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Spotlight

Disentangling the roles of circadian rhythms and sleep drive in experimental pain sensitivity

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Differentiating between circadian rhythm and sleep's effect on pain is challenging, as these two systems can be tightly coupled. A recent study by Daguet *et al*. found that circadian rhythm, rather than sleep drive, significantly contributed to the variability of experimental heat pain sensitivity in humans. These results support chronopharmacological approaches to pain management.

Although clinical pain and experimental pain sensitivity can follow a daily (~24-h) rhythm, mechanistic studies to understand the factors underlying these diurnal variations in pain sensitivity are largely lacking. The biological underpinnings of daily rhythmicity reflect a combination of two separate but interconnected systems: endogenous circadian systems (e.g., coordination of biological clocks within cells, including neurons) and homeostatic sleep drive (i.e., build-up and dissipation of sleep drive during wake and sleep, respectively). Distinguishing the role of circadian rhythms versus homeostatic sleep drive in pain rhythmicity is difficult under normal living conditions since external environmental (i.e., light) and lifestyle factors (i.e., activity and diet) can synchronize circadian rhythms.

Recently, an innovative study by Daguet and colleagues examined whether circadian rhythms or homeostatic sleep drive contributes to the diurnal (24-h) rhythm in pain sensitivity to noxious heat in healthy male adults [1]. The authors used a 34-h constant routine (CR) paradigm in a well-controlled lab setting to accomplish this goal. The CR paradigm is commonly used in other domains to distinguish between the effects of circadian rhythm and sleep-related processes by reducing the impact of exogenous cues, including light, activity (sleep–activity cycles), and diet, that can synchronize circadian rhythms. Participants were asked to stay awake for the entire CR period while their sensitivity to experimental heat pain (i.e., 2-s heat stimuli at 42°C, 44°C, and 46°C) was measured every 2 h. The authors modeled the effect of time on pain using an additive model, which included a linear component and a sinusoidal component. The sinusoidal component was constrained to have a period close to 24 h, whereas other parameters in the model were free. The researchers also measured fluctuations in body temperature, heart rate, heart rate variability, and melatonin levels, which also exhibit circadian rhythmicity.

During the study, pain sensitivity was found to change over time. Specifically, at higher stimulus temperatures (44°C, 46°C), the model of participants' reports included a linear component reflecting an increase in heat pain intensity across the 34-h CR period. This observation supports the notion of sleep drive as modulator of pain sensitivity, as the homeostatic drive for sleep increases with a constant state of wakefulness across the 34-h period. This finding is also in line with previous sleep deprivation studies showing that longer awake times are associated with greater pain sensitivity [2]. In addition, Daguet *et al*. found that pain sensitivity (at 42°C, 44°C, and 46°C) included a sinusoidal or oscillatory component, with greater pain sensitivity (acrophase) occurring in the middle of the night (03.00–04.30 h). Thus, pain sensitivity appears to be influenced not only by sleep drive (see earlier), but also by circadian rhythms. Interestingly, this oscillatory relationship was not observed for warm detection thresholds, which might suggest a specific role of the circadian timing system in pain processing, rather than circadian rhythmicity of thermal sensitivity in general. In their analyses, the authors also estimated the overall relative contributions of circadian rhythm versus sleep drive to experimental pain sensitivity in the study. According to their calculations, the circadian rhythm system accounts for ~80% of pain sensitivity variability over a 24-h period, with the remaining ~20% being accounted for by the homeostatic component. Lastly, fluctuations in body temperature, autonomic functioning, and melatonin levels exhibited robust circadian rhythmicity that paralleled changes in pain sensitivity in a lagged fashion. Overall, the study suggests that circadian rhythms significantly contributed to experimental heat pain sensitivity compared with sleep, which had a weaker influence on heat pain than previously thought [3].

The study by Daguet *et al*. is innovative and critical as it is the first to differentiate between circadian rhythm and homeostatic sleep drive in pain sensitivity through highly controlled laboratory experiments in humans. From an evolutionary perspective, the question arises as to why humans are more sensitive to pain during the middle of the night, which is typically a time when we sleep. One possibility is that we are more vulnerable during this time and, consequently, a lower stimulus intensity would be able to awaken us to potential danger. Many studies aimed to determine what causes arousal and the large intra-variability in arousal (e.g., the same stimulus will sometimes result in arousal and, in some cases, not). A recent study has suggested that functional brain connectivity pre-stimulus predicts arousal [4]. However, the study by Daguet and colleagues could point toward the involvement of circadian rhythm patterns impacting pain

sensitivity and the variability in sleep arousal. It is also possible that when it is dark and more difficult to rely on the visual sense, other senses become more sensitive. In line with this concept, blind participants often report greater pain sensitivity [5]. It is possible that the pain system becomes more sensitive during the night and, indeed, Daguet *et al*. found a circadian rhythm effect for all the tested stimulus temperatures, including the 42°C that evoked only mild pain.

It is important to note that chronic pain patients often experience nonrestorative sleep and sleep disorders [6] and, conversely, patients with sleep disorders frequently report pain-related symptoms and may have comorbid chronic pain disorders [7]. It remains to be determined whether sleep, rather than circadian rhythm, has a more significant impact on clinical pain in patients with chronic pain or sleep disorders. In addition, as circadian rhythm impacts the experience of pain, one may wonder what effects a change in our natural circadian rhythm might have on pain. Will night shift workers or residents in high latitudes (vs. regions closer to the equator) have the same diurnal variation in pain sensitivity? Finally, testing whether the findings by Daguet *et al*. extrapolate to other populations will be an important goal for future work. The study was conducted on relatively young, healthy male participants. Whether circadian rhythms may be differentially impacted in females and across the lifespan remains to be determined.

From a mechanistic standpoint, more studies are needed to identify the neurobiological pathways linking circadian rhythm to pain. Potentially relevant mechanisms include neural pathways of shared brain regions, (im)balance between inhibitory and excitatory modulation of nociceptive information, and other biological factors (e.g., autonomic nervous system, hormonal, neuroinflammation). Replicating the results using modalities other than heat stimuli, including models of pain modulation (i.e., conditioned pain modulation, temporal summation), is also needed.

The diurnal variations in clinical pain could be harnessed by the health care system, for instance, by scheduling painful procedures such as blood draws and minor surgical procedures when our body is less sensitive to pain. In addition, a chronopharmacological approach in which pain treatments are matched to the patient's circadian rhythm could lead to a greater analgesic effect and fewer pain medications [8].

Declaration of interests

The authors have no conflict of interest regarding this work.

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