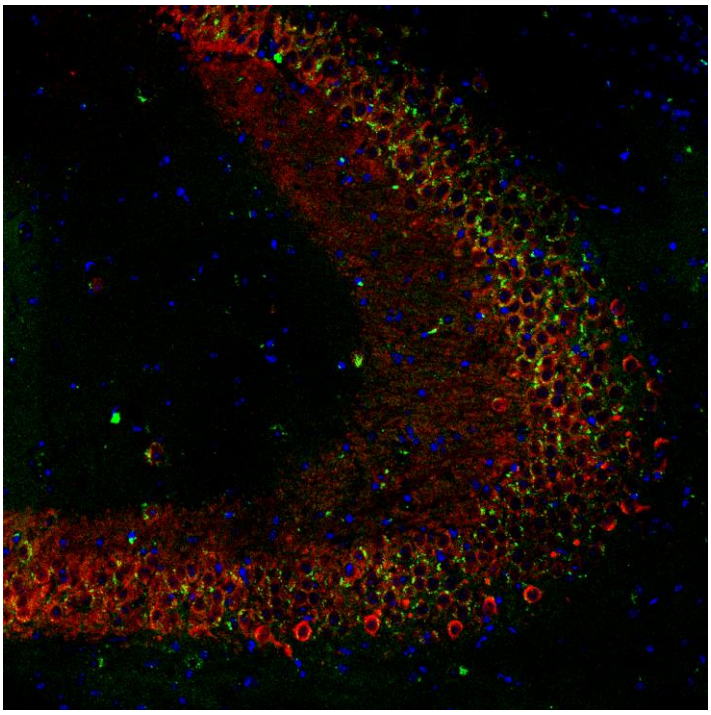
Early life stress and programming psychiatric risk

What we experience as a child often has a lasting impression on our behaviour throughout the course of our life. Stressful and adverse experience during early life of an individual can often lead to a lasting vulnerability towards developing psychiatric disorders in adult life, a question particularly pertinent to the current times when depression has emerged as one of the greatest challenges to global health. The time window surrounding birth is a critical period for establishing and shaping key circuits within the brain. Thus, if something (like the animal's environment, infection, or certain drugs) causes disruption during this period to these neurocircuits, it can lead to poor wiring of key neuronal circuits and increase the risk of developing psychiatric disorders in adult life. The cellular and circuit mechanisms that give rise to such long-lasting behavioural alterations still remain poorly understood.



Shown here are genetically engineered receptors (green) expressed by excitatory neurons in red. The blue is the nucleus of the neurons. Image credit: Praachi Tiwari (with technical assistance by K. V. Boby)

Prof. Vidita Vaidya's lab at TIFR along with others across the globe, had carried out several studies in the past decade establishing that a dysfunctional signaling via certain neurotransmitter pathways within the brain contributes to long-lasting changes in behavior, as well as neuronal structure and function. The effects of distinct models of early-life adversity seemed to be acting via a common signaling pathway in the brain, and may be responsible for programming persistent changes in emotional behaviour.

In a recent study, the Vaidya lab (https://elifesciences.org/articles/56171) has tested the idea via switching on the signaling pathway (Gq-coupled signaling) that leads to overactivation of excitatory neurons (neurons that activate other neurons) within the forebrain, using genetically engineered mice. These mice express an engineered receptor that drives Gq signaling only in the forebrain excitatory neurons, and this can be activated using a designer drug that would not activate anything else in the brain. This gives precise control over where, when, and for how long we need to increase activation of the Gq signaling pathway in a particular circuit within the brain. They activated the forebrain excitatory neurons during the first two weeks after birth, and noted a long-lasting impairment of mood-related behaviour and the way they perceive external sensory information that could often last till old age. These mice showed aberrant behaviour that is similar to anxiety, depression, and schizophrenia in humans. When they carried out similar long-term neuronal activation experiments either during adolescence or in adulthood, they did not observe any change in mood-related behaviour, highlighting the importance of this window in programming long-lasting behavioural alterations. They also shed light on the possible circuit, cellular, and molecular mechanisms that may underlie these persistent effects.

This study involved experiments spanning more than six years with contributions from several researchers in Prof. Vaidya's lab and collaborative efforts from researchers at the Centre for Cellular and Molecular Biology (Patel lab, CCMB Hyderabad) and Jawaharlal Nehru Centre For Advanced Scientific Research (Clement lab, JNCASR Bengaluru).

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