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Persistent pain changes a neural circuit and reduces willingness to work for food

By **Howard L. Fields**

Pain is arguably the most completely understood of all sensations at the molecular and neural circuit level (*1*–*3*). Noxious stimuli elicit a variety of rapid tissue-protective responses. Pain also has an unpleasant affective-motivational dimension that, when persistent, can dominate behavior. When chronic, pain produces fatigue and mood changes that diminish many of life's pleasures. In contrast to our detailed understanding of acute pain, we know much less about how persistent pain alters behaviors at the molecular and neural circuit levels. On page 535 of this issue, Schwartz *et al.* (*4*) advance our understanding of how persistent noxious stimuli affect reward-seeking behavior.

From an evolutionary perspective, animals with more complex behavioral repertoires have greater flexibility in their responses to environmental challenges. This flexibility presents an animal with the challenge of choosing the best option among concurrent conflicting goals that require different actions. Selecting requires a cost-benefit computation in which the weight assigned to the net benefit or loss of each action is determined by genetic predispositions, past experiences, and the current context. It also requires choosing the optimal actions to meet motivational drives, and then implementing the selected choice while inhibiting competing options. Schwartz *et al.* demonstrate, using mouse models, that persistent painful input produces robust synaptic changes in a specific brain circuit, resulting in reduced motivation to work for a reward (in this case, food).
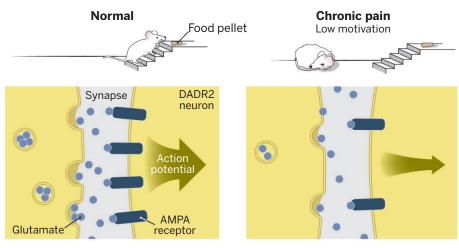
The stage for the study by Schwartz *et al.* was set by recent changes in our understanding of the neural circuits underlying appetitive motivation. Links in this so-called "reward circuit" include the midbrain ventral tegmental area and its projection targets in the cortex, amygdala, and nucleus accumbens (*5*). This circuit was originally discovered through the finding that rodents would work to receive electrical stimulation in these brain regions (*6*). These regions

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were found to overlap with the distribution of dopaminergic neurons and their projections to the prefrontal cortex and nucleus accumbens (*7*). The status of this circuit as a "pleasure center" was affirmed by studies showing that injection of nicotine or opiates into the ventral tegmental area, or of psychostimulants (which block removal of synaptic dopamine) into the nucleus accumbens, led to positive reinforcement (*5*).

Although initially considered to be largely separate from the pain circuit, these so-called reward centers include parallel opposing circuits that can elicit either reward or punishment. Thus, although most midbrain dopamine neurons respond to either unexpected or predicted rewards, a substantial subset of midbrain dopamine neurons is activated by noxious stimuli (*8*, *9*). Furthermore, when different subgroups of dopamine neurons are activated optogenetically (i.e., genetically programmed to be activated by light), they can produce either positive reinforcement or punishment (*10*). Human functional imaging studies also show extensive overlap between brain regions (including the nucleus accumbens) that are activated by reward and pain cues (*11*, *12*) and have revealed connectivity changes between the cortex and nucleus accumbens that precede and predict the transition from acute to chronic lower back pain (*13*).

Consistent with this idea of dual opposing mesolimbic circuits, there are two functionally distinct subpopulations of neurons in the nucleus accumbens that release the neurotransmitter γ-aminobutyric acid (GABA): ones that express the dopamine D1 receptor (DADR1) and others that express the dopamine D2 receptor (DADR2). DADR1 neurons promote reward seeking and positive reinforcement, whereas DADR2 neurons inhibit reward seeking and have an aversive or punishing effect (*14*). One intriguing possibility is that these two neuronal subsets interact to produce their opposing effects on behavior. Nucleus accumbens DADR1 neurons have branches that contact ventral pallidum neurons that presumably receive DADR2 neuron input, and both ventral pallidum and DADR1 neurons project directly to the midbrain (*15*).

Using two different rodent models of chronic pain—nerve injury and inflam-

Excitability and motivation. Glutamate inputs excite nucleus accumbens medium spiny neurons. Chronic pain reduces AMPA receptor function in the DADR2-expressing class of these neurons, thereby reducing their activation by glutamate input. This decreases the motivation to work for a food reward.

mation—Schwartz *et al.* noted that after a week of nociceptive input, there was a robust reduction of the mouse's motivation to work for a food reward. Although the mice showed no reduction in the consumption of easily available food, they were unwilling to exert extra effort to obtain food. The main excitatory inputs to the nucleus accumbens from the amygdala and cortex are glutamatergic. In nucleus accumbens brain slices, Schwartz *et al.* compared the function of DADR1 and DADR2 neurons in response to glutamate and observed an early increase in *N*-methyl-D-aspartate (NMDA) receptor function and a later reduction in the function of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (the NMDA and AMPA receptors are both receptors for glutamate). Surprisingly, this change only occurred in the DADR2

neurons. Furthermore, long-term depression (weakening of specific glutamate synapses) was lost in DADR2 neurons.
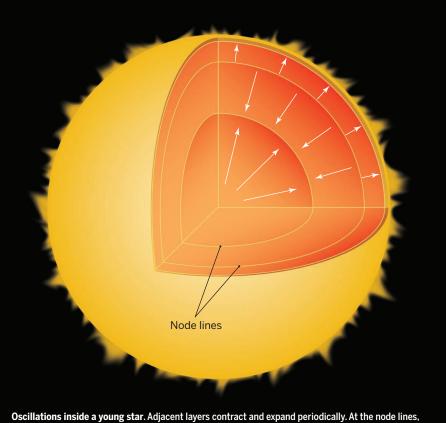
Schwartz *et al.* identified the neuropeptide galanin as the link between the selective changes in glutamate receptor function in the nucleus accumbens and the reduced motivation to work for a palatable taste reward. Decreasing galanin 1 receptor expression in the nucleus accumbens with RNA interference prevented both the behavioral and glutamate receptor changes induced by persistent pain. Furthermore, preventing NMDA-dependent long-term depression both blocked the pain-induced reduction in AMPA receptor function in DADR2 neurons and blocked the reduction in motivation to work for food. This supports a causal link between the reduction in the excitability of DADR2 neurons and the reduced motivation to work for a reward.

By identifying a critical circuit element, Schwartz *et al.* have taken a vital step toward solving the fundamental neurobiological problem of action selection in the presence of conflicting motivations. It will be informative to relate the activity of DADR2 neurons to the effort expended to obtain food in awake behaving animals and to determine how the presence of ongoing pain changes this activity. Further work is also needed to define the behavior-relevant circuit, first by identifying the input pathway to the galanin-releasing neurons in the nucleus accumbens that mediate the change in glutamate receptor function in DADR2 neurons. To understand why reduced excitability in DADR2 neurons reduces the motivation to work for palatable food, it will be essential to determine how they act on their downstream targets. ∎

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Oscillations inside a young star. Adjacent layers contract and expand periodically. At the node lines, gas remains stationary.

ASTRONOMY

The beat of young stars

Pulsations from young stars provide a new chronometer for stellar evolution

By **Steven Stahler**[1] *and* **Francesco Palla**[2]

A star is a ball of gas held together by the compressive force of self-gravity and supported from within by thermal pressure. For most of a star's life, this dynamical balance is stable; perturbing the star does not lead to explosion or collapse, but to oscillation about its equilibrium configuration. Such perturbations arise constantly from small motions within the star itself. Consequently, stars of many evolutionary phases exhibit periodic fluctuations in their luminosity (see the first figure). On page 550 of this issue, Zwintz *et al.* (*1*) report on oscillations of stars so young that they are not yet fusing hydrogen into helium. Expanding on earlier studies of such pre–main-sequence stars (*2*), Zwintz *et al.* find that the observed frequencies of oscillation of a star vary with its age, and do so in the way that theory predicts. Thus, the oscillations potentially provide a new chronometer—something greatly needed in the field of early stellar evolution.

The standard way to assess the age of a star is to measure two quantities: its luminosity, L, and its effective (or surface) temperature, T_{eff}. L is a measure of the total power emitted by the star, which is inferred from the measured flux on Earth, together with the distance to the star. T_{eff} is determined from a high-resolution spectrum of the starlight. The pattern of absorption lines reflects specific wavelengths where the flux is diminished because of absorption by atoms in the stellar surface. Given L and T_{eff}, the star can then be placed in the Hertzsprung-Russell (HR) diagram (see the second figure). The

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