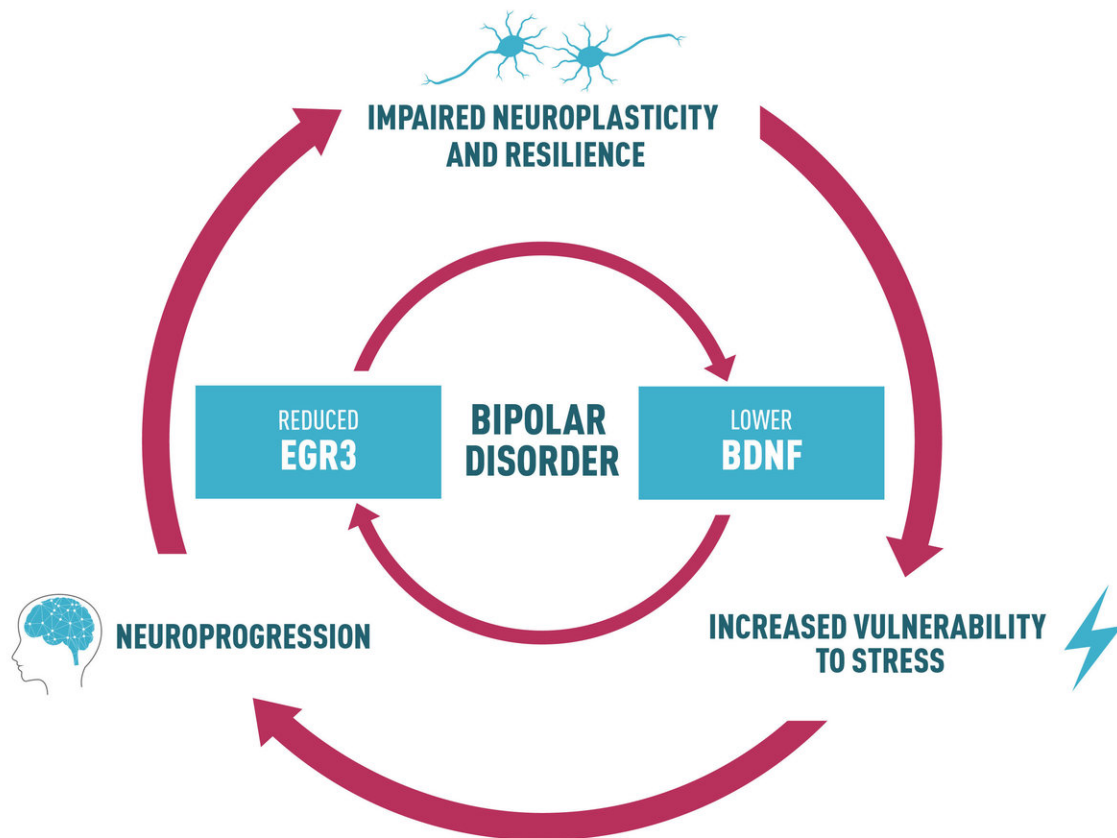


A new path into bipolar disorder comes to light

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Lower BDNF levels observed in bipolar disorder patients may lead to reduced EGR3 levels. A dysfunctional pathway impairs several biological functions, including abnormal structural brain changes and cognitive and functional decline (known as neuroprogression). Disrupted neural circuits may explain the impaired neuroplasticity and resilience, increasing vulnerability to stress and mood episodes, all well-known characteristics of BD. Credit: Cezar Farias

Bipolar disorder (BD) is a multifactorial brain disorder in which patients experience radical shifts in mood and undergo periods of depression followed by periods of mania. It has been known for some time that both environmental and genetic factors play important roles in the disease. For instance, being exposed to high levels of stress for long periods, and especially during childhood, has been associated with the development of BD.

Immediate early genes (IEGs) are a class of genes that respond very rapidly to [environmental stimuli](#), and that includes stress. IEGs respond to stressors by activating other genes that lead to neuronal plasticity, the ability of [brain](#) cells to change in form and function in response to changes in the environment. Ultimately, it is the process of neuronal plasticity that gives the brain the ability to learn from and adapt to new experiences.

One type of protein produced by IEGs is the so-called early growth response (EGR) proteins, which translate environmental influence into long-term changes in the brain. These proteins are found throughout the brain and are highly produced in response to environmental changes such as stressful stimuli and sleep deprivation. Without the action played out by these proteins, brain cells and the brain itself cannot appropriately respond to the many stimuli that are constantly received from the environment.

Effective neuronal plasticity also depends on neurotrophins, which are regulatory factors that promote development and survival of [brain cells](#). Brain-derived neurotrophic factor (BDNF) is the neurotrophin mostly found in the brain. It has been extensively investigated in BD patients and has been suggested as a hallmark of BD. Indeed, some studies have shown that the levels of BDNF in the serum of BD patients are reduced whenever patients undergo a period of depression, hypomania or mania. Other studies have shown that regardless of mood state, BD patients

present reduced levels of BDNF. Overall, changes in BDNF levels seem to be a characteristic found in BD patients that may contribute to the pathophysiology of the disease.

Now, an international team of researchers from Universidade Federal do Rio Grande do Sul in Brazil, University of Arizona College of Medicine in the United States and McMaster University in Canada have published an article connecting the dots between these two players to explain the impaired cellular resilience observed in BD that, in the grand scheme of things, may relate to the impaired resilience presented by BD patients to respond to events, including stress.

In a previous study done by the group in 2016, one type of IEG gene known as EGR3, that normally responds to environmental events and stressful stimuli was found repressed in the brain of BD patients, suggesting that when facing a stressor, the EGR3 in BD patients does not respond to the stimulus appropriately. Indeed, BD patients are highly prone to stress and have more difficulties dealing with stress or adapting to it compared to healthy individuals. What the research group is now suggesting is that both EGR3 and BDNF may each play a critical role in the impaired cellular resilience seen in BD, and that each of these two genes may affect each other's expression in the cell. "We believe that the reduced level of BDNF that has been extensively observed in BD patients is caused by the fact that EGR3 is repressed in the brain of BD patients. The two molecules are interconnected in a regulatory pathway that is disrupted in BD patients," says Fabio Klamt, leading author of the article entitled "EGR3 immediate early gene and the brain-derived neurotrophic factor in [bipolar disorder](#)" and published on February 5th in the journal *Frontiers in Behavioral Neuroscience*.

The authors also add that the fact that EGR3 responds very quickly to environmental stimuli renders the molecule a potential drug target. "It is possible to imagine that EGR3 may be modulated in order to increase its

expression and that of BDNF, which may have a positive impact on [BD patients](#)," says Bianca Pfaffenseller, a scientist working at Hospital de Clínicas de Porto Alegre, in Brazil, and the first author of the study.

The idea that mental disorders should be seen as any other chronic disease in which the underlying biology plays an important role has replaced the old descriptions of mental illnesses as the result of bad psychological influences. As Nobel prize laureate Eric Kandel has said, "all mental processes are brain processes and therefore all disorders of mental functioning are biological diseases." The perspective article authored by Fabio Klamt and colleagues supports this view by offering new insights into the underlying biology of this lifelong and devastating mental disorder affecting millions of people worldwide.

More information: *Frontiers in Behavioral Neuroscience*, www.frontiersin.org/articles/1...nbeh.2018.00015/full

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