# Study helps explain why stress in adolescence can lead to predisposition to mental illness in adulthood

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Excessive stress during adolescence can cause alterations in the profile of genes expressed in the brain, especially those associated with

bioenergy functions. These alterations may affect cell respiration, resulting in behavioral problems and psychiatric disorders in adulthood, according to a study in rats conducted by researchers at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP) in Brazil.

The results are published in the journal *Translational Psychiatry*.

It is no secret that many changes occur in our bodies and behavior during adolescence when the brain undergoes structural and functional alterations shaped both by neurobiological and social factors.

"Like the human brain, the brain of an adolescent rat is highly plastic. This plasticity is seen at the molecular level and in terms of behavior. Changes in the expression profiles of specific genes in different brain regions lead to alterations in brain cell connectivity, which spread systemically and can produce persistent alterations in adulthood that correlate with psychiatric disorders," said Thamyris Santos-Silva, first author of the article. At the time of the study, she was a Ph.D. candidate in pharmacology at FMRP-USP.

"Adolescence is a critical period for brain plasticity, which is significantly influenced by social experience," added Felipe Villela Gomes, last author of the article and a professor in FMRP-USP's Department of Pharmacology. "Susceptibility to adverse social and environmental factors, such as traumas, insults and abuse, increases during this period, and social experience can influence vulnerability and resilience to stress."

The prefrontal cortex is a brain region that is extremely susceptible to stress during adolescence. When it matures, it is crucial to enhanced cognitive control of emotions normally observed in adulthood. In rats subjected to stress during adolescence, this region displayed lower levels of expression of genes that play a key role in mitochondrial respiration.

Mitochondria are organelles found in most cells of both humans and rats, as well as many other living organisms. Through cell respiration, they are the main source of chemical energy for the functioning of neurons, one of the main types of brain cells. They therefore help regulate social behavior, including the response to stress.

The study began by analyzing behavioral responses to stress, such as anxiety, social interaction and cognition, in late-adolescent rats. The animals were exposed to a stress protocol for ten consecutive days that coincided with an intense period of brain plasticity. They were then submitted to specific tests to assess their behavior, and the results showed distinct impairment in every case.

"We found that stressed animals in this life stage displayed a markedly poor behavioral profile, with anxiety, reduced sociability and impaired cognitive function," Gomes said.

To discover whether these variations were reflected by gene expression, the researchers sent RNA samples to the Behavioral Genetics Laboratory of the Brain Mind Institute (BMI) at the Swiss Federal Institute of Technology in Lausanne (EPFL). The laboratory is led by Carmen Sandi, a professor of neuroscience.

To investigate gene expression in the rats' brains, the laboratory sequenced messenger RNA and analyzed the results using bioinformatics tools.

"The analysis showed alterations to the genes of the prefrontal cortex in the stressed animals. Among the ten most affected genes, several were associated with pathways linked to oxidative stress and mitochondrial function, a key cellular component of energy production for the brain," Gomes said.

Consumption of oxygen by mitochondria in the brains of these animals was also found to be impaired by stress. "We now have evidence of various kinds pointing to the importance of mitochondrial function in this behavioral profile," Gomes said.

Next steps for the researchers will include investigating whether this behavioral profile can serve as a basis for predicting an individual's response to stress, and to what extent this actually does lead to the development of psychiatric disorders.

"Another route to advance the study would be to focus on genetic alterations, conducting tests to find out what happens when gene expression diminishes or improves. This could provide more evidence regarding the links between stress and the alterations in question, and even point to ways to combat them," Gomes said.

**More information:** Thamyris Santos-Silva et al, Transcriptomic analysis reveals mitochondrial pathways associated with distinct adolescent behavioral phenotypes and stress response, *Translational Psychiatry* (2023). DOI: 10.1038/s41398-023-02648-3

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