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Decreased gene activity is likely involved in childhood risk for anxiety and depression

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Decreased activity of a group of genes may explain why in young children the "fear center" of the anxious brain can't learn to distinguish real threats from the imaginary, according to a new University of Wisconsin study.

The study, published this week in the Proceedings of the National Academy of Sciences (*PNAS*), lays out evidence that young primates with highly anxious temperaments have decreased activity of specific genes within the amygdala, the brain's fear center. The authors hypothesize that this may result in over activity of the brain circuit that leads to higher risk for developing disabling anxiety and depression.

This may be particularly important since the genes involved play a major role in forming the brain connections needed for learning about fears. While all children have fears and anxieties, the authors suggest that children with low levels of activity of these genes develop anxious dispositions because they fail to learn to cope by overcoming their early childhood fears.

"Working with my close collaborator and graduate student, Drew Fox, we focused on understanding the function of genes that promote learning and plasticity in the amygdala," says Dr. Ned H. Kalin, chair of psychiatry at the University of Wisconsin School of Medicine and Public Health, who led the research. "We found reduced activity in key genes that could impair the ability to sculpt the brain, resulting in a failure to develop the capacity to discriminate between real and imaginary fears."

Kalin says the study helps support the need for early intervention in children identified as excessively shy and anxious. It may also point a way to better treatments aimed at decreasing the likelihood of children developing more severe psychiatric problems. Anxiety in children is quite common and can lead to anxiety and depression in adolescence and often precedes anxiety disorders, depression and substance abuse in adults.

Most small children go through a phase when they're frightened of many things, including monsters or new social situations, Kalin says, but their maturing brains soon learn to distinguish real threats from the imaginary. But some children do not adapt, generalize their fears to numerous situations, and may later develop serious anxiety and mood disorders. These children tend to be more sensitive to stress, produce more stress hormones and have heightened nervous-system activity.

Kalin, Fox and co-authors wondered whether some differences in the developing amygdala prevent it from learning how to regulate and adapt to anxiety. Kalin's earlier work identified a subset of young monkeys, similar to extremely shy children, with an inherited anxious disposition. Using brain imaging, the authors showed that high levels of amygdala activity predicted trait-like anxiety in anxious young primates. Like their stable and enduring anxious dispositions, these individuals also had chronically elevated levels of amygdala activity.

"We believe that this pinpoints a critical region in the brain that determines an individual's level of trait anxiety," Kalin explains.

In examining a specific part of the amygdala, the central nucleus, the researchers analyzed gene expression, which reflects both environmental and inherited influences. Within the central nucleus of the amygdala the authors found that anxious individuals tended to have decreased expression of a gene called neurotrophic tyrosine kinase, receptor, type 3

(NTRK3). Low levels of this gene that encodes for a brain cell surface receptor may be why the amygdala of an anxious monkey or child is chronically overactive and unable to overcome anxiety and fears.

"This is the first demonstration that the early risk to develop anxiety and depression may be related to the underactivity of particular genes in the developing primate amygdala," Kalin says. "These findings have provided the basis for our hypothesis that can explain the early childhood risk to develop anxiety and depression. It also suggests some creative ways to help children with extreme anxiety by developing new treatments focused on increasing the activity of specific genes involved in facilitating the brain development that underlies fear learning and coping."

More information: www.pnas.org/content/early/201 … 723109.full.pdf+html

Provided by University of Wisconsin-Madison

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