Journal Club

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Human REM Sleep Delta Waves and the Blurring Distinction between NREM and REM Sleep

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Review of Bernardi et al.

Sleep is universal, irresistible, and heterogeneous. In mammals, sleep is traditionally divided into non-rapid eye movement (NREM) 1–4 and rapid eye movement (REM) stages, each with defining patterns of brain activity. Specifically, slow, synchronous delta waves, spindles, and isolated negative deflections define NREM sleep, whereas tonic, fast, unsynchronized activity characterizes REM sleep. Bi-stable neuronal activity patterns with depolarized “on-” and hyperpolarized “off-” states give rise to delta waves and are thought to enable NREM sleep to function in memory consolidation (Battaglia et al., 2004) and synaptic homeostasis (Tononi and Cirelli, 2014). In contrast, the activity patterns during REM sleep are thought to make this stage better suited for memory stabilization (Li et al., 2017) and integration (Sterpenich et al., 2014).

Recent evidence suggests that behavior is not as easily separable into brain-wide states, with emblematic neural activity programs and functions, as previously believed. Instead, ultradian cycles of neuronal synchronization and neuromodulation

may have general, brain-wide influences during which local brain activity is heterogeneous and can deviate from the global pattern. For example, local activation during NREM sleep (Nobili et al., 2011) and slow-wave activity (hereafter delta-range activities) in the awake brain (Vyazovskiy et al., 2011; Quercia et al., 2018), as well as in mouse primary cortices during REM sleep (Funk et al., 2016), has been documented; for a detailed review of these topics see Siclari and Tononi (2017). Thus, although it is convenient to divide human sleep into a small number of easily discernable stages, the reality may be far more complex. Indeed, several questions need to be addressed. Do humans, like mice, have local delta waves during REM sleep? If so, are these waves compositionally the same as those observed during NREM sleep? Do delta waves serve the same or different functions across arousal states? And is the distinction between NREM and REM sleep blurring? Many of these questions are answered by recent findings from Bernardi et al. (2019), published in the *Journal of Neuroscience*.

Using high-density electroencephalography, Bernardi et al. (2019) sought to determine whether humans have regional delta waves during REM sleep, akin to those recently shown in mice (Funk et al., 2016). Indeed, they distinguished two groups of delta waves occurring during REM sleep: slower (<2 Hz) waves, re-

corded in medial-occipital regions, present in both NREM and REM sleep, and faster (2.5–3 Hz), REM-sleep-exclusive, fronto-central/occipito-temporal “sawtooth” waves. Of these, the medial-occipital delta waves were often isolated, low in amplitude, and localized to the primary visual cortices when observed in REM sleep. Sawtooth waves appeared in bursts, were high-amplitude, and occurred alongside increases in REM. Unlike the NREM-sleep-like medial-occipital waves, which were linked to decreases in neuronal activity, sawtooth waves were positively correlated with high-frequency gamma activity and were thus considered to be cortically “activating”.

The observation of a rhythm traditionally viewed as a component of NREM sleep in specific regions of the brain during REM sleep builds on evidence indicating that sleep may operate in a local, as opposed to uniform, brain-wide, manner (Siclari and Tononi, 2017). Such local sleep is presumably accompanied or guided by quasi-global, state-specific influences and activities. That is, perhaps NREM sleep, already considered to comprise most of the total sleep period, does not turn off completely throughout the night, despite having some of its qualities periodically and regionally interrupted by REM sleep. Alternatively, activities traditionally considered as defining NREM sleep, such as delta waves, may not be stage-specific but instead operate locally

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during REM sleep, thus blurring the distinction between these stages. Regardless, it is clear that arousal states should not be distinguished solely by the detection of what have traditionally been thought to be stage-discrete activity patterns. Instead, net spectral power in the electroencephalogram and peripheral physiological measures, such as eye movement or changes in muscle tone, are the metrics that ought to be used when defining and discerning NREM and REM sleep.

The detection of NREM-sleep-like, medial-occipital delta waves during REM sleep, alongside activating, sawtooth delta bursts, supplements research indicating that waveforms operating within a defined spectral band are not limited to a single arousal state (Siclari and Tononi, 2017) and are not entirely homogeneous in structure and function (Siclari et al., 2014). When occurring in REM sleep, medial-occipital and sawtooth delta activity might be carrying out functions similar to those of NREM sleep delta, performing an unknown function specific to REM sleep, or operating more generally in sleep preservation.

During NREM sleep, brain activity in the delta range is implicated in systems memory consolidation (Maingret et al., 2016), synaptic homeostasis (Tononi and Cirelli, 2014), and sensory disconnection (Funk et al., 2016). The medial-occipital delta waves observed by Bernardi et al. (2019) might serve comparable functions in REM sleep. Although tonic neural activation during REM sleep strengthens synapses (Li et al., 2017) and might form associations (Lewis et al., 2018), elevated cholinergic tone disrupts hippocampal-neocortical dialog and likely prohibits the delta waves in this state from serving a systems-consolidation function (Gais and Born, 2004). Further, delta-range activities in NREM sleep are thought to facilitate the systems-level transfer of memory information from subcortical areas to cortical loci by phase-locking depolarizing up-states to hippocampal ripples and thalamocortical spindles (Maingret et al., 2016). The relative confinement of memory-reactivation-associated ripples and ripple-carrying spindles to NREM sleep bolsters the notion that the delta waves observed in REM sleep are not serving a systems-consolidation function. Even if an interregional dialog was to occur, delta-range activities in primary cortices (Funk et al., 2016; Bernardi et al., 2019) may impede signal propagation (Massimini et al., 2005) and preclude the integrative con-

solidation of connections to regions downstream of primary cortices, where memories typically reside (Binder et al., 2009).

Information is encoded during waking by the strengthening of synapses. Strengthened synapses are more likely to become activated and strengthen further, making these connections vulnerable to saturation. During NREM sleep, activity in the delta spectrum is thought to cause an adaptive renormalization of strengthened synapses (Tononi and Cirelli, 2014). However, the restriction of peaks in delta activity during REM sleep to lower-order cortical regions (Bernardi et al., 2019) not typically associated with memory storage makes it unlikely that synapse homeostasis is the principal function of delta waves in this state. Thus, systems memory consolidation and synapse renormalization are likely to be less prominent functions of the delta waves in REM sleep compared with those observed in NREM sleep.

During NREM sleep, the inhibition of thalamocortical relays and delta wave off-states are thought to disconnect the brain from the outside world (Lewis et al., 2015; Siclari et al., 2018). Funk et al. (2016) have suggested that the delta-range activity observed in primary, but not secondary, sensory cortices during REM sleep operates to ensure that this disconnect persists in REM sleep. The non-activating delta waves present in both human and rodent primary visual cortices during REM sleep might prevent visual stimuli and activating waveforms from evoking excessive arousal and behavioral state transitions. Such activating waveforms might include sawtooth (Bernardi et al., 2019) and ponto-geniculo-occipital (PGO) waves (Stuart and Conduit, 2009), which are discussed below. In this way, medial-occipital delta waves may ensure that memories being reactivated, strengthened, weakened, or integrated during REM sleep are not biased or contaminated by the external environment, as would occur if micro-arousals or awakenings were frequent.

Vivid, immersive, phenomenological experiences are a hallmark of REM sleep in humans. The richness of dreams relies in part on tonic cortical activation, this is evidenced by the observation that recurring off-states in NREM sleep diminish conscious experience (Siclari et al., 2018) and cause dream brevity. How then, is dream imagery so vivid during REM sleep if delta waves are present in the primary visual cortices? Dreams are often localized to higher-order multimodal areas of the

cortex and occur concomitant low-delta power in these regions (Siclari et al., 2017), although lower-order visual areas have also been implicated. The activating PGO waves observed in nonhuman species are a proposed brain substrate of dream imagery (Stuart and Conduit, 2009). The sawtooth delta bursts described by Bernardi et al. (2019) are said to resemble, and perhaps be a human correlate of, PGO waves. Therefore, these delta waves may be directly linked to one of the most defining attributes of human REM sleep, dreams.

By demonstrating local delta activity during REM sleep in humans, Bernardi et al. (2019) have provided new evidence against the notion of globally homogeneous sleep stages, with stage-discrete activities. These findings contribute to a growing body of literature indicating that sleep is largely local and that relevant activities, such as delta waves, are often not as monolithic in structure and function or as specific to a single, brain-wide state as was once believed. These discoveries mark an exciting moment for sleep science and prelude future research inquiring further into the distinctions between, and overlap of, NREM and REM sleep, as well as into the role of REM sleep delta waves.

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