How and where a painful event becomes permanently etched in the brain

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A team of researchers led by the University of Toronto has charted how and where a painful event becomes permanently etched in the brain - a discovery that has implications for pain-related emotional disorders such as anxiety and post-traumatic stress.

U of T physiology professor Min Zhuo and his colleagues Professor Bong-Kiun Kaang of Seoul National University in South Korea, and Professor Bao-Ming Li of Fudan University in China have identified where emotional fear memory and pain begin by studying the biochemical processes in a different part of the brain. In a paper published in the Sept.15 issue of Neuron the researchers use mice to show how receptors activated in the pre-frontal cortex, the portion of the brain believed to be involved with higher intellectual functions, play a critical role in the development of fear. Previous research had pointed to activation in the hippocampus, an area buried in the forebrain that regulates emotion and memory, as the origin of fear memory.

"This is critical as it changes how and where scientists thought fear was developed," says Zhuo, the EJLB-CIHR Michael Smith Chair in Neurosciences and Mental Health. "By understanding the biomolecular mechanisms behind fear, we could potentially create therapeutic ways to ease emotional pain in people. Imagine reducing the ability of distressing events, such as amputations, to be permanently imprinted in the brain."

Zhuo says that fear memory does not occur immediately after a painful event; rather, it takes time for the memory to become part of our consciousness. The initial event activates NMDA receptors - molecules on cells that receive messages and then produce specific physiological effect in the cell - which are normally quiet but triggered when the brain receives a shock. Over time, the receptors leave their imprint on brain cells.

By delivering shocks to mice, the researchers activated the NMDA receptors and traced a subunit of the molecule - a protein called NR2B - long believed to be associated with fear memory in the hippocampus and the amygdala, an almond-shaped structure in front of the hippocampus. To further test the protein's influence, researchers reduced the amount in mice and found they were less hesitant to avoid shocks. "We tested the animals using both spatial and auditory cues," Zhuo says. "In one experiment, the mice received small shocks when entering a chamber and they developed fear memory. In another experiment, we used sound tones to be associated with shocks. When NR2B was blocked, they no longer avoided the chamber or reacted to the tone."

Zhuo and his team then studied the mice's brain slices and discovered traces of NR2B in the pre-frontal cortex, supporting their theory that fear memory develops in that region. "By identifying NR2B in the pre-frontal cortex of the brain, we propose that fear memory originates from a network of receptors, rather than one simple area," Zhuo says. "It is more complex than previously thought."

The next step, according to Zhuo, is to determine how NR2B directly affects memory formation and storage in the brain. "While we know it exists in the hippocampus, amygdala and the pre-frontal cortex, we don't know exactly how it alters them," Zhuo says. "Once we understand the implications

for each part, we will be able to reduce levels of NR2B accordingly and effectively reduce fear memory. In the future, perhaps people can take therapeutic measures before experiencing a particularly discomforting situation." The University of Toronto Innovations Foundation is currently working with Zhuo to push for the translation of this finding into treatments.

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