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Study reveals potential target to better treat, cure anxiety disorders

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Researchers at Boston University School of Medicine (BUSM) have, for the first time, identified a specific group of cells in the brainstem whose activation during rapid eye movement (REM) sleep is critical for the regulation of emotional memory processing. The findings, published in the *Journal of Neuroscience*, could help lead to the development of effective behavioral and pharmacological therapies to treat anxiety disorders, such as post-traumatic stress disorder, phobias and panic attacks.

There are two main stages of sleep – REM and non-REM – and both are necessary to maintain health and to regulate multiple memory systems, including emotional memory. During non-REM sleep, the body repairs tissue, regenerates cells and improves the function of the body's immune system. During REM sleep, the brain becomes more active and the muscles of the body become paralyzed. Additionally, dreaming generally occurs during REM sleep, as well as physiological events including saccadic eye movements and rapid fluctuations of respiration, heart rate and body temperature. One particular physiological event, which is a hallmark sign of REM sleep, is the appearance of phasic pontine waves (P-waves). The P-wave is a unique brain wave generated by the activation of a group of glutamatergic cells in a specific region within the brainstem called the pons.

Memories of fearful experiences can lead to enduring alterations in emotion and behavior and sleep plays a natural emotional regulatory role after stressful and traumatic events. Persistence of sleep disturbances,

particularly of REM sleep, is predictive of developing symptoms of anxiety disorders. A core symptom of these disorders frequently reported by patients is the persistence of fear-provoking memories that they are unable to extinguish. Presently, exposure therapy, which involves controlled re-exposure to the original fearful experience, is considered one of the most effective evidence-based treatments for anxiety disorders. Exposure therapy produces a new memory, called an extinction memory, to coexist and compete with the fearful memory when the fearful cue/context is re-encountered.

The strength of the extinction memory determines the efficacy of exposure therapy. A demonstrated prerequisite for the successful development of an extinction memory is adequate sleep, particularly REM sleep, after exposure therapy. However, adequate or increased sleep alone does not universally guarantee its therapeutic efficacy.

"Given the inconsistency and unpredictability of exposure therapy, we are working to identify which process(es) during REM sleep dictate the success or failure of exposure therapy," said Subimal Datta, PhD, director and principle investigator at the Laboratory of Sleep and Cognitive Neuroscience at BUSM who served as the study's lead author.

The researchers used contextual fear extinction training, which works to turn off the conditioned fear, to study which brain mechanisms play a role in the success of exposure therapy. The study results showed that fear extinction training increased REM sleep. Surprisingly, however, only 57 percent of subjects retained fear extinction memory, meaning that they did not experience the fear, after 24 hours. There was a tremendous increase of phasic P-wave activity among those subjects. In 43 percent of subjects, however, the wave activity was absent and they failed to retain fear extinction memory, meaning that they re-experienced fear.

"The study results provide direct evidence that the activation of phasic P-wave activity within the brainstem, in conjunction with exposure therapy, is critical for the development of long-term retention of fear extinction memory," said Datta, who also is a professor of psychiatry and neurology at BUSM. In addition, the study indicates the important role that the brainstem plays in regulating emotional memory.

Future research will explore how to activate this mechanism in order to help facilitate the development of new potential pharmacological treatments that will complement exposure therapy to better treat anxiety and other psychological disorders.

According to the National Institute of Mental Health, anxiety disorders affect approximately 40 million American adults each year. While anxiety can sometimes be a normal and beneficial reaction to stress, some people experience excessive anxiety that they are unable to control, which can negatively impact their day to day life.

Provided by Boston University Medical Center