Hippocampal volume loss in depression reflects glial loss

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Depression has been associated with reduced volume of the hippocampus in magnetic resonance imaging studies in humans. A new study just published in *Biological Psychiatry* now clarifies the cellular basis of these volumetric changes, which have been unclear until now.

Beginning in the 1980s, a series of studies in rodents conducted by Robert Sapolsky and other investigators suggested that the CA3 area of the hippocampus, a brain region implicated in mood and memory, was particularly vulnerable to stress. When analyzing the brain tissue in detail, they reported loss of nerve cells called neurons with stress. Other rodent studies described reductions in the birth of new neurons in the hippocampus associated with stress.

Collectively, these studies suggest that stress-related disorders, such as depression and posttraumatic stress disorder, might be associated with hippocampal volume loss. This hypothesis is supported by numerous studies reporting reduced hippocampal volume in depressed patients.

The current study, led by Dr. Carol Shively at Wake Forest School of Medicine, extends our insight into hippocampal volume loss associated with depression by studying female nonhuman primates called cynomolgus monkeys. The researchers studied only female monkeys because, while depression is the leading cause of disability in young and middle-aged adults, it is twice as common in women as men.

"In this study we observed unique features of the depressed nonhuman

primate brain, in the hippocampus, that were unlike the rat and mouse models of depression that are currently used to develop depression medications," said Shively.

Monkeys have brains that share a lot of similarities with human brains, and medical research in primates can bridge important work being done in rodent models and in humans.

To conduct this study, Shively and her colleagues observed 16 female monkeys over 24 months, who were housed normally in stable social groups in the laboratory. Each monkey was observed weekly over the two year period and assessed for depressive behavior. Any observed depression occurred naturally, without experimental intervention or manipulation, since like humans, monkeys can become depressed.

Then, Stephanie Willard, a graduate student in the lab, examined the entire hippocampus and found that the reduced size of the hippocampus in the depressed monkeys was due to reductions in glia number and neuropil content. However, there were no differences in the number of neurons between the depressed and non-depressed monkeys. Glia surround and support neurons, aiding in communication throughout the brain. Neuropil is made up of a dense network of nerve fibers, their branches and synapses which connect glia and neurons.

"The current data highlight the glial sensitivity to stress," commented Dr. John Krystal, Editor of *Biological Psychiatry*. "Since glial loss can disturb neural communication in a number of important and well-defined ways, the current findings could have important implications for interpreting neuroimaging findings in depression and for the design of novel antidepressant treatments".

Shively agrees, adding that "new more effective medications for the nearly 15 million Americans suffering from depression are far more

likely to be developed if they include studies of medication effects in depressed nonhuman primates."

More information: The article is "Cell Number and Neuropil Alterations in Subregions of the Anterior Hippocampus in a Female Monkey Model of Depression" by Stephanie L. Willard, David R. Riddle, M. Elizabeth Forbes, and Carol A. Shively (DOI: 10.1016/j.biopsych.2013.03.013). The article appears in *Biological Psychiatry*, Volume 74, Issue 12 (December 15, 2013)

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