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Depression and the Birth and Death of Brain Cells

The turnover of neurons in the hippocampus might help to explain the onset of and recovery from clinical depression

Barry L. Jacobs, Henriette van Praag and Fred H. Gage

No one knows the precise mechanism that triggers clinical depression, but people have speculated about it for centuries. From the time of the ancient Greeks until well into the Renaissance, philosophers and scientists believed that bodily fluids called humors were responsible for our moods and personality. Specifically, they thought that one called black bile controlled depression. By the 17th century, dualism—the separation of mind and body—was the dominant dogma. Consequently, it was believed that depression, a disease of the "mind," arose from something gone awry in your physical or social environment. But eventually, by the early 20th century, even Sigmund Freud—the father of psychoanalysis—had come to believe that brain dysfunction would ultimately explain mental illness. Today, neuroscientists know that, in many cases, psychopathology arises because of dysfunctions in particular brain structures or particular brain chemicals. As described in this article, recent evidence suggests that clinical depression might arise from the brain failing to grow new neurons in a specific area.

Neurobiologists long believed that adult brains did not make new neurons, but now we know otherwise. In the early 1960s, Joseph Altman at MIT reported that new neurons were being produced in the brains of adult rats. Those findings were somewhat forgotten for the next 30 years. Recently, this work has been revived and advanced. Elizabeth Gould of Princeton University, one of this article's authors (Gage) and others have reported the birth of new neurons—neurogenesis—in the hippocampus of adult rats, monkeys and humans. This region of the brain lies beneath the cortex in the temporal lobe *(see Figure 2)*—basically the part of your brain behind your ear—and it appears to play a crucial role in forming new memories. Preventing depression might depend in part on proper control of this ongoing neurogenesis.

Currently available antipsychotic medications usually fall short of the desired therapeutic efficacy and invariably produce unwanted side effects, such as dry mouth or sleep disturbances. These treatments typically act by globally altering the chemical communication between neurons throughout the brain. More recently, cell and molecular biology have begun to exert a strong impact on our understanding and treatment of mental illness. By targeting specific molecular sites in neurons, these techniques can provide precise, powerful and effective means of influencing brain function. One of these approaches—controlling neurogenesis in the adult brain—might have a significant impact on the treatment of mental illness.

Let us first examine the current state of knowledge regarding adult brain neurogenesis. Then we shall focus specifically on the role of neurogenesis in chronic clinical depression. As we shall see, controlling neurogenesis might also be used to treat or prevent a variety of other forms of neuro- and psychopathology.

New Brain Cells

All of the cells in the body are derived from *stem cells*—primitive cells that are formed soon after fertilization and that can divide indefinitely. They can simply copy themselves, or they can make a variety of differentiated cells, including blood, muscle and neuron. They can also make progenitor cells, which can divide a limited number of times and give rise to cell types such as neurons and glia.

Most neurons in the mammalian brain and spinal cord are generated during the pre- and perinatal periods of development. Nevertheless, neurons continue to be born throughout life in the *olfactory bulb*, which processes scents, and in the *dentate gyrus* of the hippocampus. (Very recent evidence indicates that some additional brain areas might also produce new brain cells.) These new neurons are derived from progenitor cells that reside in the brain's *subventricular zone*, which lines open spaces deep in the brain called ventricles, or in a layer of the hippocampus called the *subgranular zone*. The existing neurons in the adult brain cannot divide. Some progenitor cells, however, remain, and they can go through cell division to produce two daughter neurons, or one glial cell or neuron and one progenitor cell capable of further division. Apparently, in most parts of the adult brain, something inhibits progenitor cells from dividing to produce new neurons. No one knows exactly why neurogenesis continues in some areas and not others. The olfactory

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Figure 1. Theories of the etiology of clinical depression have vacillated thoughout history between environmental and biological models. The authors propose a model in which environmental influences can produce biological changes—the suppression of production of new neurons in a portion of the hippocampus, initiating depressive episodes. This model derives from the relatively recent discovery that adult human beings do continue to produce some new neurons throughout their lives and that the rate of production can be influenced by both environmental and biochemical factors. Wilhelm Lehmbruck, who sculpted this figure, "Seated Youth," was himself a victim of depression and took his own life in 1919—a time when even Sigmund Freud was coming to believe that brain dysfunction would explain mental illness.

bulb and dentate gyrus might require constant renewal in order to process and store new information, whereas other regions might need a stable population of neurons in order to maintain ongoing function. Understanding the mechanisms involved in this process could provide the opportunity for disinhibiting progenitor cells throughout the central nervous system to allow them to produce new neurons. This, of course, could have a major impact on the repair of brain regions where cells have been lost for any of a variety of reasons: disease, trauma, aging and so on.

Investigators follow neurogenesis in the laboratory by treating animals with tritiated-thymidine or bromodeoxyuridine. These compounds get incorporated into the DNA of cells preparing to divide. Once these cells begin the process of cell division, their daughter cells can be identified by examination of postmortem brain tissue. The compound incorporated into cells can be visualized under the microscope with autoradiographic or immunologic techniques for tritiated-thymidine or bromodeoxyuridine, respectively. Investigators count the labeled cells to quantify the number of proliferating and newly born cells.

These techniques show that progenitor cells in the subgranular zone produce progeny that migrate outward to the granule-cell layer and differentiate into neurons. In this way, these new granule cells join the population of existing neurons. These newly born cells mature in the granule-cell layer and send their dendrites outward, whereas their cell processes go inward and follow paths to other structures within the hippocampus, such as the CA3 cell fields. Consequently, these new neurons get integrated in the basic circuitry of the brain.

The dentate gyrus produces 1,000–3,000 new neurons per day in rats and mice. Although this might seem like a small number, it could represent a substantial proportion of the total population over an animal's lifespan. Furthermore, these recently born neurons might serve a more important role in processing new information than those in the extant population of granule cells. So far, such data have not been collected for primates. Some investiga-

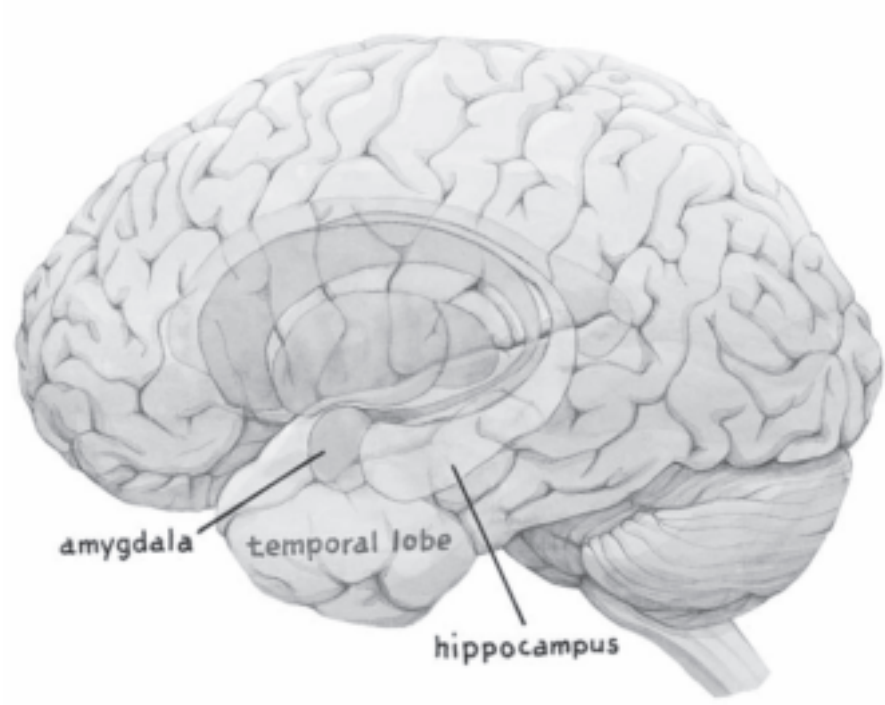


Figure 2. Hippocampus *(blue)* lies beneath the cerebral cortex in the temporal lobe, roughly behind your ear. Although neurobiologists long identified this area as playing a crucial role in forming new memories, it might also participate in various forms of neuro- and psychopathology.

tors believe that the magnitude of neurogenesis is lower in higher mammals, but that has not been proved.

Stress and Glucocorticoids

Many scientists believe that stress is the most significant causal agent—with the possible exception of genetic predisposition—in the etiology of depression. In addition, nerve cells in the hippocampal formation are among the most sensitive to the deleterious effects of stress. Consequently, a stress-induced decrease in neurogenesis in the hippocampus might be an important factor in precipitating episodes of depression. On the other hand, increasing serotonergic neurotransmission is the most effective treatment for depression, and it also augments hippocampal neurogenesis. So serotonin-induced increases in neurogenesis might promote recovery from depression. Considering all of this, we suggest that the waning and waxing of neurogenesis in the hippocampal formation might trigger the precipitation of and recovery from episodes of clinical depression.

Gould and her colleagues examined the relation between stress and hippocampal neurogenesis in several species. First, they reported that removing a rat's adrenal glands increased neurogenesis in the adult dentate gyrus. Moreover, they could reverse that effect with the glucocorticoid hormone corticosterone, which normally comes from the adrenals. The circulating level of glucocorticoids apparently suppressed the birth of neurons in the dentate gyrus under normal conditions. In an extension of these results, Gould's group showed that systemic administration of corticosterone to normal animals suppressed dentate gyrus neurogenesis.

This group also examined the effects of naturally stressful situations. For instance, they exposed a rat to the odor of one of its natural predators—a fox—and that suppressed cell proliferation in the rat's dentate gyrus. They also demonstrated reduced dentate-gyrus cell proliferation in adult tree shrews after the psychosocial stress of exposing them to same-sex individuals. Most recently, Gould's group reported suppressed cell division in a marmoset monkey's dentate gyrus after putting it in a cage with another marmoset that had already been living there. In combination, these studies show clearly that stress suppresses the rate of dentate-gyrus cell proliferation in adults of a number of species. Furthermore, it probably does so through increases in brain glucocorticoids.

Additional, but older, literature is also relevant here. Over the past 15 years, work by Robert Sapolsky of Stanford University, Bruce McEwen of Rockefeller University and others has shown, in a number of species, that stress and glucocorticoids cause widespread morphological changes and even cell death

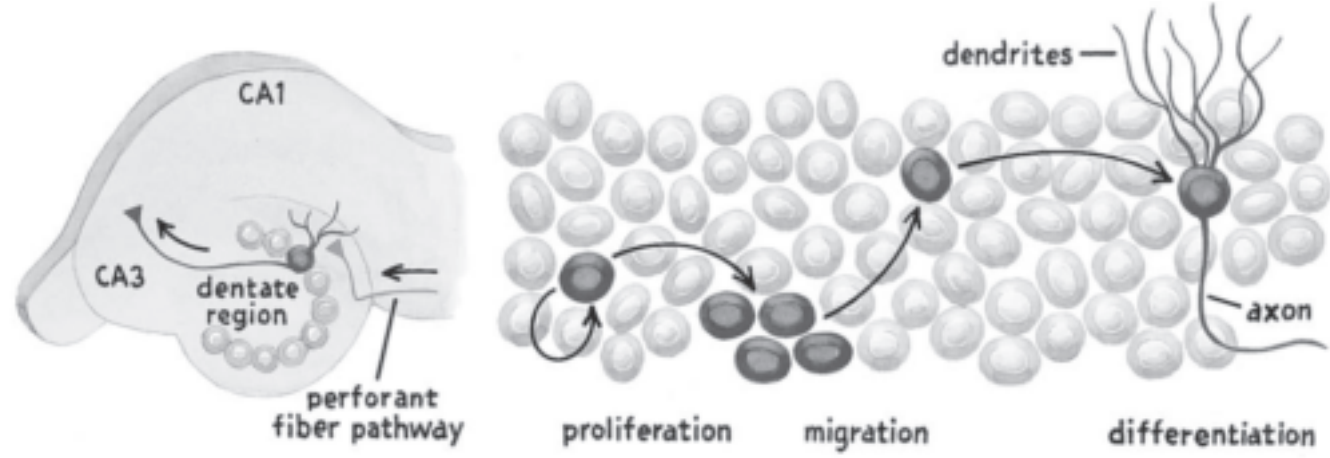


Figure 3. Dentate gyrus—a region shaped like a backward C—lies in the lower, middle area of the hippocampus *(left)*. Neurogenesis *(right)* in this region begins when a progenitor cell *(green and red)* proliferates to produce progeny, which migrate outward and differentiate into neurons. These newly born cells send their dendrites outward, whereas their cell processes go inward and follow paths to other structures within the hippocampus, such as the CA3 cell fields. Consequently, these new neurons get integrated in the basic circuitry of the brain.

in parts of the hippocampus, such as in the CA3 subfields. This region of the hippocampus is the main target of the output of neurons in the dentate gyrus. Whether this hippocampal damage is at least in part dependent on the suppression of neurogenesis in the dentate gyrus is not known.

Depression and the Hippocampus

Several pieces of evidence link clinical depression to changes in the hippocampus. Nevertheless, we do not suggest that this is the only change in the brain associated with depression, nor do we suggest that alterations in the hippocampus underlie all of the phenomenological aspects of depression.

Utilizing the brain imaging technique of MRI, Yvette Sheline and her colleagues at Washington University in St. Louis reported smaller hippocampal volumes in a group of older women with recurrent major depression. Although the subjects were in remission, they had smaller left and right hippocampal volumes—but comparable total cerebral volumes—in comparison with carefully selected controls. Sheline's group also found a significant negative correlation between total days of depression and the volume of the left hippocampal gray matter. The investigators speculate that this hippocampal loss might result from glucocorticoid-induced neurotoxicity associated with recurrent episodes of depression. In a more recent study, this same group confirmed their original report and also showed that the decrease in hippocampal volume correlated with total lifetime duration of depression and not with age. Other studies confirm the relationship between depression and hippocampal volume. For example, Premal Shah and his colleagues at the Royal Edinburgh Hospital also reported smaller hippocampal volumes in chronically depressed patients but found no decrease in hippocampal volume in recovered patients.

Temporal-lobe epilepsy also points to a connection between hippocampal damage and depression. First of all, temporal-lobe epilepsy involves a massive loss of cells in various structures in and around the hippocampus. Second, depression is the most common psychiatric complication in patients with epilepsy. Moreover, patients with temporal-lobe epilepsy experience depression more than patients with other forms of epilepsy or than patients with comparably debilitating diseases. If there is a causal relation between temporal-lobe epilepsy and depression, some evidence indicates that it might be bidirectional. Because the neuropathology in temporal-lobe epilepsy encompasses most of the temporal lobe, however, no definitive conclusion can be drawn regarding the site of specific damage that might underlie the psychopathology.

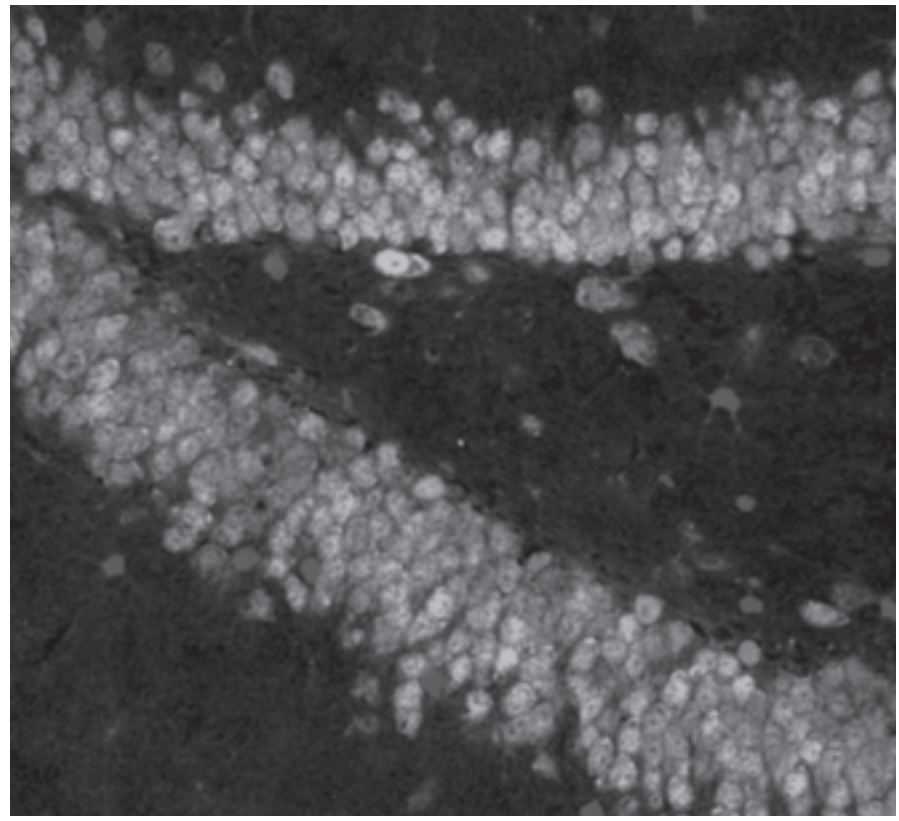


Figure 4. Photomicrograph from a mouse's brain shows the dentate gyrus, which consists primarily of mature neurons *(green)*. This mouse spent 40 days running on a wheel and then was treated with bromodeoxyuridine, which reveals newborn cells *(red)*. Some of the newborn cells are neurons *(orange*, from the combination dyes). This image also shows some glial cells *(blue)*. The exercise stimulates neurogenesis in the dentate gyrus, and a variety of evidence indicates that such neurogenesis could relieve or fend off depression. (Photomicrograph courtesy of the authors.)

Stimulation from Serotonin

As mentioned above, prescription drugs that increase serotonergic neurotransmission are currently the most common and most effective treatment for depression. Furthermore, serotonin stimulates cell division in a variety of peripheral tissues and triggers neurogenesis in the central nervous system during development. It also plays an important role in neuronal and synaptic plasticity. That evidence made serotonin worthy of further study.

Recently, one of us (Jacobs) and his colleagues used adult rats to study the effect of d,l-fenfluramine, a drug that releases serotonin throughout the central nervous system. In those studies, systemic administration of that drug increased cell division two- to threefold in the dentate gyrus. Moreover, an antago-

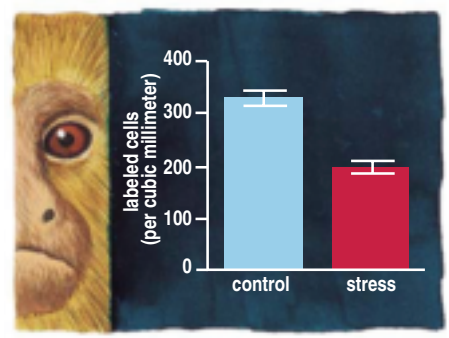
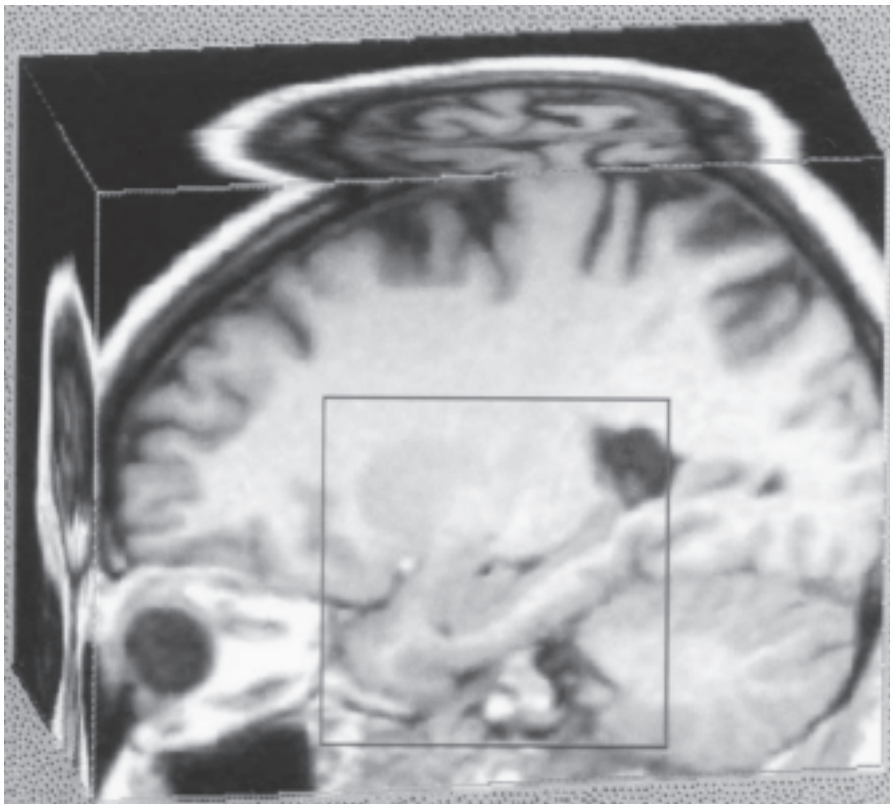


Figure 5. Stress reduces cell proliferation in the dentate gyrus of primates. When Elizabeth Gould of Princeton University and her colleagues placed a marmoset monkey in a cage with another marmoset that had already been living there, the intruders *(right)* showed fewer bromodeoxyuridine-labeled cells per cubic millimeter of dentate gyrus than did controls *(left)*. Presumably, such a stressful encounter increases brain glucocorticoids, which inhibit neurogenesis. (Adapted from Gould *et al.* 1998.)



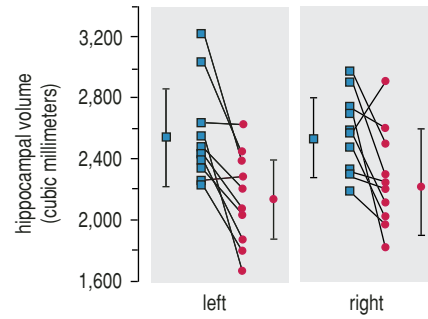


Figure 6. Magnetic resonance images *(left)* can be used to measure the volume of a person's hippocampus *(the hook-shaped structure in the middle)*. Yvette Sheline and her colleagues at Washington University used this technique to compare left and right hippocampal volumes in pairs of matched subjects *(above)*, in which one suffered from clinical depression *(red)* and the other was a control *(blue)*. Despite having comparable total cerebral volumes, the depressed subjects had smaller left and right hippocampal volumes in nearly all cases. As a result, the average hippocampal volumes for control subjects *(blue boxes on vertical error bars)* exceeded those for depressed subjects *(red dots on vertical bars)* on both the left and right sides of the brain. (Image courtesy of Yvette Sheline.)

nist for a specific serotonin receptor—called 5-HT_{1A} (serotonin is also known by the name 5-hydroxytryptamine, or 5-HT for short)—completely blocked this effect of d,l-fenfluramine. (Other serotonin receptors might also be involved in this process.) We later showed that much of this increase in cell division ended up making more neurons. So these studies highlight serotonin's impact on granule-cell neurogenesis in an adult rat's dentate gyrus.

The clinical benefit of drugs that increase serotonergic neurotransmission encouraged one of the authors (Jacobs) to test fluoxetine (Prozac), which increases brain levels of circulating serotonin by inhibiting it from being taken back into neurons that release it. We gave adult rats a three-week, systemic treatment of fluoxetine and found an approximately 70-percent increase in the number of cells produced in the dentate gyrus. Ronald Duman's group at Yale University confirmed and extended that result. They found that fluoxetine, antidepressants acting preferentially on norepinephrine and chronic electroconvulsive shock all increased cell proliferation in a rat's dentate gyrus.

In combination, the above studies demonstrate that serotonin can dramatically augment cell proliferation and that it does so, at least in part, by action at the 5-HT_{1A} receptor. Consistent with this, the hippocampus—especially the dentate gyrus—has an extremely dense concentration of these receptors.

If this receptor plays a role in depression, it would be useful to test 5-HT_{1A}-agonist drugs as therapeutic agents. Unfortunately, we lack a potent and specific 5-HT_{1A}-receptor agonist for human use. Partial agonists for the 5-HT_{1A} receptor, however, can reduce anxiety and provide some antidepressant effect. To better understand this possible mechanism, we must examine 5-HT_{1A} function in depressed patients. Sharon Cheetham and her colleagues at University College, London did report a decreased number of 5-HT_{1A} binding sites in the hippocampus of depressed suicide victims, but they did not examine specific 5-HT_{1A} binding in the hippocampus. More recently, Stanley Watson and his colleagues at the University of Michigan reported a decrease in the expression of 5-HT_{1A} mRNA in the hippocampus in a group of depressed suicide victims. These findings provide additional support for this receptor's importance in controlling depression.

A final feature of this hypothesis is that it provides a conceptually simple explanation for the therapeutic lag, in which antidepressant treatments—both drugs and electroconvulsive therapy—typically require 3–6 weeks to become effective. We suggest that this is because it takes time for newly born dentate-gyrus neurons to fully mature, extend their neurites and integrate with the existing brain circuitry.

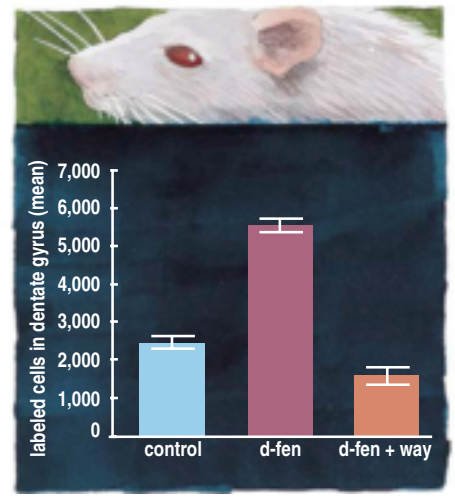


Figure 7. One of the authors (Jacobs) treated rats with d,l-fenfluramine, a drug that releases serotonin throughout the central nervous system. This drug *(center)* produced a two- to threefold increase in the number of bromodeoxyuridine-labeled cells in the dentate gyrus as compared to normal *(left)*. In addition, a proprietary drug called WAY 100, 635 *(right)*—an antagonist for a specific serotonin receptor—blocked the effect of d,l-fenfluramine. These studies and others show that the level of neurogenesis in the dentate gyrus depends on circulating levels of serotonin.

Other Possibilities

Despite proposing that alterations in hippocampal neurogenesis play a crucial role in the etiology and recovery from depression, we do not exclude other changes as being important. For example, besides suppressing neurogenesis, increased glucocorticoids might mediate additional direct neuronal effects in the cerebral cortex, hippocampus and other subcortical areas, such as the amygdala. Similarly, changes in serotonin neurotransmission might also exert direct effects in the brain stem, subcortical sites and the cortex. All of these changes, acting in concert, give rise to the complex syndrome of depression.

Although this article focuses on the augmentation of dentate-gyrus neurogenesis by serotonin, other means of increasing neurogenesis might also have clinical relevance. For example, it is well known that exercise, especially running, has an antidepressant action, and we recently found that 4–10 days of running on a wheel induces a significant increase in cell proliferation in a mouse's dentate gyrus. After several weeks of running, neurogenesis increased as well. Also, norepinephrine appears to increase cell division in the dentate gyrus. These factors might also play roles in depression.

There are also several related theories. Pierre Blier and Claude de Montigny of McGill University, for example, suggest that antidepressant therapies act in the hippocampus by increasing neurotransmission at the serotonin 5-HT_{1A} receptor and by decreasing it at the beta-adrenergic receptor, which can be activated by norepinephrine. Watson and his colleagues emphasize the importance of glucocorticoid-induced down regulation of the 5-HT_{1A} receptors in the hippocampus of experimental animals. In examining these and related theories of depression, we find that our theory does not supplant or contradict them. Rather, it complements and extends these previous ideas by pointing to a particular neural event, the rise and fall of dentate-gyrus neurogenesis.

Still, one might wonder how the hippocampus could affect depression. Historically, neurobiologists thought of it as part of the brain's cognitive circuitry and not involved in mediating mood or emotion. Nevertheless, recent evidence indicates that structures considered to be central to the brain's emotional circuitry, such as the amygdala, are strongly interconnected with the hippocampus. This connection would provide the anatomical substrate for linking cognitive and emotional information processing. Consistent with our hypothesis, clinically depressed patients have a variety of memory deficits, which would also point to hippocampal involvement.

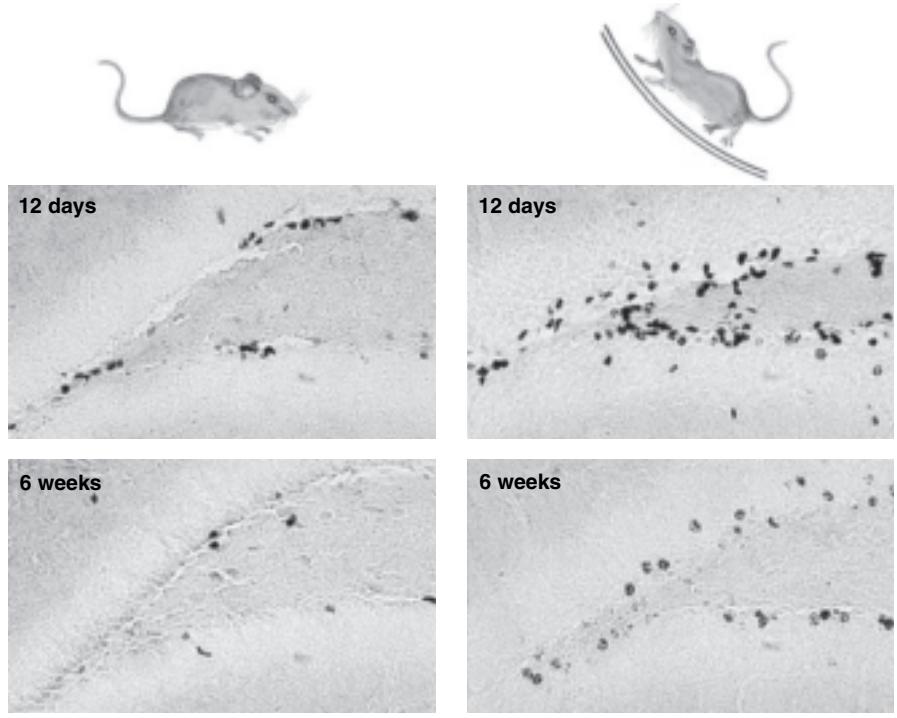


Figure 8. Exercise also affects neurogenesis in the dentate gyrus. The authors saw more bromodeoxyuridine-labeled cells in the dentate gyrus of a running mouse after 12 days *(upper right)* in comparison to a control mouse *(upper left)*. The increased level of cell survival could also be seen in running mice after six weeks *(lower right)* in comparison with controls *(lower left)*. These results might explain some of the antidepressant action of exercise.

In addition to treating clinical depression, advances in controlling neurogenesis might also be used to treat many other diseases where brain cells have died. In this context, two separate strategies are being weighed. Some investigators harvest stem cells from the adult brain, expand them in tissue culture, induce the cells to make specific cell lines, say neurons, and then transplant them to a specific brain region where they could replace or augment endogenous cells. On the other hand, cells already in the brain might be activated by pharmacological or environmental stimulation and induced to proliferate and migrate to a damaged or diseased brain region, where they would take up residence in areas to replace or augment lost function. Although progress is being made on both of these fronts, much additional work remains to make these repair strategies routine. In any case, we now know that structural correlates of neural plasticity extend beyond synaptic reorganization and include the addition of new neurons to important circuits.

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