The Ups and Downs of Firing Rate Homeostasis

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Abstract

Torrado Pacheco et al demonstrate that downward firing rate homeostasis occurs when cellular activity levels increase beyond baseline, but only during sleep-dense periods. In contrast, Hebbian-facilitated changes in firing rate occur independently of sleep and wake states.

Main Text

One of the key features of the brain is its extensive capacity for plasticity, which facilitates adaptation and learning. But if this plasticity is left unchecked, it can result in extremely high or low neural activity. Homeostatic mechanisms are proposed to balance activity levels and help maintain stable firing rates. A key aspect of proposed homeostatic mechanisms is that they are bidirectional and can adjust to compensate for activity levels that are either too high or too low. To date, firing rate homeostasis in vivo has only been demonstrated to occur when activity levels have decreased (Hengen et al., 2013; Hengen et al., 2016; Keck et al., 2017). While homeostatic mechanisms have been shown to occur in response to an increase in activity or over-stimulation (Lee and Kirkwood, 2019), it is not clear whether these mechanisms are associated with a decrease in firing rate, and thus if firing rate homeostasis is truly bidirectional.

In this issue, Torrado Pacheco et al. examine bidirectional firing rate homeostasis and its regulation by sleep state in the primary visual cortex (V1) of rats (Torrado Pacheco et al., 2020). Using chronically implanted electrodes, they record activity from cells in both hemispheres before, during and after monocular deprivation (MD) by closing a single eye with eyelid suture. The MD paradigm is an effective way to modulate neuronal activity levels. After two days, it results in a decrease in the firing rates of putative pyramidal cells in V1 in the hemisphere contralateral to the deprived eye (Fig.1, Phase I). After four days of MD, cellular firing rates homeostatically increase to their pre-deprivation levels (Fig. 1, Phase II), despite the fact that the eye is still closed and sensory input remains reduced (Hengen et al., 2013). Once this homeostatic adjustment of firing rate has occurred, increases in activity levels beyond baseline can be induced by simply reopening the eye (eye reopening, ER) (Toyoizumi et al., 2014). When the authors use this ER paradigm, they observe an increase in activity, where cellular firing rates double in the affected hemisphere after two days (Fig. 1, Phase III). Firing rates in the control hemisphere remain stable throughout. The ER paradigm thereby allows the authors to explore the homeostatic effects resulting from a sustained increase in activity. They find that four days after ER, activity levels have decreased and returned to baseline (Fig. 1, Phase IV). These data demonstrate downward firing rate homeostasis for the first time in vivo. Together with past work (Hengen et al., 2013; Hengen et al., 2016; Keck et al., 2017), these results indicate that firing rate homeostasis is bidirectional in the rodent cortex, a fundamental tenet of homeostatic plasticity that had yet to be experimentally demonstrated.

Next the authors sought to determine which plasticity mechanisms mediate the increase and subsequent decrease in activity observed during the ER plasticity paradigm. N-methyl-D-aspartate receptors (NMDARs) are known to be required for Hebbian plasticity, but not for synaptic scaling, a homeostatic mechanism that changes synaptic strength cell-wide (Toyoizumi et al., 2014). To distinguish between Hebbian and homeostatic forms of plasticity, the authors injected an NMDAR antagonist, 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), at the time of ER and found that the subsequent increase in firing rate was blocked. This result indicates that this increase is likely mediated by NMDA-dependent Hebbian synaptic

strengthening and is not simply the result of increased sensory drive (Fig. 1, Phase III). Conversely, when CPP was injected several days after ER induction when firing rates had already started to increase, it did not block the reduction of firing rate back to baseline levels. Thus, downward firing rate homeostasis is not NMDAR-dependent, suggesting that homeostatic mechanisms, such as synaptic scaling down, may be involved (Fig. 1, Phase IV). To explore this possibility, the authors performed a series of ex vivo electrophysiology experiments. In acute slices prepared from rats undergoing the same ER deprivation paradigm in vivo, they found that cells in V1 undergo synaptic scaling down that is temporally correlated with the observed decrease in firing rate. Together, these data suggest that downward firing rate homeostasis may be mediated through homeostatic mechanisms at the synaptic level.

Having demonstrated downward firing rate homeostasis in vivo, the authors next examined if ongoing firing rate adjustments are regulated by behavioral state. A prominent hypothesis – the synaptic homeostasis hypothesis (SHY) – suggests that synaptic plasticity is bidirectionally modulated across sleep and wake periods. Specifically, synaptic strength increases with ongoing experience during wake cycles, and homeostatically decreases during sleep, thereby providing balance to the effects occurring during wake (Tononi and Cirelli, 2014). There are experimental data to support this hypothesis at the synaptic level (Cirelli, 2017; Tononi and Cirelli, 2014) and one possible prediction is that changes in firing rate would parallel the sleep-wake regulated changes in synaptic strength. Recent work in the visual cortex of rats has not observed sleep or wake modulated effects on firing rate under baseline conditions; however, following an MD-induced decrease in activity, homeostatic increases in firing rate back to baseline only occur during wake-dense periods (Fig. 1, Phase II) (Hengen et al., 2016). This MD result is consistent with SHY, where increases in synaptic strength are proposed to occur during wake. Currently, it is unknown whether sleep and wake states influence downward firing rate homeostasis in response to over-stimulation or increases in activity levels. SHY suggests that decreases in synaptic strength largely occur during sleep, thus one might predict that decreases in firing rate would also occur during the sleep phase.

To determine if the homeostatic decrease in firing rates after ER is influenced by sleep, the authors compared homeostatic changes in firing rates across sleep and wake states. They found that the downward firing rate homeostasis after ER occurred only during sleep-dense periods (Fig. 1, Phase IV). There was a correlative relationship: the longer the animals slept, the larger the decrease in firing rate. These results were independent of the circadian rhythm and consistent for both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, but were not observed in the control hemisphere or during quiet wakefulness. By using a relatively mild, intermittent sleep deprivation paradigm, the authors could also demonstrate that the homeostatic decrease in firing rate was slowed down when the animals were sleep deprived, but resumed when the animals were allowed to sleep again. Importantly, the decrease in firing rates that follows MD, which has been shown to be mediated by long-term depression (LTD) (Heynen et al., 2003), was not correlated with either sleep or wake states (Fig. 1, Phase I). Combined, these results highlight the role of sleep for enabling homeostatic, but not Hebbian, plasticity-mediated decreases in firing rate.

The observations of homeostatic changes in firing rate following deprivation and over-stimulation paradigms are generally consistent with SHY – increases during wake (Fig. 1, Phase II) (Hengen et al., 2016) and decreases during sleep (Fig. 1, Phase IV) (Torrado Pacheco et al., 2020). Other results presented here do not obviously support SHY. The authors observed no effect of sleep or wake states on 1) firing rates in control animals, where homeostatic regulation is expected to be ongoing or 2) decreases in firing rates associated with the induction of Hebbian plasticity (Fig. 1, Phase I). One important consideration is that SHY describes up- and down-regulation of synaptic weights during wake and sleep, proposing a neural function for sleep. Firing rate homeostasis, on the other hand, reflects the output of a number of synaptic, cellular and network mechanisms working together to provide homeostatic regulation at a range of temporal and spatial scales (Keck et al., 2017) extending beyond the scales of SHY. Changes to inhibition levels and cellular excitability will have strong effects on neuronal firing rate (Keck et al., 2017), and the influences of these other circuit components could explain why predictions of synaptic changes in SHY do not correlate with changes in firing rate under control conditions (Cirelli, 2017). One potential interpretation is that SHY represents one of a

number of homeostatic mechanisms that help maintain stable firing rates. Further work will be critical for understanding the role of sleep and wake states, as well as other behavioral states, in homeostatic regulation during ongoing changes in activity.

These other homeostatic mechanisms may also play a role in the different time scales of homeostatic regulation. Homeostatic compensation occurring during sleep and wake states evolves over long time scales (hours to days), but in order to balance neuronal activity effectively given the nature of changing activity levels, it is critical to also have homeostatic mechanisms operating on short (seconds to minutes) time scales (Zenke and Gerstner, 2017). Thus, the changes observed during sleep-wake periods are likely only one component of the brain's mechanisms to maintain stability. Other mechanisms, such as altering the excitation and inhibition balance, could be used to regulate activity on shorter time scales and help maintain stable firing rates throughout the sleep and wake cycles, by balancing activity changes resulting from ongoing synaptic changes associated with experience-dependent plasticity. Understanding the interactions between these synaptic, cellular and network mechanisms across time scales and behavioral states will be critical for developing a more complete picture of homeostatic regulation in vivo.

Figure legend

Figure 1: Firing rate homeostasis regulation by sleep-wake state and associated plasticity mechanisms following sensory manipulation. Activity levels change over time, deviating from baseline (dashed line) as a result of sensory manipulation. Activity decreases (Phase I) and then increases (Phase II) following monocular deprivation (MD). Activity increases further (Phase III) following eye reopening (ER) and then decreases back to baseline (Phase IV). The associated plasticity mechanisms are listed for each phase, as well as the sleep or wake state that regulates the plasticity (if any).

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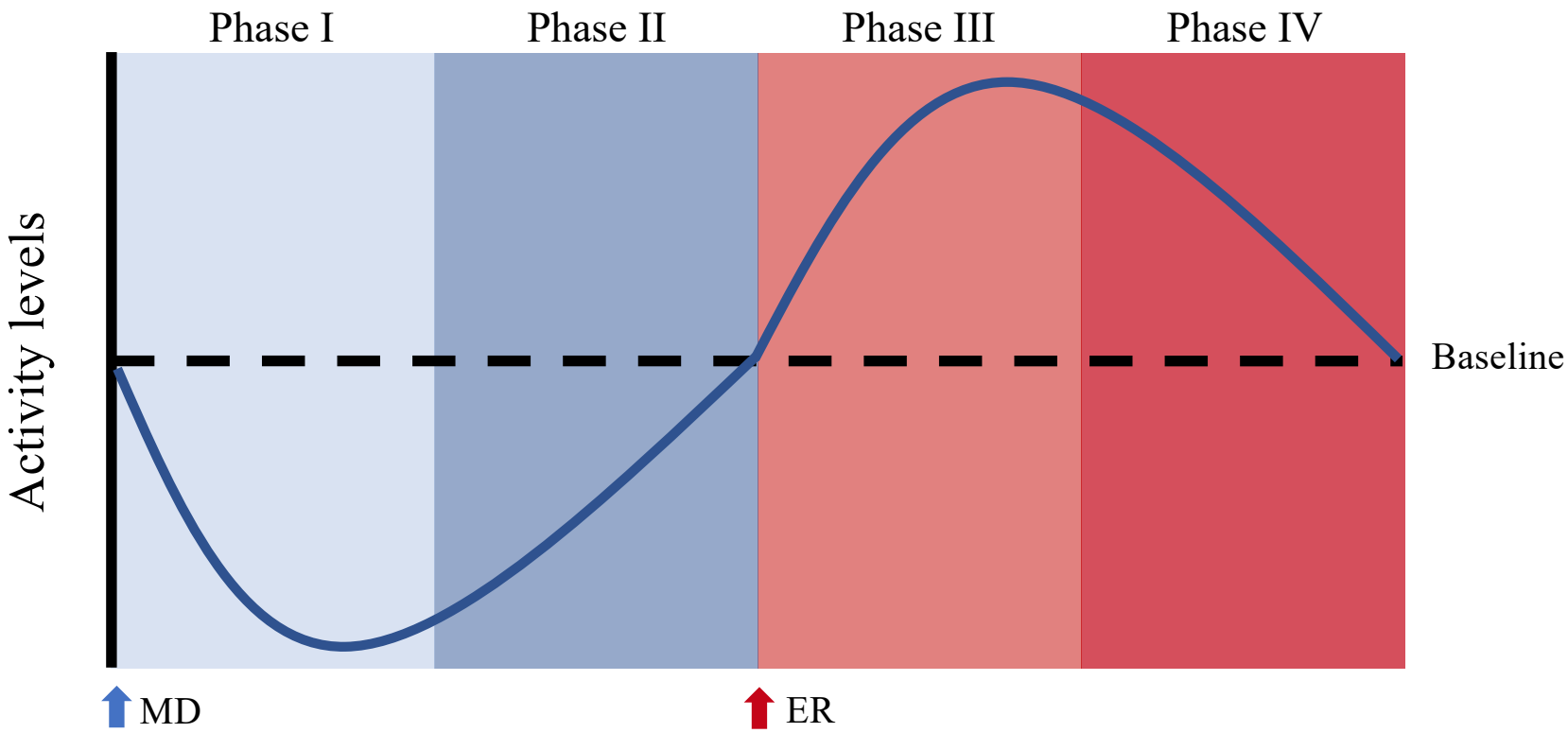

Plasticity mechanism	Hebbian LTD	Synaptic scaling up	Hebbian NMDA-dependent	Synaptic scaling down
Sleep/Wake regulation	None	Wake-dense periods	?	Sleep-dense periods