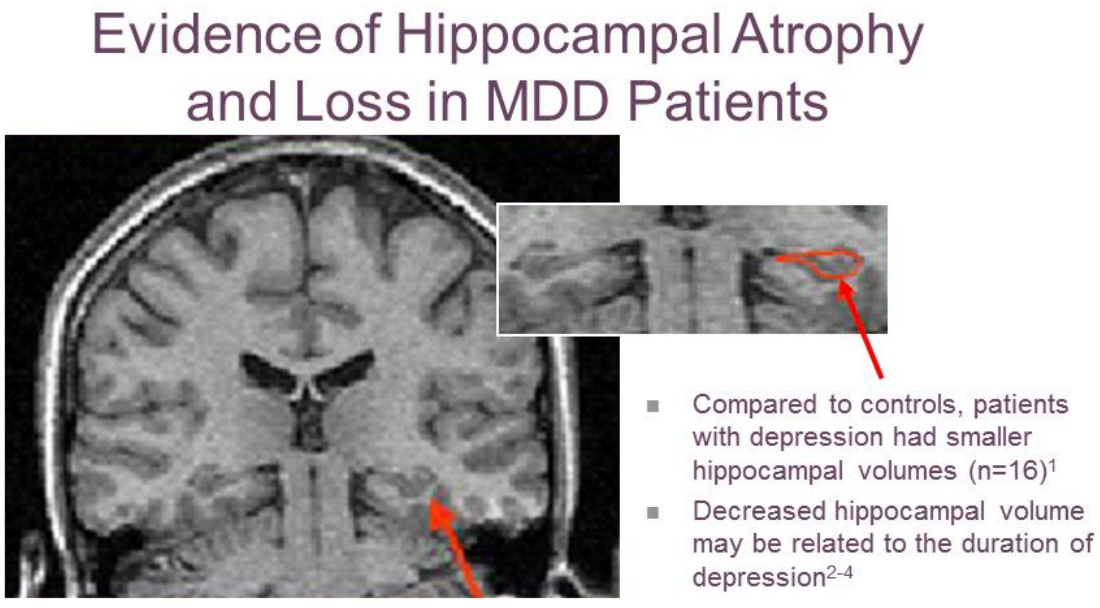
Structural brain changes

Atrophy of the hippocampus, a region of the brain involved in conscious memory, may be associated with depression.

Molecular and cellular studies of stress, depression, and antidepressants have moved the field of mood disorder research beyond the monoamine hypothesis of depression. These studies demonstrated that stress and antidepressant treatment may exert opposing actions on the expression of specific neurotrophic factors in limbic brain regions involved in the regulation of mood and cognition.[1]

Most notable are studies of BDNF. The functional significance of altered neurotrophic factor expression was highlighted by studies demonstrating that stress and depression can lead to neuronal atrophy and cell loss in key limbic brain regions implicated in depression, including the amygdala, prefrontal cortex, and hippocampus (which expresses high levels of receptors for glucocorticoids, the major stress reactive adrenal steroid).[1]

Several studies have associated depression with decreased hippocampal volume.[2,3] Furthermore, this reduction in volume has been related to the duration of depression.[3-5]



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1. Bremner JD, et al. *Am J Psychiatry.* 2000;157(1):115-118.
2. Sheline YI, et al. *J Neurosci.* 1999;19:5034-5043.
3. Sheline YI, et al. *Proc Natl Acad Sci USA.* 1996;93:3908-3913.
4. Sheline YI, et al. *Am J Psychiatry.* 2003;160:1516-1518.

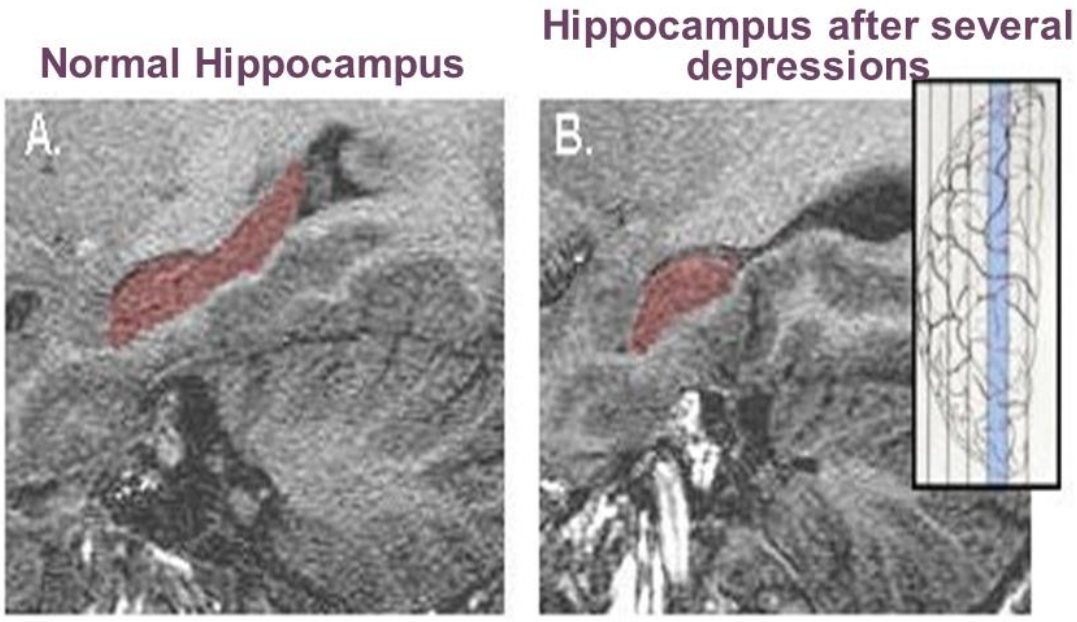
The hippocampus is one of several limbic structures that have been implicated in mood disorders. Included in the functions of hippocampal circuitry are control of learning and memory and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, both of which are altered in depression. The hippocampus has connections with the amygdala and prefrontal cortex, regions that are more directly involved in emotion and cognition and thereby contribute to other major symptoms of depression.[1]

Bremner et al studied 16 patients with a history of depression based on the Structured Interview for DSM-IV, finding hippocampal volume loss and memory deficits.[2]

In a sample of 24 women age 23 to 86 years with histories of recurrent major depression, Sheline et al found that post-depressives scored lower in verbal memory, suggesting that the hippocampal volume loss was related to an aspect of cognitive functioning. The study also found duration of depressive episode to be a predictor of hippocampal volume loss.[3]

There are a number of reasons to focus on the hippocampus, one of which is that the hippocampus is a particularly stress-sensitive region.

Several studies have demonstrated that hippocampal volume is sensitive to stress and that chronic stress or chronic depression can decrease hippocampal volume.

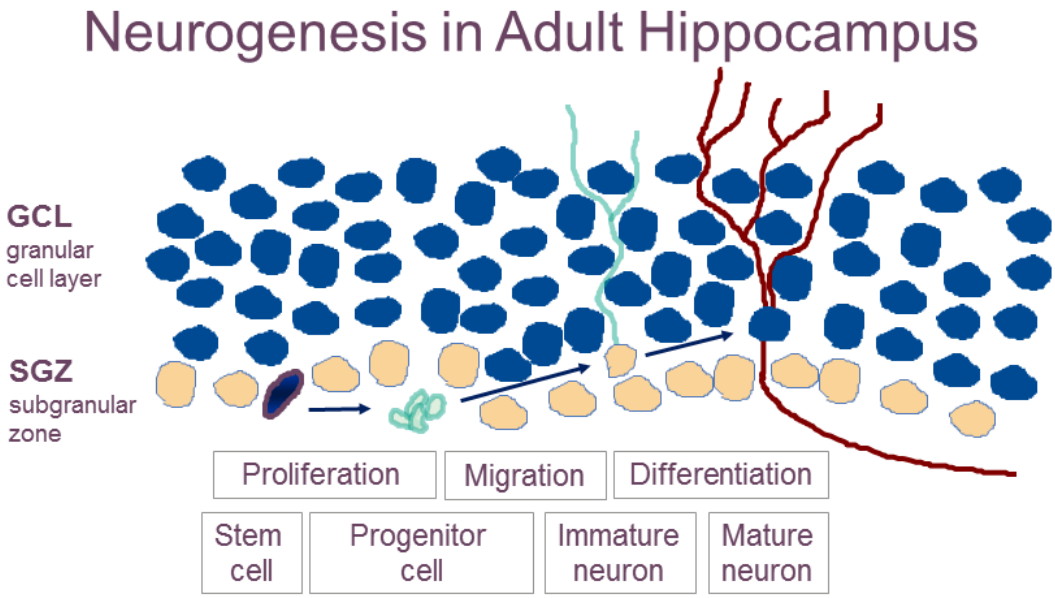


Campbell and MacQueen, J. Psych and Neuroscience: 29(6):417-426. Nov. 2004.

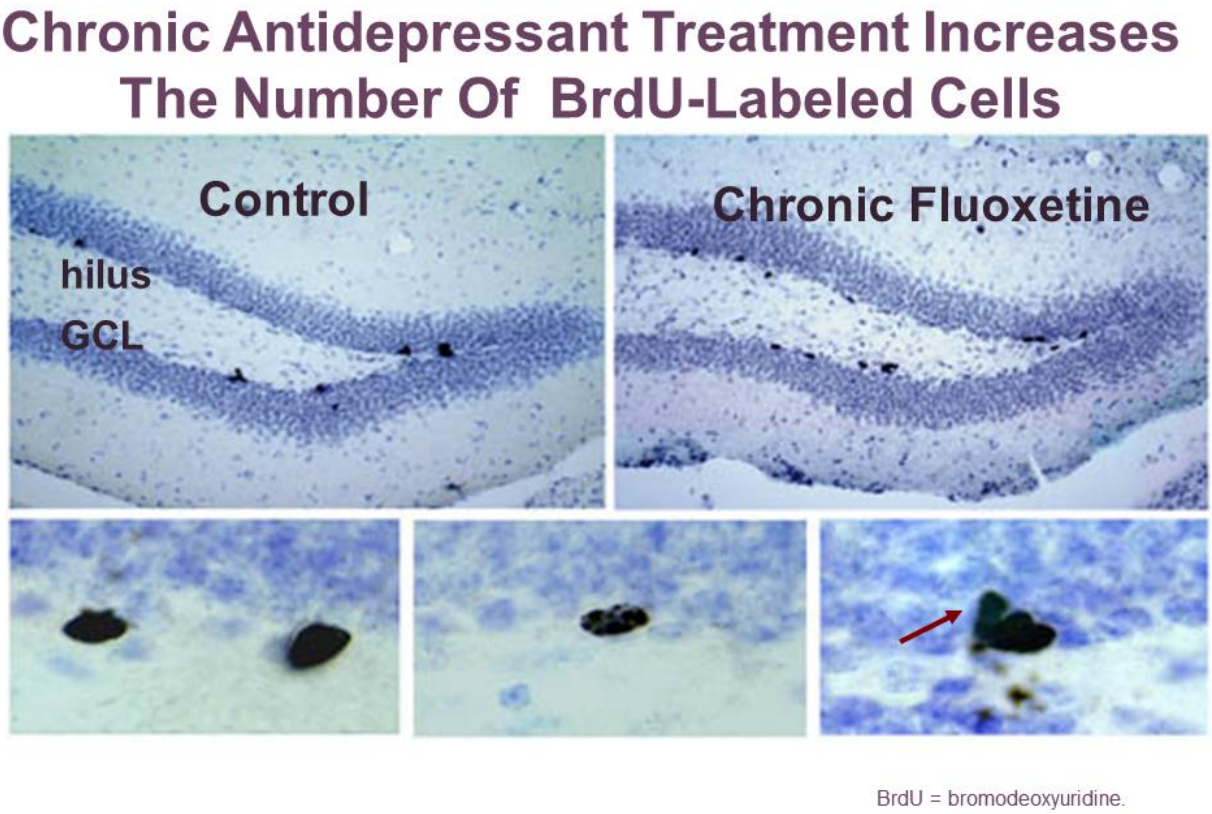
This slide shows an illustration of a normal hippocampus on the left (panel A) and the hippocampus from a patient who has experienced several depressions, on the right (panel B).

The normal volumetric is accentuated here for illustrative purposes. In most studies, the hippocampal size seems to decrease by about 15 - 20% in people who have had recurrent

depressive episodes. It is not yet known whether early remission can prevent this volume loss, but there is some preliminary data that supports that hypothesis. Currently, our best guess is that preventing the occurrence of depression, treating depressive episodes quickly and effectively and into remission, may prevent some of this loss.



Fortunately despite cell death and loss in MDD and other psychiatric conditions there is cell growth throughout life in the hippocampus that can be enhanced by treatment of MDD including antidepressant medications, exercise, ECT and learning such as CBT or psychotherapy with a possible mediator of these throughout brain derived neurotrophic factor (BDNF).



See how with treatment, in this case an antidepressant fluoxitene there is new cell growth in hippocampal regions so with treatment there is hope that can now be physicologically understood with newer research.

REFERENCES

1. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59:1116-1127.

2.Bremner JD, Narayan M, Anderson ER, et al. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000;157(1):115-118.

3.Sheline YI, Sanghavi M, Mintun MA, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. Neurosci. 1999;19:5034-5043.

4.Sheline YI, Wang PW, Gado MH, et al. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA. 1996;93:3908-3913.

5.Sheline YI, Gado MH, Kraemer HC, et al. Untreated depression and hippocampal volume loss. Am J Psychiatry. 2003;160:1516-1518.

6. Campbell and MacQueen: J Psych and Neuroscience 2004; 29(6):417-426.