Learning to overcome fear is difficult for teens, brain study finds

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A new study by Weill Cornell Medical College researchers shows that adolescents' reactions to threat remain high even when the danger is no longer present. According to researchers, once a teenager's brain is triggered by a threat, the ability to suppress an emotional response to the threat is diminished which may explain the peak in anxiety and stress-related disorders during this developmental period.

The study, published Sept. 17 in the early online edition of the Proceedings of the National Academy of Sciences (*PNAS*), is the first to decode fear acquisition and fear "extinction learning," down to the synaptic level in the brains of mice, which mirror human neuronal networks. Also, through human and rodent experiments, the study finds that acquired fear can be difficult to extinguish in some adolescents. By contrast, the study shows that adults and children do not have the same trouble learning when a threat is no longer present.

"This is the first study to show, in an experiment, that adolescent humans have diminished fear extinction learning," says the study's lead author, Dr. Siobhan S. Pattwell, a postdoctoral fellow at the Sackler Institute for Developmental Psychobiology at Weill Cornell. "Our findings are important because they might explain why epidemiologists have found that anxiety disorders seem to spike during adolescence or just before adolescence. It is estimated that over 75 percent of adults with fear-related disorders can trace the roots of their anxiety to earlier ages."

The study findings suggest there is altered plasticity in the prefrontal

cortex of the brain during adolescence, with its inability to overcome fear, says the study's senior co-investigator, Dr. Francis Lee, professor of pharmacology and psychiatry at Weill Cornell Medical College, and an attending psychiatrist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"This study is the first to show activity, at the synaptic level, for both fear acquisition and fear extinction—and we find that while these areas function well in both younger and older mice, neurons involved in fear extinction are not as active in adolescent mice," says Dr. Lee. "If adolescents have a more difficult time learning that something that once frightened them is no longer a danger, then it is clear that the standard desensitization techniques from fear may not work on them. This new knowledge about the teenage brain's synaptic connections not responding optimally will help clinicians understand that the brain region used in fear extinction may not be as efficient during this sensitive developmental period in adolescents."

Adolescent Mice Never Lose Their Fear Response

Fear learning is a highly-adaptive, evolutionarily conserved process that allows one to respond appropriately to cues associated with danger. In the case of psychiatric disorders, however, fear may persist long after a threat has passed, and this unremitting and often debilitating form of fear is a core component of many anxiety disorders, including post-traumatic stress disorders (PTSD).

Existing treatments, such as exposure therapy, are designed to expose an individual slowly to the cues associated with a perceived threat. This technique is used for a variety of fears, from wartime PTSD to fear of flying, as well as serious adolescent anxiety about school, says Dr. Lee, who treats, among others, patients with PTSD acquired during the World Trade Center collapse on September 11, 2001.

Anxiety disorders are increasingly being diagnosed in children and adolescents, but the success rate of fear extinction-based exposure therapies are currently not known in this population. This study aimed to discover if they could be effective—and why or why not.

The human experiment was conducted at the Sackler Institute for Developmental Psychobiology at Weill Cornell in collaboration with its director, Dr. B.J. Casey, a study senior co-investigator, who is the Sackler Professor of Developmental Psychobiology and professor of psychology in psychiatry at Weill Cornell. In the experiment, a group of volunteers—children, adolescents and adults —wore headphones and skin sweat meters and were asked to look at a computer screen with a sequence of blue or yellow square images. One of the squares was paired with a really unpleasant sound. For example, 50 percent of the time the blue square would set off the noise.

If the participants acquired a fear of the noise, they showed increased sweat when viewing the image that was paired with it, says Dr. Pattwell. The same group was brought back the next day, and again viewed a sequence of blue or yellow squares, but this time there was no associated noise. "But teenagers didn't decrease their fear response, and maintained their fear throughout subsequent trials when no noise was played," she says. However, the researchers documented that, unlike the teens participating in this study aged 12-17, both children and adults quickly learned that neither square was linked to a noxious sound, and this understanding rapidly decreased their fear response.

The mouse experiment, which used standard fear conditioning common in these types of animal studies, obtained similar findings. Adolescent mice (29 days old) did not decrease their fear response to stimuli that no longer existed, but younger and older mice did. Interestingly, the adolescent mice never lost their fear response as they aged.

The research team then monitored the brains of mice as they participated in the experiment. With the assistance of study senior co-investigator, Dr. Ipe Ninan, an electrophysiologist at NYU Langone Medical Center who is an assistant professor of psychiatry, the research team found that the prelimbic region in the prefrontal cortex, the brain region that processes emotion, is activated during acquisition of fear, and the infralimbic prefrontal cortex is used to extinguish this fear association. While other groups have suggested that the prefrontal cortex plays a role in extinction, no one has shown that this activity is at the level of the synapse—the connections between the neurons.

"In young and old mice, we see plasticity, which is activity in the infralimbic cortex, which helps the animals decrease their fear response when a threat no longer applies," says Dr. Pattwell. "Interestingly, we didn't witness similar activity in adolescent mice."

According to researchers there is much more to explore about the fear response and its decoding in human adolescents, such as whether genes contribute to susceptibility to altered fear learning, and most importantly, what can be done to help the adolescent population overcome fear.

"We need to investigate personalized approaches to treatment of these fear and anxiety disorders in teens," says Dr. Lee. "It is essential that we find a way to help teenagers become more resilient to the fear they experience during adolescence to prevent it from leading to a lifetime of anxiety and depression."

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