from bats and pangolins indicate that further adaptions, either in animal hosts or in humans, occurred before the virus caused the COVID-19 pandemic (*13*). Therefore, an animal species that has a high population density to allow natural selection and a competent ACE2 protein for SARS-CoV-2—mink, for example—would be a possible host of the direct progenitor of SARS-CoV-2.

Another debate concerns the source of SARS-CoV-2 that caused the COVID-19 outbreak at the end of 2019. The current data question the animal origin of SARS-CoV-2 in the seafood market where the early cases were identified in Wuhan, China. Given the finding of SARS-CoV-2 on the surface of imported food packages, contact with contaminated uncooked food could be an important source of SARS-CoV-2 transmission (*8*). Recently, SARS-CoV-2 antibodies were found in human serum samples taken outside of China before the COVID-19 outbreak was detected (*14*, *15*), which suggests that SARS-CoV-2 existed for some time before the first cases were described in Wuhan. Retrospective investigations of pre-outbreak samples from mink or other susceptible animals, as well as humans, should be conducted to identify the hosts of the direct progenitor virus and to determine when the virus spilled over into humans. ■

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NEUROSCIENCE

How mice feel each other's pain or fear

Distinct neuronal pathways mediate empathy with different affective states

By **Alexandra S. Klein**[1,2] *and* **Nadine Gogolla**[1]

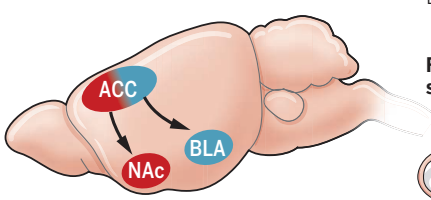
Empathic behaviors play crucial roles in human society by regulating social interactions, promoting cooperation toward a common goal, and providing the basis for moral decision-making (*1*, *2*). Understanding the neural basis of empathy is crucial to understanding not only the human mind but also the neural mechanisms that give rise to social behaviors and the principles of our societies. Functional imaging studies in humans have identified essential brain regions that are engaged when people empathize with the affective experiences of others. However, human neuroimaging studies provide only limited spatial resolution and are solely correlative in nature. It has thus remained unclear how empathy with distinct affective experiences is set apart within the brain. On page 153 of this issue, Smith *et al.* (*3*) investigated the social transfer of pain, pain relief, or fear in mice to address how the sharing of diverse affective states is differentiated within the brain.

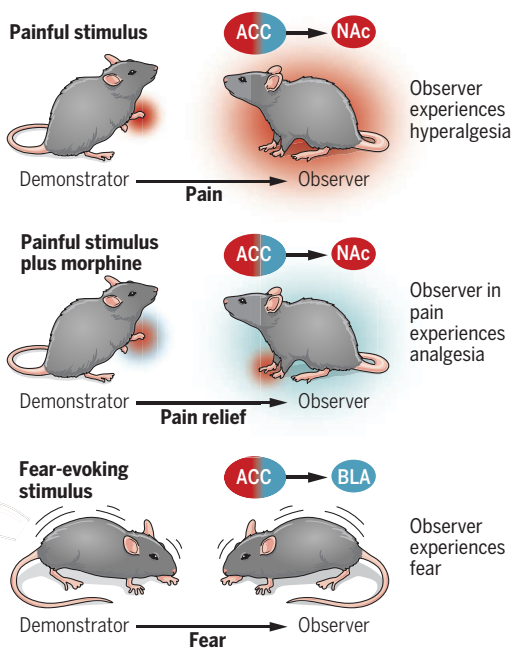
Although long thought of as an exclusively human ability, a basic requirement for empathy is "the ability to share the affective state of others" (*4*, *5*). It was proposed that empathy can be viewed as a multilevel process, in which the simplest form—namely, adopting another's affective state (emotion contagion)—lies at the core of all empathic behaviors. More complex levels of empathy, including prosocial behaviors and learning from the state of the other, evolved later and build on this core of affect sharing (*4*, *5*). According to this definition, there is ample evidence that many animal species exhibit primitive forms of empathy, suggesting that the building blocks of human empathy are deeply rooted in evolution.

To date, numerous studies have demonstrated that rodents also express empathic behaviors, including emotion contagion, but also observational affective learning, or prosocial behaviors such as consolation or helping behaviors (*6*–*8*). Furthermore, homologous brain regions have consistently been described to underlie empathy in humans and animals. One of the most consistently found brain regions in humans and rodents, the anterior cingulate cortex (ACC), has been shown to be involved when

Empathy circuits in mice

Smith *et al.* induced three different affective states in demonstrator mice and investigated the neuronal pathways required in the observer mice to share the diverse affective states of the other. Although the pathway from the anterior cingulate cortex (ACC) to the nucleus accumbens (NAc) was essential for the transfer of both pain and pain relief, a neuronal pathway from the ACC to the basolateral amygdala (BLA) mediated the social transfer of fear.





GRAPHIC: KELLEY K. CHALOTHORN/SCIENCE

empathizing with different sensory and affective states, including pain, disgust, or fear (*9*–*14*). However, whether the ACC contributes to discrimination of the transfer of different affective states that elicit distinct empathic behaviors is an important unanswered issue.

Smith *et al.* demonstrate that the social transfer of pain or fear are mediated by two separate projections from the ACC to distinct subcortical targets in mice (see the figure). Social transfer of pain refers to the phenomenon that a brief exposure to a conspecific (an animal of the same species) who is experiencing pain will lead to a transfer of the same emotion state to the observer. As a result, the observer, who has not experienced any pain itself, is more sensitive to painful stimuli and experiences pain more easily, a phenomenon called hyperalgesia. Similarly, observing a conspecific being in fear will transfer and induce fear reactions in the observer. Using these primitive forms of empathy-like behaviors in mice, Smith *et al.* demonstrate that social transfer of pain relied on a neural pathway from the ACC to the nucleus accumbens (NAc) in the observer mouse. However, this pathway was not required for the social transfer of fear, which involved a separate pathway from the ACC to the basolateral amygdala (BLA). Notably, the authors also found that a positive affective state, the relief from pain, could be socially transmitted. Observer mice who were in pain themselves exhibited lessened pain responses when they had a chance to observe other mice that had undergone pain-relief treatment with morphine. A deeper understanding of how and why analgesia can be transmitted socially may well have important future implications for pain management in humans.

The authors report that the same neuronal pathway from the ACC to the NAc is involved in both the socially mediated positive and negative modulation of subjective pain. How does this single neuronal pathway drive socially transferred analgesia and hyperalgesia at the same time? Perhaps different cell types are targeted in the NAc, which affect distinct downstream brain regions. Understanding this will be an important matter for future studies. Disentangling the circuits for social transmission more generally for positive versus negative affective states may improve our understanding of social and emotion disorders in humans.

The findings of Smith *et al.* also raise the question of whether the ACC-to-BLA fear projection might be involved not only in the social transfer of fear but also in the "relief from fear." It has already been shown that mice are able to reduce their fear behavior in the presence of a nonfearful partner (*6*, *15*). However, the neuronal basis of this social buffering of fear remains elusive. The ACC-to-BLA projection may be a promising candidate for this phenomenon.

One of the most accepted theories for the neuronal mechanisms of empathy is the "perception-action model" (PAM) (*4*, *5*). According to this view, attending to another's affective state is assumed to activate the observer's own neuronal representation and associated feelings of the same state. Smith *et al.* could show that a socially shared emotion causes a generalized pain state in the observer. Both hyperalgesia and analgesia modulated different forms of pain sensitivity and affected the entire body of the observer mouse, suggesting that the observer mouse may truly experience a generalized change of internal state. Indeed, studies in monkeys and rodents have demonstrated the existence of "mirror neurons" in the ACC. These are single nerve cells that are activated both when an individual observes a sensory experience or motor action, or experiences or performs the same condition itself. Pain-sensitive mirror neurons have recently been reported in the ACC of rats (*12*). It will be important to investigate whether it is the activity in mirror neurons or other neuronal mechanisms that account for the social modulation of pain. ■

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CHEMICAL PHYSICS

Between a hydrogen and a covalent bond

The bonds in aqueous FHF^- are neither simple hydrogen nor covalent bonds

By **Mischa Bonn** *and* **Johannes Hunger**

The concept of a molecule as a unit of bound atoms can be traced to Robert Boyle's 1661 treatise "The Sceptical Chymist" (*1*). Chemists often depict the strong covalent bonds in molecules formed through electronic interactions of atoms by sticks or springs. By contrast, much weaker attractive forces between molecules in liquids and solids, such as van der Waals forces, are typically unspecific and nondirectional and cannot be represented by sticks or springs. An exception is the hydrogen bond (H-bond) (*2*), which can create relatively strong directional interactions between molecules when the atoms that carry opposite partial charges attract each other. Discrimination between very strong H-bonds and covalent bonds can become somewhat arbitrary. On page 160 of this issue, Dereka *et al.* (*3*) study what happens if the strength of an intramolecular hydrogen bond becomes comparable to the strength of the intermolecular covalent bonds, blurring the concept of what a "molecule" is.

This study touches on the foundations of chemistry, in that our understanding of chemical bonding as sticks or springs is not without contention. Indeed, it is not evident how to precisely define such "chemical bonds" (*4*), and as recently as 2013, an international conference was called to explore new ways to define, describe, and make sense of chemical bonding (*5*). Such efforts are not purely academic exercises. During chemical conversion, covalent bonds often have to convert to weaker H-bonds (*6*), and proton transport in water relies on the continuous interconversion of covalent and H-bonds.

Dereka *et al.* captured the intermediate case in a liquid for a negatively charged fluoride-hydrogen-fluoride (FHF^-) com-

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