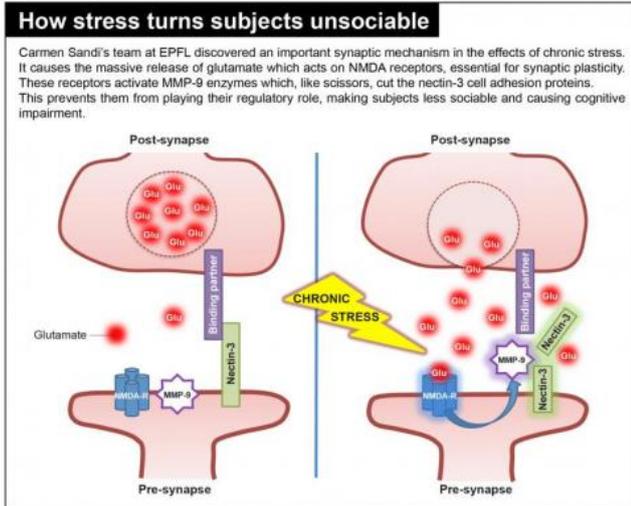


How stress tears us apart

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Carmen Sandi's team at EPFL discovered an important synaptic mechanism in the effects of chronic stress. It causes the massive release of glutamate which acts on NMDA receptors, essential for synaptic plasticity. These receptors activate MMP-9 enzymes which, like scissors, cut the nectin-3 cell adhesion proteins. This prevents them from playing their regulatory role, making subjects less sociable and causing cognitive impairment. Credit: EPFL

Why is it that when people are too stressed they are often grouchy, grumpy, nasty, distracted or forgetful? Researchers from the Brain Mind Institute (BMI) at EPFL have just highlighted a fundamental synaptic mechanism that explains the relationship between chronic stress and the loss of social skills and cognitive impairment. When triggered by stress, an enzyme attacks a synaptic regulatory molecule in the brain. This was revealed by a work published in *Nature Communications*.

Carmen Sandi's team went to look for answers in a region of the hippocampus known for its involvement in behavior and cognitive skills. In there, scientists were interested in a molecule, the nectin-3 [cell adhesion protein](#), whose role is to ensure adherence, at the synaptic level, between

two neurons. Positioned in the postsynaptic part, these proteins bind to the molecules of the presynaptic portion, thus ensuring the synaptic function. However, the researchers found that on rat models affected by [chronic stress](#), nectin-3 molecules were significantly reduced in number.

The investigations conducted by the researchers led them to an enzyme involved in the process of protein degradation: MMP-9. It was already known that chronic stress causes a massive release of glutamate, a molecule that acts on NMDA receptors, which are essential for synaptic plasticity and thus for memory. What these researchers found now is that these receptors activated the MMP-9 enzymes which, like scissors, literally cut the nectin-3 cell adhesion proteins. "When this happens, nectin-3 becomes unable to perform its role as a modulator of [synaptic plasticity](#)" explained Carmen Sandi. In turn, these effects lead subjects to lose their sociability, avoid interactions with their peers and have impaired memory or understanding.

The researchers, in conjunction with Polish neuroscientists, were able to confirm this mechanism in rodents both in vitro and in vivo. By means of external treatments that either activated nectin-3 or inhibited MMP-9, they showed that stressed subjects could regain their sociability and normal [cognitive skills](#). "The identification of this mechanism is important because it suggests potential treatments for neuropsychiatric disorders related to chronic stress, particularly depression," said Carmen Sandi, member of the NCCR-Synapsy, which studies the neurobiological roots of psychiatric disorders.

Interestingly, MMP-9 expression is also involved in other pathologies, such as neurodegenerative diseases, including ALS or epilepsy. "This result opens new research avenues on the still unknown consequences of chronic stress," concluded Carmen Sandi, the BMI's director.

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