# Erasing Fear: The Search for PTSD Treatment

By Katrina Verbrugge '13

According to the National Institute of Mental Health, 7.7 million American adults suffer from post-traumatic stress disorder (PTSD) in a given year (1). In PTSD, exposure to terrifying ordeals triggers debilitating reactions, such as reliving the experience. These reactions are largely based on fearful memories, which are memories of traumatic events that can resurface spontaneously with accompanying physical symptoms such as increased heart rate. Treatments for the disorder rely on understanding how to control fearful memories, and progress on this has been made through recent neurobiological studies on the neural basis of fear extinction in rats and the perineuronal nets that prevent fearful memory erasure in adult mice.

Three areas of the brain play a role in the extinction and renewal of fear memories: the amygdala, medial prefrontal cortex, and hippocampus. The basolateral amygdala receives sensory information about the stimuli and the central nucleus of the amygdala sends the processed information to the hippocampus to produce physiological and behavioral responses. The medial prefrontal cortex is believed to store long-term extinction memories (2).

In order to study the neurocircuitry of fear memories, researchers redesigned Ivan Pavlov's classical conditioning experiment. Pavlov conditioned dogs to salivate at the sound of a bell by repeatedly presenting food while sounding the bell. The food acted as an unconditioned stimulus (US) that produced a salivary response, and over time the dogs learned to associate the bell with the food and salivated merely at the sound of the bell, which acted as the conditioned stimulus (CS)(3). In fear conditioning a small electric foot shock acts as an aversive US, since rats naturally display fear responses such as freezing when encountering a shock, and a tone acts as the CS. The rats form a long-lasting fear memory associated with the CS, freezing upon its sound even in the absence of the shock (4).

Fear extinction is new learning that eventually inhibits a conditioned behavior but does not erase the fear memory. In extinction learning, the CS is presented repeatedly in the absence of the US so the association between the two weakens. After this learning process, the rats no longer present characteristic behavioral and physiological responses to danger when the CS is presented. (5).

Since extinction is not erasure, the rats can regain the conditioned fear responses after the extinction training if the CS is presented during or after exposure to a dangerous situation. The rats exhibit spontaneous recovery if tested in the extinction context and context-dependent renewal if tested in the initial fear conditioning setting (6). The knowledge that recovery depends partially on setting has important implications for PTSD treatment, as mere reminders of war or abuse can reignite fear memories and flood sufferers with flashbacks. Extinction, therefore, cannot completely treat PTSD since those with the disorder must avoid certain settings.

During conditioning, the activity of certain basolateral amygdala neurons (fear neurons) is enhanced through long-term potentiation as the synapses between the neurons and hypothalamus strengthen so the CS evokes a stronger response. However, during extinction, inhibitory neurotransmitters block the long-term potentiation of these fear neurons so they no longer fire in response to the CS. Instead, another population of neurons (extinction neurons) emerges which fire in response to the CS. Upon fear renewal the fear neurons reactivate and the extinction neurons stop firing (7).

Clusters of inhibitory neurons called intercalated cell masses (ICMs) control the amygdala's output during extinction. Extinc-

tion neurons are connected to the medial prefrontal cortex, and the neurons leading from the medial prefrontal cortex innervate ICM neurons. These ICM neurons' activity may inhibit the amygdala's output to the hippocampus during extinction, reducing behavioral and physiological fear responses. ICM neurons also inhibit output neurons in the central nucleus by shifting the inputs from the fear neurons (8).

A research team from the Center for Molecular and Behavioral Neuroscience at Rutgers University demonstrated that ICM neurons are necessary in the extinction process by infusing the toxin saporin to selectively destroy ICM neurons. As the number of ICM cells decreased, the deficit in the expression of extinction increased, suggesting the cells to play a key role in extinction. This leads to the possibility of pharmacological treatments for anxiety disorders like PTSD that could enhance the excitability of the ICM neurons and thus facilitate extinction. ICM neurons have specialized receptors that are not prevalent in the surrounding neural tissue, so pharmacological treatment could specifically target these neurons without interfering with other neural activity (9).

Perineuronal nets (PNNs) are highly organized extracellular matrices that also have a large role in fear extinction. Mice develop these PNNs during the first four postnatal weeks until they are at adult levels, with the largest increase occurring around 16- 21 days after birth. A recent study at the Friedrich Miescher Institute of Biomedical Research in Switzerland found that young mice conditioned before they were 16 days old did not show increased fear response seven days after extinction training while those conditioned after they were 23 days old showed significant spontaneous recovery and renewal. Thus, the switch of fear memories from erasure-prone to erasure-resistant occurs at the same time as the maturation of PNNs, indicating fear memories are protected from erasure by PNNs.

Further proof of this is the ability of adult mice to lose fear memories completely if the PNNs are dissolved with chondroitinase ABC

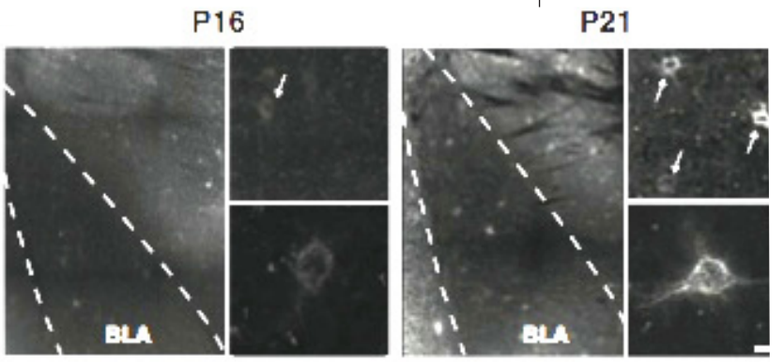


Figure 1. The basolateral amygdala stained with Wisteria floribunda agglutinin (WFA) showing perineuronal nets. The number of detectable PNNs dramatically increases between 16 and 21 days post birth. This corresponds to the age at which there is a switch in fear memories from erasure-prone to erasure-resistant.

before the original fear conditioning. Since PNNs actively protect fear memories from erasure, further research about them could help create new strategies to prevent the development of extinction resistant fear, like that in anxiety disorders and PTSD (6).

Further research into the neuronal circuitry of fear extinction, especially the inhibitory capabilities of intercalated cell mass neurons and perineuronal nets, will help provide a basis to develop specific treatments for anxiety disorders if the results are applicable to humans as well. New strategies could include pharmacological interventions targeted towards strengthening extinction and preemptively dissolving PNNs to prevent development of extinction-resistant memories. Overall, the new findings have led to both increased understanding of controlling fear memories and opened doors for further investigation. H

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