To be or not to be afraid: Neuronal encoding of the switch from specific to generalized fear

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Fear memories are crucial for survival. However, excessive generalization of such memories, characterized by a failure to discriminate dangerous from safe stimuli, is common in anxiety disorders. We identified distinct neuronal populations in the amygdala that signaled generalized versus cue-specific associations and determined

how their distributions switched during fear generalization. These results provide a cellular basis in the amygdala for the alteration of emotional states from normal to pathological fear.

"I can't get the memories out of my mind!... I am right back in Vietnam, in the middle of the monsoon season at my guard post. My hands are freezing, yet sweat pours from my entire body...I smell a damp sulfur smell. Suddenly I see what's left of my buddy Troy, his head on a bamboo platter, sent back to our camp by the Viet Cong."i

This veteran of the US army, who served in Vietnam, has intense flashbacks of his decapitated friend whenever he hears a clap of thunder, touches a bamboo mat, or sees an Oriental woman. Although the traumatic incident happened decades ago in a battlefield half way around the world, his vivid memories continue to produce a state of hyperarousal and intense fear similar to what he experienced that fateful day.

How did that specific trauma morph into a state of generalized fear and anxiety, leading to the soldier's post-traumatic stress disorder (PTSD)?

Now, a study published in *Nature Neuroscience*, by Professor Sumantra Chattarji, a neuroscientist at the National Centre for Biological Sciences (NCBS) in Bangalore and his student Supriya Ghosh, gives new insight into how the brain's ability to distinguish safe from dangerous stimuli can go badly wrong, potentially leading to a state of generalized fear.

The fear conditioning experiments, done with live rats, showed that individual neurons in the amygdala, the emotional hub of the brain, that were initially capable of telling apart safe from dangerous stimuli can start firing indiscriminately—causing the rat to become fearful of non-threatening stimuli. Faced with the potential for greater danger, the neurons reflect the animal's tendency to err on the side of caution.

Fear conditioning is learning by association. A widely known example of this type of learning came from the work of the Russian physiologist Ivan Pavlov. In his experiments, a dog did not respond to the ring of a bell on its own. However, when the same bell ring was followed by food, a later exposure to the bell alone caused the dog to salivate. It remembered that the bell predicts a reward.

Interestingly, Pavlov's dogs salivated not just to the original bell, but to other sounds as well; especially to sounds similar to the original bell. In other words, animals generalize from one stimulus to another not only because they cannot discriminate them, but because they expect that the stimuli are likely to have the same consequence. If the consequence is not a reward but a painful punishment or a dangerous situation, then the stakes are obviously higher. If an animal under-generalizes it may overlook future signs of danger, whereas if it over-generalizes it may be too afraid to explore and thereby miss opportunities for feeding, mating, etc. So, striking the right balance is essential for survival.

In this latest study Ghosh and Chattarji used a variation of Pavlov's classical conditioning paradigm. Instead of the ring of a single bell, rats were exposed to two distinctly different sounds, one of which was paired with a mild electric shock, while the other was not. Thus, one of the tones predicted danger and the other one was "safe". The rats quickly learned to discriminate between the two by showing a bigger fear response only to the dangerous but not the safe tone. As the animals learned, the researchers recorded electrical signals from individual neurons in the amygdala, a brain structure that forms memories of fearful experiences.

These recordings revealed that the learning experience changes electrical activity of the amygdala neurons. Electrical signals in a majority of amygdala neurons mirrored the animal's behavior - they fired more in response to the dangerous tone compared to the safe one. In other words,

just like the whole animal, a single neuron in the amygdala was capable of discriminating between the dangerous and safe stimuli. The authors also noticed that a small number of neurons did not possess this ability - they fired indiscriminately to both tones; but these were vastly outnumbered by neurons that responded only to the dangerous tone.

Strikingly, when the shock associated with the dangerous tone was made stronger, the same animals lost their ability to discriminate between the two stimuli and began showing a greater fear response to the safe tone too. Thus, the animal became more afraid of the safe tone, although the tone was never paired with a shock. The potentially greater cost of failing to discriminate correctly pushed the animals towards playing it safe - they acted as if potential danger lurked behind the safe tone too.

In animals that started fearing the safe tone, there was a significant shift in the electrical activity of amygdala neurons. Compared to when the animal was capable of remembering what was truly dangerous, now almost five to six times as many neurons in the amygdala responded just as strongly to both the safe and dangerous tones. Thus, a much larger proportion of amygdala neurons lost their ability to discriminate between the safe and dangerous stimuli—causing the observed fearful behavior in the rats.

Remarkably, this study finds that the same neuron that was initially capable of discriminating safe from dangerous lost its ability to do so when the animal exhibits generalized fear. Thus, faced with the potential for greater danger, neurons in the amygdala reflect the animal's tendency to play it safe. This study provides a breakthrough in our understanding of how information processed in the amygdala - one cell at a time - maintains the delicate balance between whether one should or should not be afraid.

This path breaking discovery also gives new insights into the neural basis

of psychiatric disorders such as PTSD, a debilitating disorder triggered by a traumatic or life-threatening experience. Originally described as "shell shock" in soldiers, PTSD has subsequently been reported in victims of sexual violence, accidents, natural disasters and terrorism. In addition to repeated flashbacks, patients respond with intense fear and hyperarousal, similar to that experienced during the original traumatic event, to the most inconsequential sensory stimuli that by themselves pose no threat, such as the bamboo mat in the case of the US soldier described earlier. Thus, excessive generalization of the original fearful stimulus is a major symptom of PTSD. Although earlier brain imaging studies found the amygdala to be hyperactive in PTSD, the underlying cause for this was poorly understood.

Ghosh and Chattarji's new findings explain how aberrant electrical signaling in individual neurons can add up to give rise to amygdala hyperactivity and generalization of fear in PTSD. Further, they identify a specific biochemical signaling mechanism inside amygdala neurons that can mediate this transition to generalized fear, which could potentially serve as a target for designing new treatments against PTSD.

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