

# Neurogenesis and Depression: Etiology or Epiphenomenon?

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*The concept that decreased neurogenesis might be the cause of depression is supported by the effects of stress on neurogenesis and the demonstration that neurogenesis seems to be necessary for antidepressant action. Data from the animal models tested to date show that decreasing the rate of neurogenesis does not lead to depressive behavior. Furthermore, evidence shows that an effective treatment for depression, transcranial magnetic stimulation, does not alter rates of neurogenesis. On the basis of these findings, it is suggested that neurogenesis might play a subtle role in depression but that it is not the primary factor in the final common pathway leading to depression.*

**Key Words:** Depression, neurogenesis, animal models, antidepressants, behavioral responses

The finding that the fully developed mammalian brain has two areas containing progenitor cells that develop and differentiate into a variety of cell types, including fully functional neurons, has led to a re-examination of the possibility that neurogenesis might be a mechanism of the central nervous system to adapt to environmental influences. One suggested hypothesis, which seems to be consistent with many lines of evidence, is that a decrease in the formation of new neurons might be a final common pathway in the etiology of depression (Duman et al 2000; Jacobs et al 2000). To evaluate this hypothesis, it is necessary to look at the factors that influence the rate of neurogenesis, attempt to determine the role of new neurons, and to look at the timing of their integration into neural networks.

The idea that the brain adapts or exhibits plasticity goes back to Hebb (1949), who thought that this could be accomplished by strengthening or weakening existing synapses. A clear example of this is long-term potentiation. Subsequently, changes in structure were postulated, and eventually it was shown that synaptic remodeling could be brought about by aging or experience (Greenough et al 1978). Additionally, Altman and Das (1965) showed that new neurons are produced in the dentate gyrus of the hippocampus; this observation was subsequently confirmed with the use of better labeling methods. These cells have increasingly been implicated in central nervous system plasticity. Neurogenesis seems to occur in only two areas of the mammalian brain: the subventricular zone (SVZ), which leads to new neurons in the olfactory bulb, and the subgranular zone (SGZ), which leads to new neurons in the dentate gyrus of the hippocampus. Interestingly, stress seems to be a major regulator of the rate of new cell formation in the SGZ but does not affect the SVZ. Thus, the hippocampus seems to be the focus for hypotheses related to stress and its effects.

## Regulation of Neurogenesis

Factors that seem to influence the birth and survival of new cells include a variety of stressors, from tube restraint (Vollmayr et al 2003) to predator odor (Tanapat et al 2001), probably mediated through the hypothalamic–pituitary–adrenal (HPA) axis. It has been shown that corticosterone decreases new cell formation in the hippocampus (Cameron and Gould 1994;

Cameron and McKay 1999). Long-term changes in neurogenesis can also be induced by prenatal stress (Coe et al 2003; Lemaire et al 2000). Several factors also seem to increase new cell proliferation or survival, including exposure to an enriched environment (Kempermann et al 1997), running on a running wheel (van Praag et al 1999), or increased estrogen levels (Tanapat et al 1999).

The most provocative and important function that has been postulated to involve newly formed neurons in the adult brain is learning. This was first proposed by Barnea and Nottebohm (1994) for song birds. In mammals, Gould and her collaborators (Gould et al 1999; Shors et al 2001, 2002) have provided evidence that trace conditioning leads to a greater survival rate of new neurons. The learning tasks that seem to depend on new neurons in mammalian species are limited. In a recent report, Shors et al (2002) were able to show that neither performance in the Morris water maze nor fear conditioning required newly formed neurons. These studies also indicated that it was not the increased birth of new neurons from progenitor cells but rather the continued survival of cells that were born approximately 5 days before the learning trials that was important for learning. The evidence for a specific role for neurogenesis in learning is limited to aspects of associative learning with temporal dimensions that are hippocampal dependent. Recent work by Deisseroth et al (unpublished data) suggests that newly born cells tend to reduce the expression of genes that promote glial cell formation when they detect excitation; that is, neuronal turnover seems to be regulated in an activity-dependent manner. This could explain why it is the survival of already-born cells that is critical to learning. These cells sense the activity and then are activated to integrate themselves into the neuronal network in the area. Such an interpretation emphasizes that it is not the birth of more cells but rather the activation and survival of already-born cells into neuronal networks that is important for learning. Thus, neurogenesis might clearly influence specific aspects of learning that play a role in a variety of behavioral changes, including depression.

To begin to understand the roles newly formed neurons and glia might have in the hippocampus, it is necessary to have an estimate of how quantitatively important neurogenesis is. Cameron and McKay (1999) have shown that approximately 9000 new cells are produced daily; this in a structure (the dentate gyrus) that contains between 1 and 2 million cells, suggests that the structure could completely turn over in 4–8 months. Because it seems that not all cells are turned over this rapidly in the hippocampus, it might be that new cells are specifically used in the acquisition of specific types of memories and that these are turned over relatively quickly, with the memories subsequently going to cortical sites and new cells used for the short-term

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acquisition of the next memory. This fits with the suggestion of McClelland et al (1995), that the initial encoding of new information takes place in the hippocampus to protect the cortex from “catastrophic interference,” which occurs when new connections are continually added to a network. The mechanism described above would protect the hippocampus from a similar fate through turnover of the network elements. This is consistent with a computational model proposed by the Stanford group (Singla et al, unpublished data) and provides an explanation as to why the hippocampus is so important in short-term memory formation but seems to play no role in long-term memory retention. This model suggests that new neurons are necessary to form new memories with a limited half-life in the hippocampus and that turnover is necessary to allow the continual formation of new networks encoding new memories. Such a model for understanding the role of neurogenesis in the hippocampus would suggest a plausible role for this process in the etiology of depression. Lower levels of neuron formation as a result of stress could lead to less adaptive behavior and the acquisition of a helpless attitude and depressive affect. This is consistent with Beck’s cognitive formulation of depression and offers a reasonable hypothesis for a final common neurobiological pathway.

### **Evidence Supporting a Role for Neurogenesis in the Etiology of Depression**

Evidence from clinical studies concerning neurogenesis is indirect and related to the effects of depression on the volume of the hippocampus. Many studies suggest that depression results in a decrease in hippocampal volume; however, these are by no means consistent (see Davidson et al 2002). Hippocampal changes are also seen, again with some inconsistency, in bipolar disorder and posttraumatic stress disorder. In all these cases, it has been suggested that this might well be related to HPA dysfunction and increased glucocorticoid concentrations in the hippocampus leading to neuronal degeneration (see Gold et al 1988; Sapolsky 2000). Recent evidence suggests that these changes might be reversible (Frodl et al 2002). Proponents of the neurogenesis hypothesis of depression have argued that these volume changes might be due to changes in the rate of production of new cells (Jacobs 2002). Although these data might be suggestive, they are far from conclusive. This has led to a series of indirect animal studies aimed at assessing the effect of stress and antidepressant treatment on neurogenesis.

As reported above, several stressors have clearly been shown to decrease the rate of cell proliferation and neurogenesis. Although consistent with a role for neurogenesis in depression, this line of research imparts no specificity for depression, in that stress plays a role in a variety of psychiatric illnesses, such as posttraumatic stress disorder and bipolar disorder, which also show volume reduction in the hippocampus. This suggests that all stress-related illnesses, at least when they become chronic and show decreased hippocampal volume, might have as a component of their pathophysiology decreases in the rate of neurogenesis. In an effort to specifically test this, a variety of groups have looked at the role of antidepressants on neurogenesis.

Almost all currently clinically active antidepressants act through either the serotonin (5HT) and/or norepinephrine (NE) systems. These compounds are able to alter synaptic levels of the catecholamines relatively rapidly; however, antidepressants are known to act with a lag time of from 10 days to 3 weeks, and this lag period has been one of the central reasons that depression research has pushed beyond the monoamine receptors and

transporters. An event that underscored the importance of examining the effects of alterations in the signal transduction cascade (and downstream effects) was the publication by Duman et al (1997) of a molecular and cellular theory of depression. This has helped focus depression research on the possible structural and functional alterations secondary to changes in monoamine activity and has led to an attempt to define a common final structural pathway that would have an appropriate lag period. A major requirement for such a pathway to be a candidate for the final common pathway involved in depression is that all effective clinical treatments for depression should induce similar changes in this pathway. The corollary of this is that changes opposite to those brought about by antidepressant treatment should result in depression.

The idea that changes in the rate of neurogenesis could be the final common pathway leading to depression was proposed by Jacobs et al (2000) and Duman et al (2000) and amplified by Kempermann (2002), D’Sa and Duman (2002), Jacobs (2002), and Kempermann and Kronenberg (2003). The evidence cited above plus the clear role of the 5HT system in controlling rates of neurogenesis was cited as the basis for the hypothesis. Tests of this hypothesis involved looking at the action of antidepressants on the rates of cell proliferation and neurogenesis. Malberg et al (2000) were able to show that chronic antidepressant administration increased neurogenesis in the hippocampus and that a common antipsychotic did not produce this effect. Czeh et al (2001), working with the tree shrew, were able to show that antidepressant treatment was protective when the animals were stressed and that hippocampal volume reductions were avoided and neurogenesis was stimulated by tianeptine. The most effective treatment in dealing with severe depression remains electroconvulsive therapy (ECT). Madsen et al (2000) showed that both a single ECT treatment and chronic ECT increased neurogenesis in the adult rat hippocampus. Thus, it seems that a consistent finding in animals is that antidepressant therapies seem to increase the rate of neurogenesis. There were two problems in fully accepting these data. The first involved the question of correlation or cause and posed the question: is neurogenesis necessary for antidepressant activity? The second is more subtle and involves the question of the effects of drugs on wild-type animals as opposed to animals having the pathologic condition.

The first question, whether neurogenesis is really necessary for the action of antidepressants, was addressed in part by Santarelli et al (2003). In their study, these investigators used two methods to interrupt cell proliferation. In the first case they used x-ray treatment of the hippocampus to abolish neurogenesis and showed that this disrupted the behavioral effects of two antidepressants, fluoxetine and imipramine. They used an anxiety test to assess depression, which is somewhat questionable because this test is used to screen for anti-anxiety agents and is very responsive to benzodiazepines, which are ineffective in treating depression. The test they chose was novelty suppressed feeding, in which an animal is placed in an open field with a brightly illuminated center; in the center is food, and the animal must overcome fear of brightly lit spaces to reach the food. The latency to begin feeding is a measure of anxiety, which in this study was taken as a measure of depression. Both imipramine and fluoxetine reduced the latency to feeding and increased the rate of neurogenesis after 28 days of treatment but not after 5 days of treatment. The authors then carefully irradiated the hippocampus of the animals and were able to show that they had reduced the rate of cell proliferation by more than 80%, as assessed by bromodeoxyuridine (BrdU) labeling on day 27. Irradiated mice

did not show a significant response to the antidepressants fluoxetine or imipramine. This suggests that the drugs worked through increasing neurogenesis. The second approach was specific to the 5HT system, in that 5HT<sub>1A</sub>-knockout mice were used. It was shown that these mice were insensitive to the effects of fluoxetine on behavior or neurogenesis; however, effects on both neurogenesis and behavior were seen when antidepressants that act through NE as well as 5HT were used. It was also noted that the knockout mice had a greater latency to feed than wild-type mice but had exactly the same rate of cell proliferation. This suggests that changes in neurogenesis might not be necessary for changes in this behavior. If latency to feed can really be viewed as depressive, then the knockout mice are more depressive but have the same rate of neurogenesis. In looking at the radiation data, the same sort of paradox is seen: the irradiated animals had only a very low level of cell proliferation but showed exactly the same latency to feed as wild-type animals. Thus, decreased neurogenesis apparently does not lead to altered behavior in this model.

In a subsequent study, Malberg and Duman (2003) used a much more realistic animal model of depression to assess the role of antidepressants on neurogenesis. We believe that the use of an appropriate model is critical in these tests. The question of differences in pharmacologic effects on wild-type as opposed to pathologic tissue is almost never considered; however, in the case of depression, we have evidence that it could be critical. We use a very carefully developed version of the learned helplessness test, which shows excellent face validity to test this. Using learned helpless animals, we have shown that the NE  $\beta$  receptor is upregulated in helplessness and downregulated by all classes of antidepressants, including selective serotonin reuptake inhibitors (Henn et al, unpublished data). Because the prevailing evidence concerning  $\beta$  receptor downregulation was obtained on wild-type animals, the role of this receptor has fallen from consideration. Selective serotonin reuptake inhibitors clearly do not downregulate normal  $\beta$  receptors, only those that seem to be pathologically upregulated. Although we certainly do not believe that the NE  $\beta$  receptor is the central etiologic target in depression, these studies illustrate the possibility that wild-type tissue will react differently from pathologic tissue. This needs to be kept in mind in studies of drug action and tested in a variety of appropriate models.

Thus, the use of an inescapable stress model to test the effects of antidepressants on neurogenesis is welcome and addresses the question of whether an antidepressant acts similarly on a pathologic model. What Malberg and Duman (2003) did was to use inescapable shock to form a group of helpless animals and compare these animals with control animals that received no inescapable shock. After 9 days the control animals were split into two groups; half were analyzed for cell proliferation and half were given a shuttle box avoidance test. The group of helpless animals was also given a shuttle box avoidance test, and cell proliferation was determined after that test. The results show that the animals exposed to inescapable shock had a much longer latency to respond in the avoidance test. Interestingly, both the control and experimental animals exposed to inescapable shock had an approximately 40% reduction in cell proliferation after the avoidance task. In a second experiment, another group of helpless animals was formed; half were treated for 7 days with fluoxetine, and half were given saline. Fluoxetine reversed the increased latency in the shuttle box avoidance task. Inescapable shock had no effects on cell proliferation when measured 9 days later or on corticosterone production at 9 days. These results

support the idea that fluoxetine can reverse the behavioral effects of inescapable shock and that there is a statistically significant increase in cell proliferation at day 9 due to fluoxetine treatment.

### Evidence Against Neurogenesis Being an Etiologic Factor in Depression

In an attempt to demonstrate that decreases in neurogenesis might lead to depressive-like behavior, we further examined the learned helplessness model (Vollmayr et al 2003). We trained and tested a cohort of animals and formed two extreme groups, those showing helpless behavior and those showing no helplessness. We looked at the effect of helplessness training on cell proliferation and found a decrease in labeled cells beginning on day 3 after testing. This was not evident 24 hours after training, a point when helpless behavior was firmly established, but by 3 days both the helpless and nonhelpless animals had a significant decrease in cells labeled with BrdU. Although the helpless animals had slightly fewer cells, there was no statistical difference between the helpless and nonhelpless animals at day 3, or for that matter at any time point measured. This suggested to us that although the stress of helplessness training had an effect on the survival of new cells, this effect was identical in those animals showing behavioral changes and those showing no behavioral changes. That is, a decrease in new cells did not lead to helpless behavior. We examined this in another way by using restraint stress to decrease the rate of cell proliferation by approximately 40%; these animals were then subjected to helplessness training. The idea behind this experiment was that if a decrease in neurogenesis predisposes to depression, we would see a higher proportion of animals develop helplessness after exposure to restraint stress. To our surprise, this was not the case: there was no change in the proportion of animals that developed helplessness. One problem with these experiments was that we only measured BrdU labeling and could not be sure that this reflected changes in new neurons. In a replication, we analyzed specifically for neurons, astrocytes, and oligodendrocytes and obtained similar results. Our conclusion was that there is no evidence that a decrease in neurogenesis leads to depressive-like behavior in animals. This is consistent with the results of Santarelli et al (2003) and with the data of Malberg and Duman (2003). In their experiment, Malberg and Duman showed that aversion testing alone reduces labeling, and these animals showed no behavioral deficit. It is well known that after one exposure to aversion training, subsequent testing will lead to an even shorter latency of response, thus the decrease in cell proliferation does not result in a behavioral defect; in fact, improved performance is often seen.

Even if a decrease in neurogenesis does not lead to depressive-like behavior, perhaps increasing neurogenesis is still the mechanism by which antidepressants act. If this is the case, then all treatments that show clinical effectiveness should increase neurogenesis. Recent data suggest that this might not be the case. Czeh et al (2002) reported that transcranial magnetic stimulation was able to reverse the effects on the HPA axis produced by stress but did not stimulate cell proliferation in rats. Similar results were obtained by Scalia et al (unpublished data) in rhesus monkeys. They compared six weeks of ECT and transcranial magnetic stimulation in terms of BrdU incorporation and mossy fiber sprouting. They were able to show that, as expected, ECT increased both mossy fiber sprouting and cell proliferation, whereas magnetic stimulation showed no increased labeling with BrdU compared with sham treatment and only a moderate

**Table 1.** Comparison of Effects Seen in Depression and Seen by Decreasing Neurogenesis

Effect	Depression	Decreased Neurogenesis
Long-Term Changes in Vegetative Symptoms	Yes	No, in animal studies
Long-Term HPA Changes	Approximately 80%	Less than 10% in animals
SSRIs, Tricyclic Antidepressants Relieve the Illness	Yes	Increases rate of neurogenesis
ECT Reverses	Yes	Increases rate of neurogenesis
TMS Reverses	In majority of studies	No change in neurogenesis
Tube Restraint Stress	No development of depressive symptoms in animals	40% reduction in rate of neurogenesis

HPA, hypothalamic–pituitary–adrenal axis; SSRIs, selective serotonin reuptake inhibitors; ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation.

increase in mossy fiber sprouting in the hippocampus. The question remains, is transcranial magnetic stimulation an effective treatment for depression? A recent, carefully controlled trial with treatment-resistant patients suggests clearly that it is (Fitzgerald et al 2003). In this study, severely ill, treatment-resistant patients received a 4-week trial of either low- or high-frequency stimulation, and both groups showed a good response compared with a matched control group. It was clear that at least 4 weeks of treatment were necessary for a response. Thus, the study by Scalia et al, which involved 6 weeks of treatment, was an ideal model of an effective antidepressant treatment. These studies suggest that it is possible to dissociate the effect of antidepressant treatment from changes in cell proliferation. Effective antidepressant treatments apparently do not require changes in cell proliferation (Table 1).

## Issues of Timing

If the evidence produced by Deisseroth et al (unpublished data) can be reproduced and amplified, it would suggest that it is not the fact of cell division but rather the direction cell differentiation takes after cell division within a short time window, during which the cell's fate is not yet determined, that might be crucial in learning. The direction the cell takes seems to be a function of the activity it senses in its immediate environment. From the work of Dayer et al (2003), it seems that cells begin to die at approximately day 4 after cell division and that by 1 month more than half of the new cells have died. Those that differentiate into granule cells and survive 1 month live at least for half a year. Thus, it might be that only those cells that sense specific activity are able to differentiate, integrate into circuits, and survive. This suggests that it is not changes in the rate of cell division but rather changes in which cells survive that will mark a learning event. The experiments on trace conditioning (see Shors et al 2002) involved labeling cells 5 days before the conditioning experiment. Thus, cells at the critical developmental juncture would have been labeled. In totally ruling out an etiologic role of neurogenesis in helplessness, and by analogy depression, it would be necessary to look at the fate of cells 4–6 days old when helplessness training takes place. Such experi-

ments are now under way and should help us determine whether there is a role for neurogenesis in affective disorders.

Another timing issue that is critical is the rate of onset of depression. In regularly treating severely depressed patients, we are impressed by how some patients can specify the hour when their depression began. It is textbook knowledge that depression has an acute onset, but the realization that it occurs so rapidly in many cases must make us consider whether such an onset is consistent with structural changes. This observation suggests a two-phase hypothesis of depression, in which acute neurochemical changes precipitate a depressive episode and slower structural changes might occur that allow the condition to persist and increase the vulnerability to subsequent episodes. We would suggest that changes in the rate of neurogenesis are totally inconsistent with the rapid onset often seen in major depression.

## Summary

We have reviewed the evidence that changes in neurogenesis can lead to depressive behavior. In all the studies in which there are data on this point, including those studies that claim to support a role for neurogenesis in depression, we have found no evidence that decreased cell proliferation leads to depressive-like behavior. On the contrary, it seems clear that decreasing the rate of cell proliferation does not alter behavior in any test of anxiety or depression used to date. In looking at the mechanism of action of antidepressant treatments, it is clear that many but not all can increase cell proliferation. Thus, it does not seem that increasing neurogenesis is necessary for effective antidepressant action, although it might contribute to antidepressant activity in some cases. These findings suggest to us that at present neurogenesis must be considered more of an epiphenomenon than an etiologic variable in depression. The possibility that some learning event associated with stress might involve neurogenesis and might play a role in depression has not been totally ruled out but seems unlikely at present.

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