Major depression now believed to be caused by abnormalities in immune cells of the brain

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Major depression now believed to be caused by abnormalities in immune cells of the brain; may revolutionize next-gneration psychiatric medication treatment, according to Hebrew University of Jerusalem researchers.

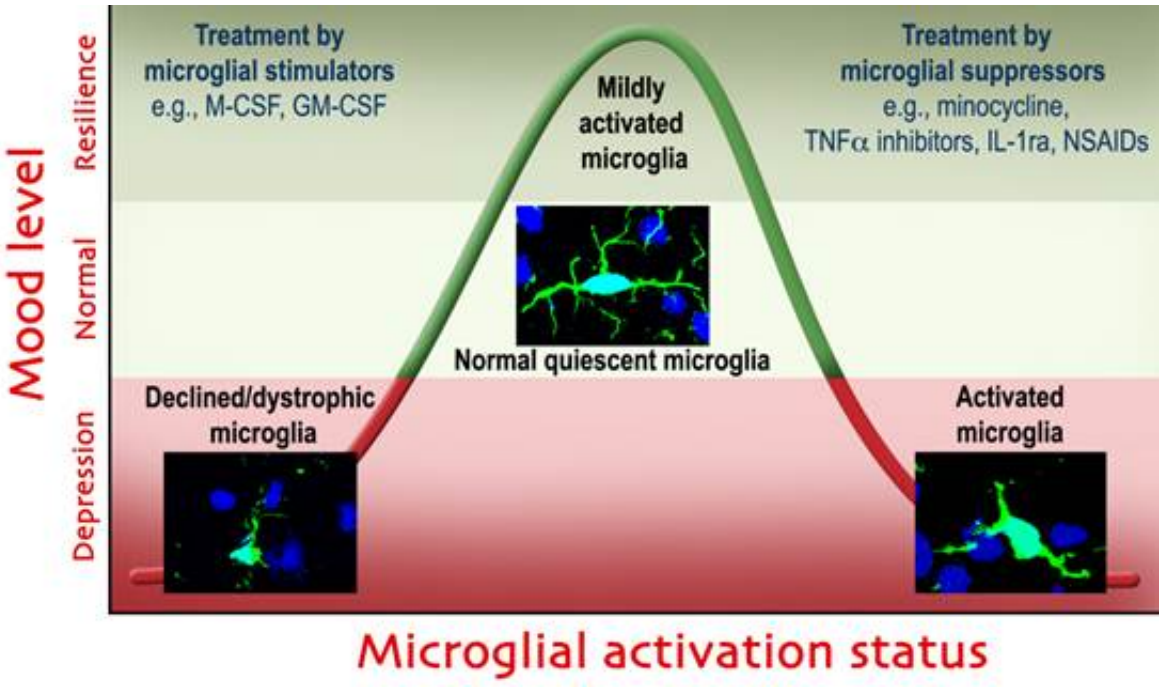
"Microglia" cells in the brain, acting as first and main form of active

immune defense of central nervous system, may be a key to causing depression. Latest theory opens door to development of a new generation of anti-depressant medications.

Major depression, which afflicts one in six people at some point in their life, is the leading global cause of disability – surpassing cardiovascular and respiratory diseases, cancer and HIV/AIDS combined.

In a groundbreaking theoretical review paper published in the peer-reviewed journal, Trends in Neurosciences, researchers from the Hebrew University of Jerusalem suggest that "progress in the understanding of the biology of depression has been slow," requiring expanding beyond the "abnormalities in the functioning of neurons." The contribution of other brain cells—often neglected by researchers—may be more relevant in causing depression, according to psychobiology Prof. Raz Yirmiya, director of the Hebrew University's Laboratory for PsychoNeuroImmunology, and senior author of the journal's paper, titled "Depression as a microglial disease."
authors.elsevier.com/a/1RpN8botpXeIf

Recent research at the Hebrew University's laboratory and elsewhere finds that some forms of depression may result from malfunctioning brain cells, termed "microglia." "However," Prof. Yirmiya cautions, "this does not mean that all sub-types of depression or other psychiatric diseases are originated by abnormalities in these cells."



Credit: Hebrew University of Jerusalem

Prof. Yirmiya's new research could have a profound impact on the future development of anti-depressant medications. Present drugs do not always have the desired effect on patients, so there is an urgent need to discover novel biological mechanisms and drug targets for diagnosing the root cause of depression and for treating depressed patients appropriately.

In *Trends in Neuroscience*, the Hebrew University researchers claim that diseased microglia can cause depression and drugs that restore the normal functioning of these cells can be effective as fast-acting anti-depressants.

Microglia, which comprise 10% of all brain cells, are the brain's immune cells. They fight infectious bacteria and viruses in the brain. They also promote repairing and healing processes of damages caused by brain

injury and trauma.

"Our views on microglia have dramatically changed over the last decade," Prof. Yirmiya says. "We now know that these cells play a role in the formation and fine-tuning of the connections between neurons (synapses) during brain development, as well as in changes of these connections throughout life. These roles are important for normal brain and behavioral functions, including pain, mood and cognitive abilities."

"Studies in humans, using post-mortem brain tissues or special imaging techniques, as well as studies in animal models of depression, demonstrated that when the structure and function of microglia change, these cells can no longer regulate normal brain and behavior processes and this can lead to depression," Prof. Yirmiya says.

Indeed, changes in microglia occur during many conditions associated with high incidence of depression, including infection, injury, trauma, aging, autoimmune diseases such as multiple sclerosis and neurodegenerative diseases such as Alzheimer's disease. In these conditions, microglia assume an "activated" state in which they become big and round, and secrete compounds that orchestrate an inflammatory response in the brain.

The shape and function of microglia can be also changed following exposure to chronic unpredictable psychological stress, which is one of the leading causes of depression in humans. Importantly, research in Prof. Yirmiya's laboratory recently discovered that following exposure to such stress, some microglia die and the remaining cells appear small and degenerated.

These findings have both theoretical and clinical implications. According to the new theory, either activation or decline of microglia can lead to depression. Therefore, the same class of drugs cannot treat the disease

uniformly.

Prof. Yirmiya asserts that a personalized medical approach should be adopted in which the status of the microglia in the individual patient should be established first. Based on this initial assessment, treatment with drugs that either inhibit the over-active microglia or stimulate the suppressed microglia should be employed.

More information: Raz Yirmiya et al. Depression as a Microglial Disease, *Trends in Neurosciences* (2015). DOI: 10.1016/j.tins.2015.08.001

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