Not only trauma but also the reversal of trauma is inherited

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Behaviors caused by traumatic experiences in early life are reversible. Credit: Lukas von Ziegler, UZH

Traumatic experiences in childhood increase the risk of developing behavioral and psychiatric disorders later in life. It is also known that the

consequences of a trauma can likewise be observed in the children of people affected even if those children have themselves not experienced any trauma. However, childhood trauma in some conditions can also help individuals deal better with difficult situations later in life. This ability, too, is passed onto following generations. These findings have recently been uncovered by Isabelle Mansuy, Professor of Neuroepigenetics at the University of Zurich and ETH Zurich, during investigations carried out in mice.

A positive environment reverses behavioral symptoms

Mansuy's team of researchers has now demonstrated for the first time that such trauma-related behavioral alterations are reversible in mice. If male mice exposed to trauma in early postnatal life live in pleasant conditions as an adult, their behavior and the behavior of their offspring returns to normal. "Long after the traumatic experiences themselves, living in enriched conditions reverses the behavioral symptoms in adult animals and also prevents the transmission of these symptoms to the progeny", summarizes Isabelle Mansuy the new findings.

Lead author Katharina Gapp and her colleagues exposed newborn male mice to traumatic stress by separating them from their mothers at irregular intervals and stressing their mother unpredictably during separation. Subsequently, the male mice and their male offspring behaved significantly differently from the control mice when exposed to challenging situations. Examples related to their natural avoidance of bright light or their behavior when confronted with complex and constantly changing tasks, for example to obtain a water ration when thirsty.

Epigenetic dysregulation of the glucocorticoid receptor gene is reversible

At the molecular level, these behavioral alterations are associated with an increased level of the glucocorticoid receptor in the hippocampus - a brain area essential for cognitive processes and that contributes to stress responses. This altered expression results from an epigenetic dysregulation of the gene for the receptor that binds stress hormones like cortisone. The activity of this gene is normally reduced by DNA methylation, an epigenetic mark that silences genes. Traumatic experiences lead to the removal of some of these DNA methylation marks which results in an increase in gene activity and an increased production of the glucocorticoid receptor.

The epigenetic alterations are not only found in the hippocampus of the offspring of traumatized mice, but also in the germ cells of their fathers. The scientists thus assume that alterations in DNA methylation are transmitted to the progeny through the sperm. Isabelle Mansuy and her team have now shown that the impact of childhood trauma can be corrected by a low-stress and enriched environment in adult life. At the same time, the correction the of DNA methylation pattern prevents the symptoms from being inherited by the offspring.

A universal mechanism for transmitting characteristics caused by the environment

"Until now, only pharmacological drugs were known to correct epigenetic alterations in a consequential way for behavior. Now we know that this is also possible through environmental manipulations such as enriched conditions", highlights Isabelle Mansuy. The researchers suspect that this reversible epigenetic transmission is an universal mechanism that may also be partially responsible for transmitting other characteristics to the offspring, for example metabolic disorders due to poor nutrition or pathologies induced by endocrine disruptors.

More information: Katharina Gapp et al, Potential of Environmental Enrichment to Prevent Transgenerational Effects of Paternal Trauma, *Neuropsychopharmacology* (2016). DOI: 10.1038/npp.2016.87