Study finds brain origins of variation in pathological anxiety

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New findings from nonhuman primates suggest that an overactive core circuit in the brain, and its interaction with other specialized circuits, accounts for the variability in symptoms shown by patients with severe anxiety. In a brain-imaging study to be published online today in the *Proceedings of the National Academy of Sciences* (*PNAS*), researchers from the University of Wisconsin School of Medicine and Public Health describe work that for the first time provides an understanding of the root causes of clinical variability in anxiety disorders.

Using a well-established nonhuman primate model of childhood anxiety, the scientists identified a core circuit that is chronically over-active in all anxious individuals, regardless of their particular pattern of symptoms. They also identified a set of more specialized circuits that are over- or under-active in individuals prone to particular symptoms, such as chronically high levels of the stress-hormone cortisol.

"These findings provide important new insights into altered brain functioning that explain why people with anxiety have such different symptoms and clinical presentations, and it also gives us new ideas, based on an understanding of altered brain function, for helping people with different types of anxiety," says Dr. Ned Kalin, senior author, chair of Psychiatry and director of the HealthEmotions Research Institute.

"There is a large need for new treatment strategies, because our current treatments don't work well for many anxious adults and children who come to us for help."

In the study, key anxiety-related symptoms were measured in 238 young rhesus monkeys using behavioral and hormonal measurement procedures similar to those routinely used to assess extreme shyness in children. Young monkeys are ideally suited for these studies because of their similarities in brain development and social behavior, Kalin noted. Variation in brain activity was quantified in the monkeys using positron emission tomography (PET) imaging, a method that is also used in humans.

Combining behavioral measures of shyness, physiological measures of the stress-hormone cortisol, and brain metabolic imaging, co-lead authors Dr. Alexander Shackman, Andrew Fox, and their collaborators showed that a core neural system marked by elevated activity in the central nucleus of the amygdala was a consistent brain signature shared by young monkeys with chronically high levels of anxiety. This was true despite striking differences across monkeys in the predominance of particular anxiety-related symptoms.

The Wisconsin researchers also showed that young monkeys with particular anxiety profiles, such as high levels of shyness, showed changes in symptom-specific brain circuits. Finally, Shackman, Fox, and colleagues uncovered evidence that the two kinds of brain circuits, one shared by all anxious individuals, the other specific to those with particular symptoms, work together to produce different presentations of pathological anxiety.

The new study builds upon earlier work by the Kalin laboratory demonstrating that activity in the amygdala is strongly shaped by early-life experiences, such as parenting and social interactions. They hypothesize that extreme anxiety stems from problems with the normal maturation of brain systems involved in emotional learning, which suggests that anxious children have difficulty learning to effectively regulate brain anxiety circuits. Taken together, this line of research sets

the stage for improved strategies for preventing extreme childhood anxiety from blossoming into full-blown anxiety disorders.

"This means the amygdala is an extremely attractive target for new, broad-spectrum anxiety treatments," says Shackman. "The central nucleus of the amygdala is a uniquely malleable substrate for anxiety, one that can help to trigger a wide range of symptoms."

The work also suggests more specific brain targets for different symptom profiles. Such therapies could range from new, more selectively targeted medications to intensive therapies that seek to re-train the amygdala, ranging from conventional cognitive-behavioral therapies to training in mindfulness and other techniques, Shackman noted. To further understand the clinical significance of these observations, the laboratory is conducting a parallel study in young children suffering from anxiety disorders.

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