resolution) recordings [2], a fraction of what is typically considered necessary to define sleep. Among the key implications is that it might be possible to detect slow wave sleep from neural activity without notable oscillations (fifth row, center panel; the gray dots highlight the data points that are magnified in the bottom row). This nonoscillatory activity constitutes the main source of EEG background activity and displays an inverse relationship between frequency and power, which scales across many orders of magnitude, from milliseconds to minutes. An intriguing hypothesis for future work is that the identified spatiotemporal scaling can be extrapolated to human EEG activity based on state-specific scaling laws (fifth row, right panel, broken lines) [5–8]. This approach might help reach a better understanding of the neural dynamics of mammalian sleep. Abbreviation: REM, rapid eye movement.

predicted the success of overnight memory consolidation [8].

In sum, the findings by Parks, Schneider *et al.* provide a fresh perspective on the neurophysiological substrates that define brain states in mice, which opens multiple new avenues for future research. One exciting direction relates to the notion that

sleep not only constitutes a global phenomenon, but might also occur locally, with different brain areas drifting in and out of distinct sleep stages at different times [9]. While local sleep dynamics (as indexed by sleep oscillations) have previously been observed [10], the automated classification approach now enables a more nuanced perspective. It will be of

interest to understand how sleep oscillations in concert with nonoscillatory brain states jointly exert the benefits of sleep on cognitive and mental functions. Last, we foresee that the application of machine learning tools for automated brain state classification might help to illuminate the neurophysiological principles underlying altered brain states, such as coma or anesthesia, which are also characterized by ample slow wave activity. Ultimately, these advances might pave the way to addressing the fundamental question of why we spend one-third of our lives asleep.

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Declaration of interests

The authors declare no competing interests.

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References

- Nir, Y. and de Lecea, L. (2023) Sleep and vigilance states: embracing spatiotemporal dynamics. *Neuron* 111, 1998–2011
- Parks, D.F. *et al.* (2024) A nonoscillatory, millisecond-scale embedding of brain state provides insight into behavior. *Nat. Neurosci.* 27, 1829–1843
- Freeman, W.J. (2006) Origin, structure, and role of background EEG activity. Part 4: neural frame simulation. *Clin. Neurophysiol.* 117, 572–589
- Miller, K.J. *et al.* (2009) Power-law scaling in the brain surface electric potential. *PLoS Comput. Biol.* 5, e1000609
- Donoghue, T. *et al.* (2020) Parameterizing neural power spectra into periodic and aperiodic components. *Nat. Neurosci.* 23, 1655–1665

6. Kozhemiako, N. *et al.* (2022) Sources of variation in the spectral slope of the sleep EEG. *eNeuro* 9, ENEURO.0094-22.2022
7. Gao, R. *et al.* (2017) Inferring synaptic excitation/inhibition balance from field potentials. *Neuroimage* 158, 70–78
8. Lendner, J.D. *et al.* (2023) Human REM sleep recalibrates neural activity in support of memory formation. *Sci. Adv.* 9, eadj1895
9. Durán, E. *et al.* (2018) Sleep stage dynamics in neocortex and hippocampus. *Sleep* 41, zsy060
10. Nir, Y. *et al.* (2011) Regional slow waves and spindles in human sleep. *Neuron* 70, 153–169