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Sleepy Circuits in Vigilant Mice? A Slow Cortical Oscillation Occurring during Multiple Arousal States

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Review of Einstein et al.

Slow, synchronized neuronal oscillations in thalamocortical systems are hallmarks of sleep and inattentiveness. Sleep rhythms, such as slow (<1 Hz), delta (1–4 Hz), and spindle (7–14) oscillations, are associated with alternating periods of neuronal activation and quiescence that are synchronously enforced across disparate cortical and thalamic regions (Steriade et al., 1993a, b, c; Neske, 2016). This slow synchronized activity is thought to be well suited for synaptic plasticity and internally generated signaling (Steriade and Timofeev, 2003). In contrast, faster, more desynchronized activity characterizes active wakefulness, where it is thought to promote faithful encoding of complex sensory signals (Steriade, 2000). Slow rhythms do occur occasionally in the waking brain, but they usually occur more locally during wakefulness (Vyazovskiy et al., 2011), and they are abolished by active behavior or sensory stimulation (Poulet and Petersen, 2008; Tan et al., 2014).

A recent study in *The Journal of Neuroscience* (Einstein et al., 2017) presents several intriguing findings that challenge the notion that slow rhythms in the awake brain occur only during behavioral quiescence. Using whole-cell intracellular recordings from several neuron types in the primary visual cortex (V1) of awake, behaving mice, Einstein et al. (2017) found 3–5 Hz oscillations in neuronal membrane potential (V_m) that occurred with surprisingly high frequency (~1–7 oscillations per minute). While slow V_m oscillations in the delta frequency range have previously been reported from the cortex of awake mice, particularly during behavioral quiescence (Poulet and Petersen, 2008; Bennett et al., 2013; Reimer et al., 2014; Schneider et al., 2014; McGinley et al., 2015a), as discussed below, the oscillations reported by Einstein et al. (2017) exhibited several noteworthy features that have not been previously described or analyzed.

An immediately notable characteristic of the 3–5 Hz oscillations reported by Einstein et al. (2017) was their rhythmicity, curiously reminiscent of the clocklike delta oscillations of slow-wave sleep. Both within a recording from a single neuron and comparing across recordings of multiple neurons, the oscillations exhibited a stereotyped V_m signature: a sudden hyperpolarization, followed invariably within 250 ms by short (~100 ms), high-amplitude (~20 mV) depolarizing potentials occurring at 3–5 Hz, with a sharp peak in V_m power at 4 Hz. These oscillations lasted for ~2 s before the V_m returned to the low-amplitude, high-frequency activity classically associated with waking.

Another interesting feature of the 3–5 Hz oscillations was their dependence on visual stimulation. While the responses of V1 neurons to drifting sine-wave gratings diminished during the 3–5 Hz oscillations, the probability of occurrence of these oscillations strongly depended on the presence of visual stimuli. Specifically, oscillation probability rapidly increased within 2 s of stimulus onset. The authors probed the visual-stimulus dependence of the oscillations in two contexts: one in which the stimulus carried no behavioral relevance (passive viewing) and one in which the stimulus predicted reward during a Go-NoGo task in which mice had to discriminate the stimulus from a stimulus of an orthogonal orientation. While both passive viewing of the stimulus and presentation of the stimulus in the context of the task enhanced oscillation probability, the timing of the enhancement differed between these two conditions. During passive viewing, increased oscillation probability was locked to stimulus offset, whereas during presentation within the task, enhancement was locked to stimulus onset. Interestingly, the presence of oscillations did not clearly affect behavioral performance when the rewarded stimulus was presented: oscillation probability was comparable between hit and miss responses. Rather, oscillations often coincided with a suppression of a licking response, particularly during

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NoGo trials; oscillation probability was significantly higher during correct rejection compared with false alarm responses. In the language of signal detection theory (Green and Swets, 1966), 3–5 Hz oscillations seemed predominately associated with changes in decision bias rather than perceptual discriminability.

The most remarkable feature of the 3–5 Hz oscillations described by Einstein et al. (2017) was their apparent lack of dependence on behavioral or brain state. Several recent publications have combined pupillometry and locomotion monitoring with electrophysiological recordings in multiple cortical areas of waking mice, demonstrating that slow (<10 Hz) cortical activity is associated with low arousal (constricted pupil) and lack of locomotion, whereas this slow activity is consistently abolished during high arousal (dilated pupil) and locomotion (Reimer et al., 2014; Vinck et al., 2015; McGinley et al., 2015a,b). Yet, Einstein et al. (2017) found that 3–5 Hz oscillations were equally compatible with low and high arousal; oscillations occurred with comparable probability across a range of pupil diameters and during both locomotion and stillness. While the oscillations occurred regardless of baseline arousal level (as indexed by baseline pupil diameter), the onset of oscillations coincided with pupillary constriction and a reduction in walking speed, perhaps suggesting that the oscillations are associated with phasic decreases in arousal rather than low tonic arousal levels.

The observation of slow, rhythmic V_m oscillations in awake V1 is a significant finding, especially in light of the high probability with which these oscillations occur, even during high arousal states. Several questions emerge from this work. First, to what degree are 3–5 Hz oscillations spatially synchronized across cortex? Are they synchronized to a similar degree as sleep delta oscillations, or do they occur more locally? Einstein et al. (2017) performed electrocorticographic recordings in V1 simultaneously with their whole-cell recordings, and the results suggested that the oscillations are synchronized network phenomena, at least within V1. It would be informative to perform dual intracellular recordings in V1 and a higher-order visual area, or even in cortex of a different sensory modality, to gauge the spatial synchrony of these waking 3–5 Hz oscillations.

Related to the issue of spatial synchronization, do waking 3–5 Hz oscillations share similar rhythmogenic mechanisms with sleep delta oscillations? Sleep delta rhythms are thought to be generated by thalamocortical (TC) neurons, which are synchronized in their rhythmic output by corticothalamic projections (Timofeev and Steriade, 1996). During deep slow-wave sleep, TC cells are at their most hyperpolarized V_m, giving rise to an oscillatory interaction between the h-current (I_h) and T-current (I_T) in these cells (McCormick and Pape, 1990), which leads to burst firing at delta frequencies. This interaction is abolished when TC cells depolarize upon enhanced neuromodulatory tone (Steriade et al., 1991). Could the highly rhythmic delta-frequency activity Einstein et al. (2017) recorded in awake V1 originate from the same thalamic mechanisms as sleep delta oscillations? This would be an unusual scenario because TC cells would need to be hyperpolarized to a degree typically only seen during deep slow-wave sleep. Another sleep rhythm, the spindle oscillation, results from the synaptic interplay between bursting TC cells and GABAergic cells in the thalamic reticular nucleus. During waking periods, it is conceivable that corticothalamic projections could excite thalamic reticular nucleus cells strongly enough such that TC cells are sufficiently hyperpolarized to fire I_T-dependent bursts. Indeed, this mechanism may be responsible for a rhythmic 7–12 Hz corticothalamic oscillation occurring during whisker twitching in awake, immobile rodents (Fanselow et al., 2001). Yet, this waking spindle-frequency oscillation is faster than the delta-frequency oscillation observed by Einstein et al. (2017). Intracellular recordings from TC and thalamic reticular nucleus cells in awake mice would be ideal to reveal the behavior of these cells during the 3–5 Hz oscillations, and determine whether they exhibit the characteristic V_m dynamics of either sleep delta or spindle oscillations.

If the waking 3–5 Hz oscillations observed by Einstein et al. (2017) are not thalamically generated, another possibility is that they are generated within local cortical circuits. Certain pyramidal neurons in cortical layer 5 generate rhythmic oscillations at delta frequencies under different activating conditions and at a variety of membrane potentials (Silva et al., 1991). The less restricted set of conditions under which layer 5 pyramidal cells exhibit delta oscillations seems to make layer 5 pyramidal cells a more likely candidate for the generation of a synchronized 3–5 Hz rhythm during wakefulness. Optogenetic inactivation of thalamus or cortical layer 5 triggered by real-time detection of 3–5 Hz oscillations might allow for a more definitive resolution regarding the necessity of thalamus or cortex for these oscillations.

What conditions are necessary for triggering waking 3–5 Hz oscillations in the first place? While Einstein et al. (2017) observed the oscillations in the absence of sensory stimulation, the oscillations were far more frequent when mice viewed drifting sine-wave gratings. Furthermore, the onset of oscillations was generally time-locked to visual stimulus onset, though with a rather long latency (~2 s). What is the mechanistic basis for the visual-stimulus dependence of the 3–5 Hz oscillations? It is possible that the spatially and temporally rhythmic nature of the repeatedly presented sine-wave gratings evokes a comparatively rhythmic response in the thalamocortical network. Yet, the notion that the 3–5 Hz oscillation is simply a visually evoked response is inconsistent with their onset latency, which is much longer than that of typical evoked responses in mouse V1 (Gao et al., 2010). It will be important to determine whether 3–5 Hz oscillations in V1 also occur under presentation of visual stimuli with broader spatial and temporal frequency spectra, such as Gaussian white noise movies.

Although Einstein et al. (2017) did not find a relationship between baseline arousal and 3–5 Hz oscillation probability, they did report that oscillation onset coincided with pupillary constriction. It has recently been shown that, whereas activity of ascending cholinergic projections tracks baseline pupil diameter, activity in noradrenergic projections tracks rapid changes in pupil diameter (Reimer et al., 2016). Thus, 3–5 Hz oscillations might be triggered by rapid decreases in noradrenergic tone, although the connection between such decreases and visual stimulation would need to be elucidated.

Last, how do 3–5 Hz oscillations influence visual encoding and visually guided behavior? Several pieces of data in Einstein et al. (2017) begin to provide an answer. When 3–5 Hz oscillations coincided with the presentation of a sine-wave grating, the evoked V_m response was reduced, compared with periods without oscillations. This result is consistent with previous observations of reduced neuronal responsiveness to sensory stimulation during the slow oscillatory cortical and thalamic activity of sleep (Steriade and Paré, 2007). Interestingly, however, in the context of a visual discrimination task, 3–5 Hz oscillations did not appear to impair visual behavioral performance. Rather, high oscillation probability was primarily associated with a suppression

of a licking response, especially when NoGo stimuli were presented. It will be important to determine whether 3–5 Hz oscillations perhaps affect perceptual decision-making performance when changes in stimulus parameters are closer to perceptual threshold; in their task, Einstein et al. (2017) used sine-wave gratings of orthogonal orientations, a difference that is likely far above perceptual threshold. The notion that 3–5 Hz oscillations might be used for goal-directed visual behavior is suggested by the difference in oscillation onset time when stimuli were presented passively versus when they were presented in the context of a task. Einstein et al. (2017) discuss the possibility that 3–5 Hz oscillations might serve as a mechanism for filtering out task-irrelevant visual information. The design of future behavioral tasks and causal interventions on waking 3–5 Hz oscillations will hopefully clarify whether these oscillations are a bug the cortex must tolerate, or a feature under adaptive control during active behavior.

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