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A physiological cause to empathy deficits in a mouse model of FTD

Zhen Yan[1,*]
[1]Department of Physiology and Biophysics, State University of New York at Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY 14203, USA
*Correspondence: zhenyan@buffalo.edu
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Loss of empathy is a core behavioral symptom of frontotemporal dementia (FTD). In this issue of *Neuron*, a study by Phillips et al.[1] reveals that hypoactivity of dorsomedial prefrontal cortex is causally linked to empathy deficits in a mouse model of FTD.

Empathy, the ability to understand the emotional experience of others and to give a caring response to someone else's distress, is an important trait conserved in multiple species. Loss of empathy is one of the common behavioral changes in various neurological and psychiatric disorders. Patients with frontotemporal dementia (FTD), a neurodegenerative disorder associated with progressive deterioration of frontal and/or temporal lobes, demonstrate severe deficits in empathy.[2] What is the cause underlying the manifestation of this cardinal symptom of FTD? In this issue of *Neuron*, Phillips et al. tackle this question by using an elegant combination of behavioral, electrophysiological, optogenetic, and chemogenetic approaches in a mouse model of FTD.[1]

Phillips et al. first designed a behavioral paradigm to examine empathy in mice. Briefly, two mice were first allowed to freely interact. Then one mouse (demonstrator) was given repetitive foot-shocks with another mouse (observer) watching nearby. After this observational fear conditioning session, the two mice were put together to allow their interaction. The authors found that observers displayed robust prosocial behaviors toward distressed demonstrators, including allogrooming and body contact, which significantly decreased anxiety in demonstrators. In addition to these affiliative behaviors directed by others, observers also exhibited increased observational fear, an indicator of the spread of emotions across individuals. Thus, this mouse behavioral paradigm captures two major aspects of empathy: distress-induced, other-directed consolation and affect-sharing emotional contagion.

Using this empathy behavioral paradigm, the authors examined a mouse model of FTD that expresses 66 GGGGCC repeat expansions in a common FTD gene, C9orf72 (hereon referred to as "FTD mice"). At ~12 months (equivalent to 45–50 human years when most FTD symptoms peak), these FTD mice displayed 20%–25% neuron loss in prefrontal cortex (PFC). Moreover, FTD observers showed a marked loss of affiliative behaviors toward distressed demonstrators and significantly less observational fear, suggesting loss of empathy. Thus, this study established a mouse model of FTD that exhibits not only prefrontal atrophy but also empathy deficits.[1]

To understand the neuronal basis of the observed empathy deficits in FTD mice, Phillips et al. turned their attention to the PFC, a brain region that plays a key role in regulating emotional, cognitive, and social behaviors.[3–5] They found that the intrinsic excitability of dorsomedial PFC (dmPFC) projection neurons was significantly dampened in FTD mice, as indicated by the increased difficulty of firing action potentials and reduced firing frequencies.[1]

To find out whether the dmPFC hypoexcitability was causally linked to empathy loss in FTD mice, the authors employed a two-pronged approach. In wild-type mice, optogenetic inhibition of the dmPFC potently inhibited other-directed affiliative behaviors and significantly decreased observational fear. In the FTD mice, chemogenetic stimulation of dmPFC restored both other-directed affiliative behaviors and observational fear. These data suggest that dmPFC hypoactivity is both necessary and sufficient for empathy loss in a mouse model of FTD.

The findings by Phillips et al. have many important implications. First, it confirms that empathy can be modeled in rodents, consistent with prior observations of emotional contagion and consolation in mice.[6,7] Second, it uncovers empathy deficits in an FTD mouse model, reconstituting a primary symptom of human FTD. Third, it reveals dmPFC hypoexcitability as the pathophysiological basis of empathy loss in FTD mice. Fourth, it suggests that enhancing the activity of frontotemporal cortex is a viable therapeutic strategy to restore empathy even at an advanced disease stage.

These intriguing findings will stimulate further studies on empathy in health and diseases. One key question to be answered is how mutant *C9orf72* causes the diminished intrinsic excitability of dmPFC projection neurons. Non-coding repeat expansion in the *C9ORF72* gene is the most frequent cause of FTD. *C9orf72* has been found to regulate autophagy, vesicular trafficking, mTORC1 signaling, actin dynamics, and endosomal recycling of synaptic GluR1 in neurons.[8] While alterations of subthreshold-operating ion channels are suggested to underlie dmPFC hypoactivity in FTD mice,[1] the ionic basis and the connection to mutant *C9orf72* are largely unknown.

Another set of questions is related to the specificity of the main findings. For example, are there activity changes in other brain regions of FTD mice? Is the identified neural mechanism generally applicable to loss of empathy in other brain diseases? Does dmPFC hypoactivity underlie other phenotypes in behavioral variant FTD, such as lack of interest (apathy), executive dysfunction and loss of inhibition?[2] Recent *in vivo* electrophysiological recordings of behaving animals have demonstrated that PFC hypoactivity

is directly linked to disinhibition of inappropriate actions.[9] In male mice exposed to chronic adolescent social isolation stress, the spiking activity of PFC pyramidal neurons was diminished during prolonged aggressive attack epochs in resident-intruder tests, suggesting that PFC hypoexcitability in stressed animals drives heightened aggression,[9] a kind of inappropriate emotional reactivity to perceived social threats.

To find out the translational value of this preclinical study, it will be interesting to know whether dmPFC shows altered activity in FTD patients at various stages, and whether the physiological alterations are well correlated with behavioral changes in FTD patients. If so, normalizing the activity of specific neural circuits with implanted intracranial electrodes could be a potential avenue to mitigate behavioral disturbances in FTD. An electrostimulation-response mapping in a severely depressed patient has provided proof of concept for personalized, circuit-specific medicine in psychiatry.[10]

Recent advances in brain circuit mapping using innovative technologies have revealed the physiological basis of many sophisticated behaviors. It is important to identify specific neural networks and activity patterns that are crucial for exerting certain functions. The knowledge provides unprecedented opportunities for understanding exactly how the brain enables the body to act and respond. More circuitry studies in pathological conditions, such as the one described here,[1] are needed to guide the development of highly precise deep brain stimulations as a novel therapy for a wide range of diseases.

DECLARATION OF INTERESTS

The author declares no competing interests.

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Forming new connections: Advances in human stem-cell-derived interneuron therapy for treating epilepsy

Jyoti Gupta[2] and Janice R. Naegele[1,*]
[1]Department of Biology, Program in Neuroscience and Behavior, Wesleyan University, Middletown, CT, USA
[2]Department of Neuroscience, Yale School of Medicine, New Haven, CT, USA
*Correspondence: jnaegele@wesleyan.edu
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Inhibitory interneuron progenitors capable of integrating into epileptic host circuitry hold great potential for correcting network hyperexcitability and reducing seizures in temporal lobe epilepsy. In this issue of *Neuron*, Zhu and colleagues[1] report robust seizure suppression by hPSC-derived interneurons up to 9 months post-transplantation, significantly extending the duration observed previously.

Generating neural progenitors for stem-cell-based treatments of human neurological disorders is a long-standing challenge. Inhibitory GABAergic interneurons, in particular, have an enormous potential for correcting network hyperexcitability in temporal lobe epilepsy (TLE). However, obtaining purified populations of human GABAergic progenitors, which can