anxiety, as reported by Yu *et al*., is not equivocal: Are these phenomena causally linked or do they occur in parallel? A causal relationship is suggested by the observation that VTA$^{Vgat\text{-}Sst}$ stimulation during artificial sleep deprivation after social defeat cannot restrain anxiety, nor (fully) normalize stress hormone concentrations in plasma. Yet, chemogenetic stimulation of VTA$^{Vgat\text{-}Sst}$ cells (in the absence of social defeat) increases sleep but does not affect concentrations of the stress hormones corticotropin-releasing factor (CRF) and corticosterone. This suggests that parallel pathways might regulate sleep and anxiety, which is also supported by recent studies showing the importance of a reciprocal loop between the VTA and parts of the amygdala in social defeat–induced anxiety (*6, 7*). The parallel pathways of VTA–lateral hypothalamus to regulate sleep and VTA-amygdala to regulate anxiety are reminiscent of the observation that glucocorticoid receptor deletion in prefrontal dopaminoceptive neurons decreases social avoidance but not anxiety and fear memories after mice were subjected to 10 days of social defeat (*8*).

It could be hypothesized that sleep induced by the hypothalamus and activation of the hypothalamic–pituitary–adrenal (HPA) axis (which eventually causes a rise in circulating corticosterone concentration) may affect social aversion, and through a parallel pathway involving limbic regions, reduce anxiety (*9, 10*). Thus, during sleep, events experienced while awake are replayed, binding elements of the experience in various parts of the brain and forming a memory of the situation (*11*). Such memory-enhancing effects of sleep are particularly strong for locations with an aversive connotation, as in the case of a social defeat experience. Eventually this results in the formation of gist-like memories. REM sleep is proposed to depotentiate amygdala reactivation (which is associated with anxiety), tuning down amygdala inputs to the hippocampus (*12*). This would allow contextual elements to be stored, freed from the anxious context. Overall, interconnected parallel loops appear to be involved in the processing of various elements that are intrinsic to a social defeat experience (see the figure).

Sleep and stress entertain a complex courtship. Intuitively, falling asleep after experiencing stress may not sound logical: Almost all mood and anxiety disorders are characterized by sleep abnormalities, which in turn exacerbate the susceptibility to new episodes and progression of such disorders (*12, 13*). However, there may be two important differences between such pathological conditions and the one described by Yu *et al*. Single stressors may have different consequences than the wear and tear caused by a chronic state of (unpredictable) stress. Furthermore, the induction of sleep may be specific for stressful situations such as social defeat that have little ambiguity, whereas stressors with a more uncertain outcome may affect sleep negatively. Even though social defeat is a negative live event, it is relatively straightforward: The defeated mouse knows exactly what the consequence is—i.e., a subordinate position.

Not all individuals may respond to social defeat with a bout of sleep. Recent findings showed that social stress promotes sleep-like inactivity in mice, with a large degree of variation among experimental animals (*14*). This variation is also noticeable in the experiments by Yu *et al*.: About half of the animals showed a strong increase in REM sleep duration, whereas the remaining mice slept the same amount as controls. This requires further investigation in larger groups of mice (*15*), which would also be helpful to probe the robustness of the current explorative study. The source of interindividual variation could arise from the animal's sex (the social defeat model is optimized for male mice), and genetic predisposition, and be modulated by life events, affecting the sleep pattern, personality, stress responsivity, ability to contextualize, and so on—or any combination of these. Knowing the essential steps in the brain may help steer future interventions in rodents and perhaps even humans after stressful experiences, be it through cognitive therapy or pharmacotherapy or maybe, one day, genetic interference. ■

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HEALTH TECHNOLOGY

Cooling the pain

A miniaturized, flexible cooling device can be used for precise analgesia

By **Shan Jiang**[1,2] *and* **Guosong Hong**[1,2]

As one of the most critical health problems, pain afflicts one in five adults in the world (*1*). Despite the efficacy of opioids in treating pain, opioid use disorder and overdose have motivated the development of nonopioid alternatives, such as other analgesics (*2*), electrical stimulation (*3*), and acupuncture (*4*) for pain management. Among these alternatives, analgesic nerve cooling offers an effective and reversible strategy to alleviate pain (*5*). On page 109 of this issue, Reeder *et al*. (*6*) report a miniaturized and implantable cooling system that integrates state-of-the-art microfluidic and flexible electronic technologies in a biodegradable platform for localized temperature control and precise pain relief.

Analgesic nerve cooling leverages the temperature dependence of chemical reaction rates to effectively reduce the metabolic, electrogenic, and ionic activity in the neural tissue at lower temperatures (*7*). A moderate temperature decrease in nerves to 15°C has been reported to block the transmission of compound nerve action potentials, whereas a complete nerve conduction block can be achieved at 5°C (*8*). The risk of inducing nerve damage at an even lower temperature calls for precise control of local cooling. Conventional nerve-cooling methods rely on precooled liquids, such as methanol, delivered through a metal or silicone loop or a thermoelectric device (*9*). These interfaces are constrained by their bulky and rigid structures, nonspecific cooling, and high-power requirement, thus limiting their chronic application in the peripheral nervous system.

An implantable cooling device with on-demand local analgesia will be a game changer for long-term pain management. Reeder *et al*. capitalized on their expertise in advanced flexible microsystems (*10*) to create a microfluidic cooling device with real-time temperature feedback. Compared

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with other approaches to achieving nerve blocks, their device outperforms conventional in vivo cooling methods for several reasons (see the figure). Composed of serpentine architectures and elastomeric materials with similar elasticity to those of peripheral nerves, the device is soft, flexible, and stretchable. Because of its tissue-like mechanical properties, this device readily wraps around the nerve like a cuff electrode, forming an intimate interface to facilitate effective heat transfer. The device is also bioresorbable; it dissolves in physiological fluids over months and yields a minimal inflammatory response in the tissue. The gradual biodegradation of the device is attributed to a bioresorbable elastomer known as poly(octanediol citrate), which is used to build the microfluidic system. In addition, the device leverages an evaporative mechanism to produce rapid cooling, in contrast to conventional precooled liquids with slower temperature reduction kinetics. Because the spatial spread of heat diffusion scales with time, more rapid cooling, along with the low heat capacity of exhaust gas, yields greater spatial confinement and more localized analgesia down to the millimeter scale. Lastly, this device incorporates a temperature sensor in an electronic layer alongside the microfluidic system, which provides real-time feedback for precise control of local temperatures.

In achieving spatiotemporally precise cooling, Reeder *et al.* demonstrate the power of engineering advances in addressing unmet biomedical needs. The evaporative cooling scheme has been applied in the thermal management of high-density electronics (*11*). However, its application in pain management in living organisms has so far been limited. This is largely because of the shape mismatch at the thermal interface because these devices usually come in the form of rigid parallel plates (*12*), making them less than ideal for accompanying nerves, which, by contrast, are soft and geometrically complex.

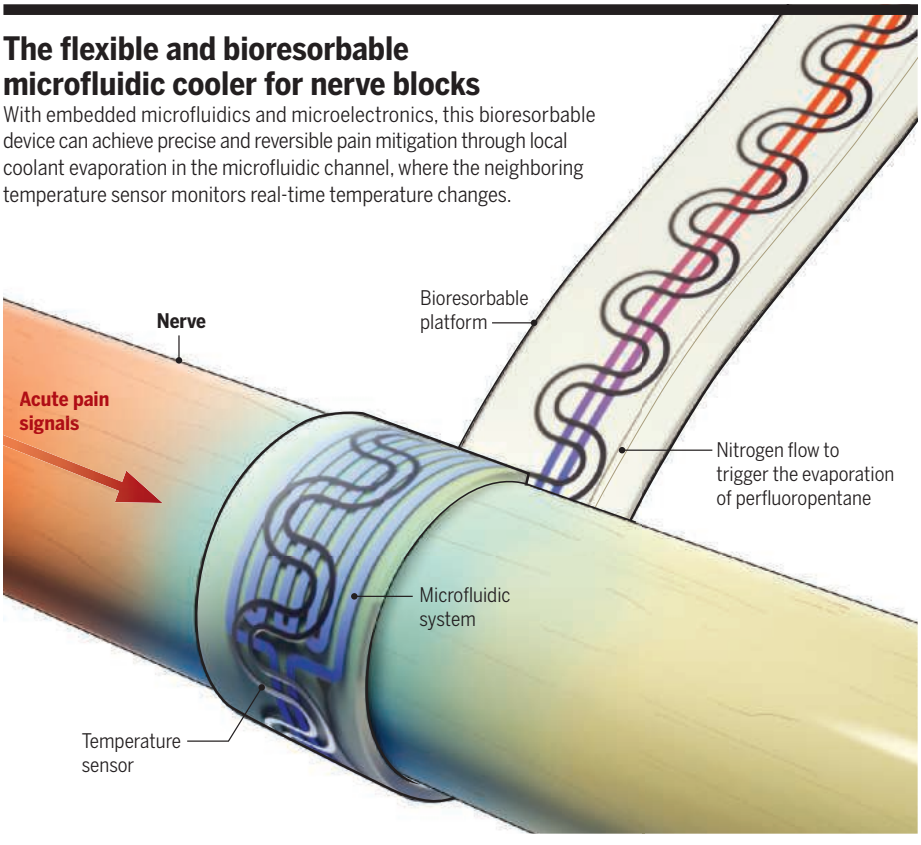
Reeder *et al.* applied evaporative cooling in a soft and stretchable microfluidic platform, which has previously been used for drug delivery in the nervous system. The bioinertness of perfluoropentane and its clinically approved use as an intravenous ultrasound contrast agent justify its use as a biocompatible liquid coolant in vivo. By taking advantage of the low boiling point and high enthalpy of vaporization of perfluoropentane (*13*) alongside the use of dry nitrogen gas, the device created by Reeder *et al.* achieved a maximum cooling rate of 3°C/s.

When tested on rats, their device produced highly localized cooling and enabled efficacious and reversible conduction blocks of rat sciatic nerves, as observed by electromyography, compound nerve action potential, and muscle-force measurements. Furthermore, the stretchable cooling device achieved analgesia in freely moving rats with neuropathic pain over several weeks after implantation, as demonstrated in von Frey anesthesiometer measurements and histological analyses. This stable interface, along with its degradation over time, enables on-demand pain management with long-term utility while obviating the need for surgical extraction after the period of intervention.

Besides the demonstrated strengths of the miniaturized, flexible cooling device for pain mitigation, the technology presents further opportunities for neuroscience research and neurological practice. Specifically, cortical cooling has been used as a nongenetic means to silence neural activities and investigate circuit dynamics in the brain (*14*). The localized, reversible cooling effect represents an attractive method for manipulating neural activities with high spatiotemporal resolutions, chronic utility, and minimal invasiveness in nonhuman primates and even humans. In addition, this technology offers a nonopioid alternative for targeted, on-demand pain relief in current hospital settings. A wearable cooling device with a more compact integration of its components helps achieve point-of-care pain management. By leveraging the latest advances in flexible and stretchable bioelectronics, an all-in-one nerve interface with cooling, temperature monitoring, and electrophysiological recordings may be possible in the future, offering real-time adjustment of cooling temperatures, duration, and intermittency to achieve desired physiological and therapeutic effects. ■

The flexible and bioresorbable microfluidic cooler for nerve blocks

With embedded microfluidics and microelectronics, this bioresorbable device can achieve precise and reversible pain mitigation through local coolant evaporation in the microfluidic channel, where the neighboring temperature sensor monitors real-time temperature changes.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*

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