behaviour, such as entanglement, in mechanical oscillators is exceptionally challenging — largely because it is difficult to prevent these objects from being disturbed by their surroundings. The oscillators usually have low vibrational frequencies and are therefore susceptible to disruption from the thermal jiggling of surrounding atoms. By contrast, the electromagnetic field associated with light has extremely high-frequency oscillations, which means that light is completely insensitive to thermal fluctuations at room temperature. As a result, it is relatively easy to control the properties of light with the exquisite precision required to reveal quantum effects, and the production of entangled light has become almost routine.

The experiments of Riedinger *et al.* and Ockeloen–Korppi *et al.* differed in detail, but shared several key ingredients. To counter the effects of thermal fluctuations, both groups of authors used micrometre-scale mechanical oscillators, which ensured that the vibrational frequencies were not too low, and cooled the oscillators to temperatures of less than 0.1 kelvin. In both experiments, electromagnetic radiation (in the form of light or microwaves) provided the means to generate and detect the entanglement of the oscillators[6,7].

Riedinger and colleagues used a pair of oscillators in the form of 10-μm-long silicon beams — rods that were clamped at both ends and suspended in the middle (Fig. 1a). Each beam contained small holes designed to trap light, that coupled to rapid oscillations (with frequencies of about 5 gigahertz) in the beam's width. The authors shone weak pulses of light on the beams, and monitored the light that was scattered, using a sophisticated scheme that did not reveal which beam the light came from. The detection of such light meant that energy had been transferred from a pulse to the vibrations of a beam, but because there was no information about which oscillator was involved, the vibrations of the two beams were entangled.

The trick of using light to generate entanglement in this way[8] works only if the light scatters from objects that are almost perfect copies of each other. This is difficult to achieve using small mechanical beams, because such objects are produced by a destructive process in which they are essentially sculpted out of a monolithic slab of material. Riedinger *et al.* therefore produced chips containing hundreds of beams from which they selected the best-matched pair.

Ockeloen–Korppi *et al.* used a pair of metal drumheads that vibrated up and down above fixed metal plates (Fig. 1b). The drumheads had diameters of about 15 μm and low vibrational frequencies (about 10 MHz). The authors connected the drumheads by an electrical circuit in which microwaves could bounce back and forth. The microwaves influenced the motion of the drumheads, but were also affected by this motion, coupling the oscillators in the same way that a spring can link two pendulums. This allowed an entangled state to form, and to persist indefinitely, despite the low vibrational frequencies of the drumheads[9].

Taken together, these two experiments provide an elegant illustration of the power and versatility of electromagnetic radiation as a tool for exploring quantum features of mechanical motion. Each experiment has its advantages. Riedinger and colleagues' beams interface directly with light and are not connected by wires, which means that these devices could be readily integrated into future optical communication networks designed to exploit the effects of entanglement. Ockeloen–Korppi and colleagues' results are particularly striking, given the low vibrational frequencies that they used; and their approach avoids the need for mass fabrication, because the oscillators need not be almost identical.

It was only in 2009 that entanglement was first reported between mechanical oscillators consisting of just two atomic ions[10]. Since then, experiments have demonstrated entangled vibrations in the lattices of crystals[11], at frequencies much higher than even those of Riedinger and colleagues' beams. In terms of the number of atoms involved, the oscillators used by Riedinger *et al.* and Ockeloen–Korppi *et al.* are both a big step up from atomic ions, but they are still much smaller than the macroscopic objects encountered in everyday life. It will be fascinating to see how much further up in scale experiments are able to go in the next decade. Such progress could lead to exciting insights — for example, larger mechanical oscillators in entangled states might provide answers to outstanding questions about how gravity relates to quantum physics[12]. ■

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NEUROSCIENCE

Hunger is a gatekeeper of pain

A neuronal population has now been found that regulates two competing needs — hunger and pain. Urgent pain overrides hunger, but appetite-inducing neuronal activity dampens long-term pain responses to enable feeding.

ALEXEY PONOMARENKO & TATIANA KOROTKOVA

The body's basic needs include a timely supply of nutrients and the avoidance of tissue damage, which are signalled in the brain by hunger and pain, respectively. But these needs cannot be fulfilled simultaneously, because their resolution involves mutually exclusive behaviours. How does the brain prioritize the more urgent need? Writing in *Cell*, Alhadeff *et al.*[1] report that the brain's priorities are set depending on the type of pain involved. Hunger-mediating neurons suppress long-term inflammatory pain, but acute pain, which signals an immediate threat, dampens the activity of these neurons and thus deprioritizes feeding.

Alhadeff and colleagues deprived mice of food for 24 hours, and analysed how the hungry animals responded to pain. The researchers found that responses to long-term inflammatory pain — of the type associated with chronic disease and recovery from injury — were reduced in the food-deprived animals compared with controls. By contrast, short-term responses to acute pain that was induced by chemicals, heat or force remained intact in hungry mice.

The brain's hypothalamus contains several structures involved in regulating food intake. One of these, the arcuate nucleus, harbours a population of neurons that express agouti-related protein (AgRP), and help to signal nutritional needs — activation of these neurons evokes voracious feeding[2], whereas their ablation leads to starvation[3,4]. Alhadeff *et al.* found that stimulation of the AgRP-expressing

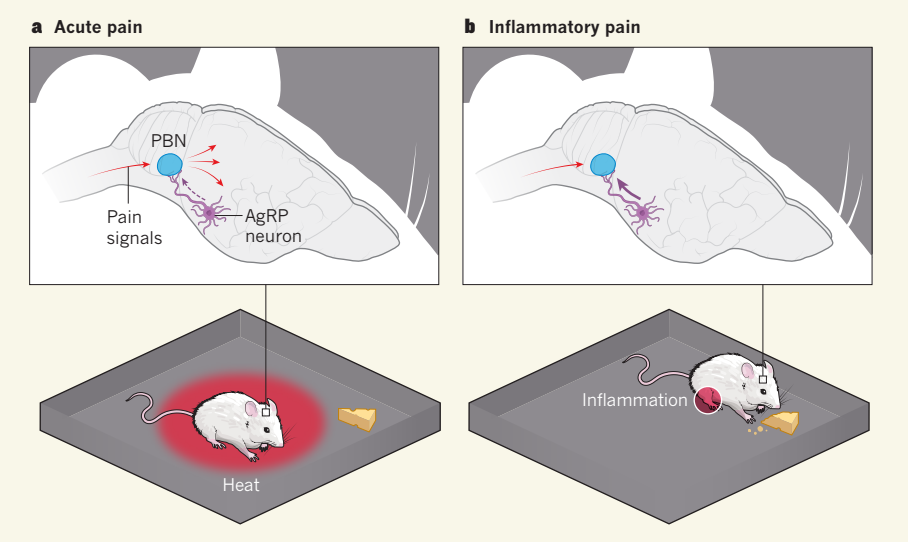

Figure 1 | Getting priorities right in the brain. Alhadeff *et al.*[1] have described a population of neurons that express agouti-related protein (AgRP) and regulate the competing needs of hunger and pain in the mouse brain. **a**, When a mouse is subject to acute pain, AgRP-expressing neurons are inhibited (dashed arrow), and feeding is suppressed. Pain signals from the spinal cord are transmitted throughout the brain via a region called the parabrachial nucleus (PBN). **b**, By contrast, AgRP-expressing neurons remain active during long-term pain, such as that caused by inflammation. The neurons send signals to the PBN to prevent pain transmission to other brain regions, and so feeding is supported.

neurons mimicked the pain-inhibiting effect of hunger in mice. By contrast, silencing of these cells blocked the reduction of inflammatory pain.

AgRP cells send projections to many brain regions. Not all of these projections directly regulate feeding[5,6] — some therefore probably have other roles. Alhadeff and colleagues systematically activated AgRP projections to seven brain regions, to search for the projections that mediate the neurons' pain-relieving effect during inflammation. They found a powerful reduction in inflammatory pain following stimulation of AgRP-cell projections to a single target region in the hindbrain, the parabrachial nucleus (PBN). This structure is part of a central pain-processing circuit that relays pain signals from the spinal cord to various brain regions. Notably, the neurons that receive AgRP inputs, which are found in the lateral portion of the PBN (the lPBN), are activated by painful stimuli[7] and inhibited during feeding[7,8]. Presumably, then, lPBN neurons act to suppress appetite in threatening conditions, when eating might be dangerous, whereas their inhibition by input from AgRP neurons supports feeding in conditions of inflammatory pain.

AgRP neurons produce three neurotransmitter molecules that stimulate feeding[9]: AgRP itself, γ-aminobutyric acid (GABA) and neuropeptide Y (NPY). Such co-transmission of signals by multiple molecules is widespread in the brain, but breaking down co-transmission into its constituent parts to understand its functions is challenging. Alhadeff *et al.* overcame this challenge, investigating which of the three molecules were essential for the pain-inhibiting effect of AgRP neurons by injecting each neurotransmitter into the lPBN. Neither AgRP nor GABA had a pain-relieving effect. But NPY suppressed inflammatory pain by acting through the Y1 receptor on lPBN neurons.

Finally, the authors demonstrated that acute pain led to a sharp decrease in the activity of AgRP neurons. A similar decrease in AgRP activity occurs when an animal first senses food[10], and this change in activity is thought to be important for the termination of further food seeking and a transition to food intake, which is then positively reinforced by structures in the hypothalamus other than the arcuate nucleus[11]. Taking this together with the authors' data, a picture emerges in which acute pain prompts a behavioural transition by suppressing the activity of AgRP neurons. This inhibition prevents the AgRP cells from activating downstream brain regions involved in feeding, and enables pain signals from the spine to spread from the lPBN to other brain regions, indicating the need to avoid noxious stimuli (Fig. 1a).

By contrast, inflammatory pain does not require rapid behavioural responses and is filtered out by active AgRP cells, which might reduce the activity of lPBN neurons to prevent spreading of pain information to other brain regions and so maintain food seeking (Fig. 1b). This previously unknown mechanism for the management of competing needs provides insights into how hypothalamic computations use both the neurochemical properties and the connectivity of neural circuits to make adaptive decisions about behaviour.

Alhadeff and colleagues' work has several implications. First, it provides evidence that the potency of AgRP-mediated long-term pain relief is comparable to that of opiates — at least, in the authors' long-term pain test. As they point out, differences in the processing of acute and chronic pain suggest that treatments for the two should be aimed at different target cells or proteins. In addition, designing painkillers that lack the off-target effects of opiates is desirable. Alhadeff and colleagues point to NPY–Y1-receptor signalling in the lPBN as a potential site of action for chronic painkillers.

Second, the authors' thorough characterization of a pathway in which signals for two negative states (hunger and pain) interact paves the way to understanding the biological mechanisms that define other complex and dynamic hierarchies in human and animal behaviours. Similar principles at work in other brain regions might further support unaltered food intake during inflammatory pain in hungry mice — for example, by promoting pain inhibition during meals. This painkilling effect probably would not rely on AgRP cells, because their activity is reduced after the sensory detection of food[10], so the behavioural hierarchy at work during feeding itself is probably controlled by other neuronal populations. One possibility is that this hierachy is mediated by neurons in the lateral hypothalamus, which is connected to the PBN (ref. 12) and contains several groups of neurons that are active during feeding[13–15].

As another example, concurrent negative states of hunger and food aversion contribute to eating disorders such as anorexia nervosa: food-related cues elicit aversion, impairing food intake. Delineating interactions between the neurons that mediate hunger and those that control emotional responses to food could shed light on the mechanisms underlying eating disorders. ■

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This article was published online on 23 April 2018.