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What's familiarity got to do with it? Neural mechanisms of observational fear in siblings and strangers

Inbal Ben-Ami Bartal[1,*]
[1]School of Psychological Sciences & Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
*Correspondence: inbalbe@tauex.tau.ac.il
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Social modulation of pain sensitivity is considered part of the empathic response. In this issue of *Neuron*, Zhang at al. (2022) uncover the neurobiological basis of observational pain in mice. They report increased synaptic transmission from the insular cortex to the basolateral amygdala and explore genes mediating this effect.

Brian Wallach had a very hard week. "It has been one of the most difficult weeks of my life," he posted on April 30th (https://twitter.com/bsw5020/status/1520119782242148353). He didn't elaborate much. He didn't need to—a couple of sentences were enough to elicit an outpouring of empathy and encouragement from thousands of people. Do you know Brian? I didn't, until his tweet showed up on my feed and I started following his journey living with amyotrophic lateral sclerosis (ALS), a currently terminal disease. Since his diagnosis, Brian has been sharing his daily life and his herculean ALS advocacy campaign. He has garnered over 100k followers, many, like myself, strangers with no personal link to ALS, who have become emotionally engaged. Like the prophet in Phillip K. Dick's classic *Do Androids Dream of Electric Sheep*, which inspired the film *Blade Runner*, Brian is endlessly going up a figurative mountain while being hit by stones. And we, like the novel's sparse human population, share in his journey through our "empathy boxes."

As humans, we possess powerful built-in empathy boxes: our brains. We show remarkable sensitivity to others' pain and distress, which is often coupled with a strong prosocial motivation to act for their well-being. Let's call this phenomenon "empathy" (Eisenberg et al., 2010). How and why does the brain experience empathy? Importantly, why do we care so much about the suffering of some yet remain oblivious to the distress of other individuals or groups? This is exactly what Zhang et al. (2022) set out to find in their investigation published in this issue of *Neuron*. To study empathy at the molecular level, Zhang and authors rely on a seminal discovery by Jeffery Mogil's group (Langford et al., 2006), on the social modulation of pain sensitivity in mice. While "empathy" is an elusive structure to measure even in humans, pain is easy to elicit and quantify with well-established behavioral paradigms. The finding that mice show hyperalgesia (i.e., increased sensitivity to pain) when observing cagemates, but not strangers, in pain was a game changer in the field, convincing many that empathy stems from neural and endocrine systems evolutionarily conserved across mammals. Subsequent studies have demonstrated that in rodents, as in humans, a shared neural network is active both for self-pain and for observed pain, including the anterior cingulate cortex (ACC), insular cortex (IC), and other regions, composing a common mammalian circuit for empathic arousal (Meyza and Knapska, 2018).

Employing a model of nerve ligation, Zhang et al. (2022) similarly found that mice responded to siblings', but not strangers', pain with decreased mechanical pain threshold ("observational pain" or OP). Through a series of immunohistochemistry and tracing studies in a FOS-Cre driver line (activity tagging via immediate-early gene expression), they identified increased FOS expression in the IC-basolateral amygdala (BLA) projection selectively in the sibling condition. This result suggests that the IC-BLA projection is preferentially engaged during OP, an effect that was selectively observed in the right hemisphere. Next, using *in vitro* electrophysiology recordings and optogenetic methods, the authors showed increased synaptic transmission in right IC projections to both excitatory pyramidal cells and inhibitory interneurons in the right BLA. Virally ablating postsynaptic pyramidal BLA cells abolished OP, whereas ablation of postsynaptic GABAergic BLA interneurons increased OP—effects that were found only in the right hemisphere. Therefore, the occurrence of OP depended on glutamatergic activation of IC projections to BLA pyramidal cells, whereas IC projections to BLA interneurons modulated OP intensity. Using chemogenetic methods, OP was elicited for stranger mice and blocked for siblings via excitation or inhibition of the IC-BLA projection, respectively. As above, right-side laterality was demonstrated. Molecular screening techniques identified synaptotagmin-2 (Syt2) and Rab3-interacting molecule-3 (RIM3), genes involved in synaptic transmission, as upregulated in the right hemisphere of IC and BLA in the sibling condition. Strikingly, suppression of Syt2 and RIM3 specifically in the IC-BLA projection via RNAi knockdown caused a drastic reduction of OP. The effect of Syt2 primarily affected presynaptic glutamate release, whereas RIM3 affected postsynaptic NMDAR-mediated responses, with Syt2 knockdown causing an overall shift to slow neurotransmitter release. In summary, Zhang and colleagues uncovered synaptic and molecular mechanisms underlying OP, converging on the idea that potentiated excitatory transmission of right hemisphere IC-BLA projections mediate OP observed selectively in the sibling condition.

The lack of response to strangers' pain is an important aspect of these findings. As a stand-alone phenomenon, OP could be interpreted as a self-oriented response, promoting the observers' survival by preparing the body for quick escape or priming the immune response to potential wounding (Keysers and Gazzola, 2021). Yet, in that case, a non-selective OP response would be more adaptive, because identity is irrelevant as an alarm signal. The striking absence of response for strangers suggests that OP is inherently a social response, important for directing behavior toward others.

The question of whether OP in rodents is associated with prosocial motivation, or intent to reduce the others' distress, led me to develop, a decade ago, a helping behavior paradigm aimed at testing this idea in rats. Our team found that rats are motivated to help a distressed cagemate and learn to release casemates from a restrainer, consistently and without training or external reward (Ben-Ami Bartal et al., 2011). Additional demonstrations of prosocial behaviors, including consolation, providing food, and rescue, have since provided further evidence for targeted helping in response to distress cues in rodents (Cox and Reichel, 2020). Like OP, helping is socially selective, and rats only release others of their own social group (Ben-Ami Bartal et al., 2014). Furthermore, we found that ACC-NAc activity was correlated with helping, which was offered to cagemates but not to strangers of another strain (Ben-Ami Bartal et al., 2021). Zhang et al. also found increased activity in the ACC-NAc pathway on the first day of testing but not on later sessions. This is in line with the idea that IC-BLA and ACC-NAc pathways play distinct roles for emotional contagion and prosocial motivation. The amygdala, which participates in both empathy (Meyza and Knapska, 2018) and social reward (Hu et al., 2021) in rodents, may integrate between these functions.

It is yet unknown how familiarity influences empathy. Interestingly, Zhang et al. (2022) report that after 2 weeks of testing, OP for strangers started occurring. Congruently, co-housing induced helping for strangers of the previously unfamiliar strain (Ben-Ami Bartal et al., 2014). The emergence of OP and helping with familiarity may reflect decreased threat arousal, increased saliency of the distress signals, increased value for the others' outcome, or a combination of these things. Understanding what happens as familiarity is established, to turn "foes to friends," is critical for advancing solutions to the increasing polarization and empathy gap for outgroups.

In conclusion, this paper provides insight into the different roles of IC-BLA and ACC-NAc for the social modulation of pain in mice. The social selectivity of this response suggests it is linked with a prosocial motivation. Whether prosocial behavior is causally dependent on emotional contagion or if these are two separate, albeit often parallel, processes remains to be determined. Brian Wallach's ability to elicit empathy in strangers is changing the lives of ALS patients by advancing funding and awareness and boasting the recent signing of the "ACT of ALS" bill, which budgets $100 million *yearly* for research and patient support. This was achieved by myriad people who were moved to action by their empathy for Brian, demonstrating the power empathy can have when it elicits prosocial behavior. Empathy is best viewed as a call for action. To end with another literary allusion, we need to realize, like 10-year-old Bastian in Ende's *The NeverEnding Story*, that the purpose of our "empathy box" is to mobilize our own personal voice and to use it in favor of strangers whose pain we are privileged to witness from the sidelines.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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