

Depression: A Case of Neuronal Life and Death?

Ronald S. Duman

Preclinical and clinical studies have demonstrated that stress or depression can lead to atrophy and cell loss in limbic brain structures that are critically involved in depression, including the hippocampus. Studies in experimental animals demonstrate that decreased birth of new neurons in adult hippocampus could contribute to this atrophy. In contrast, antidepressant treatment increases neurogenesis in the hippocampus of adult animals and blocks the effects of stress. Moreover, blockade of hippocampal neurogenesis blocks the actions of antidepressants in behavioral models of depression, demonstrating a direct link between behavior and new cell birth. This perspective reviews the literature in support of the hypothesis that altered birth of new neurons in the adult brain contributes to the etiology and treatment of depression and considers research strategies to test this hypothesis.

Previous hypotheses to explain the cause and treatment of depression have been based in part on the acute actions of antidepressants (i.e., blockade of serotonin and norepinephrine reuptake or breakdown); however, the time lag for a therapeutic response has led to the hypothesis that adaptations to the acute actions of antidepressants are necessary. Cellular adaptations can occur at many levels, including regulation of neurotransmitter receptors, signal transduction cascades, and gene transcription. Advances in cell biology and imaging have revealed that these neurochemical adaptations can lead to alterations in cell morphology (e.g., alterations in the length and complexity of neuronal processes) and even the birth of new neurons. Moreover, it is now clear that alterations in neuronal morphology and cell number represent fundamental mechanisms of neuronal plasticity that allow an animal to adapt to environmental, behavioral, and pharmacologic stimuli and thereby make appropriate long-term responses. These concepts and advances have been applied to studies of antidepressants and have resulted in the novel hypothesis that altered neurogenesis plays a role in the etiology and treatment of depression (Duman et al 2001; Kempermann and Gage 2002). The focus of this perspective is to review the evidence in favor of this hypothesis. Avenues of research that can be developed to test this exciting hypothesis are also discussed.

Neurogenesis in Adult Brain

The presence of neural progenitor cells that give rise to new neurons in the adult brains of a variety of species, including humans, has been firmly established (Figure 1; Duman et al 2001; Gage 2000; Gould et al 1999). Adult neurogenesis is restricted to the subventricular zone, which gives rise to granule cells in the olfactory bulb and in the subgranular zone, which generates new granule cells in the adult hippocampus. Immature neurons in subgranular zone of the hippocampus migrate into the granule cell layer, extend processes, and mature into granule cells that have physiologic characteristics that are similar to existing granule cells (van Praag et al 2002). In rodent brain, it is estimated that approximately 250,000 new neurons, or approximately 6% of the granule cell layer, are formed each month (Cameron and McKay 2001). The estimates of the number of new neurons are much smaller in primates than rodents (~10%; Gould et al 1999;

Kornack and Rakic 2001), but even this lower rate of neurogenesis over longer periods of time may be sufficient to have functional significance.

Clinical Evidence for Atrophy of Hippocampus in Mood Disorders

Indirect evidence suggesting that altered neurogenesis could occur in mood disorders is provided by brain imaging studies of hippocampus. These studies report that hippocampus volume is decreased in patients with depression (Bremner et al 2000; Frodl et al 2002; MacQueen et al 2003; Mervaala et al 2000; Saarelainen et al 2003; Shah et al 1998; Sheline et al 1996, 1999, 2003; Steffens et al 2000; Vermetten et al 2003). Other studies have reported no reduction in hippocampal volume, although specific measurements of hippocampus were not conducted or included the amygdala (Axelson et al 1993; Vakali et al 2000; for complete references, see Posener et al 2003). One study found no change in volume but reported that the shape of the hippocampus is different in depressed patients (Posener et al 2003). The magnitude of the reduction in volume is reported to be directly related to the length of illness (Sheline et al 2000). Moreover, antidepressant medication reduces or even reverses hippocampal atrophy in depressed or PTSD patients (Sheline et al 2003; Vermetten et al 2003). Imaging studies of other brain regions also report altered brain morphology, including reduced volume of prefrontal cortex (Bremner et al 2000; Drevets et al 1997). In addition, postmortem studies demonstrate that there is a reduction in the size of neurons and number of glia that could underlie the reduction in cortical volume (Cotter et al 2001; Ongur et al 1998; Rajkowska et al 1999). It is unlikely that decreased neurogenesis contributes to the atrophy of these cortical brain regions because most studies to date have not observed neurogenesis in adult cerebral cortex (Koketsu et al 2003; Kornack and Rakic 2001), although this has been a controversial subject (Gould et al 1999, 2001).

The imaging studies provide indirect evidence for alterations in cell number or morphology in the hippocampus in mood disorders and a major goal of current research is to identify these cellular changes. One possibility is that decreased neurogenesis contributes to hippocampal atrophy and thereby underlies the pathophysiology of depression and stress-related disorders; however, it is likely that other mechanisms such as death or atrophy of existing neuronal processes or loss of glia could also contribute to the reduced volume of hippocampus (McEwen 1999; Sapolsky 2002). Detailed postmortem analysis of the hippocampus of depressed patients will be necessary to address this issue.

From the Division of Molecular Psychiatry, Departments of Psychiatry and Pharmacology, Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Ronald S. Duman, Ph.D., 34 Park Street, New Haven, CT 06508.

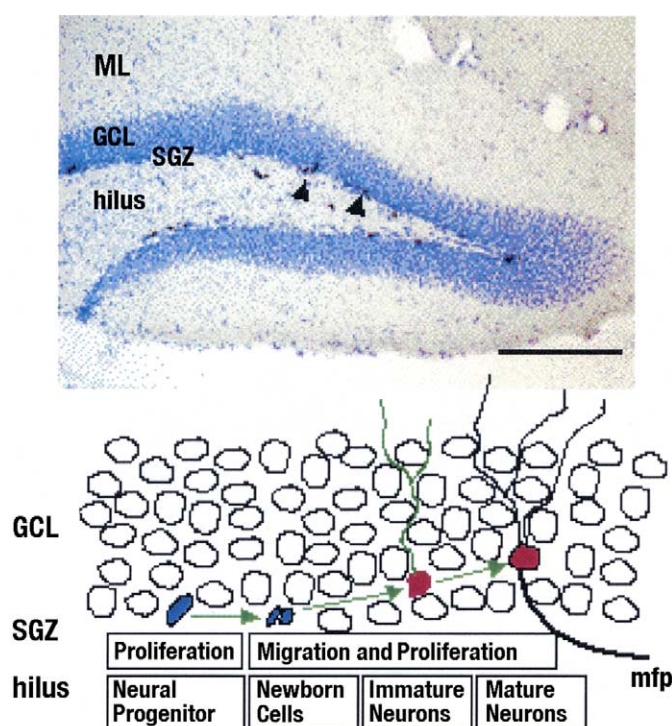


Figure 1. Model of neurogenesis in adult hippocampus. The upper panel demonstrates immunohistochemical analysis of neurogenesis in adult rat hippocampus. In dividing cells a thymidine analog, bromodeoxy uridine (BrdU) is incorporated into newly synthesized DNA, and an antibody against BrdU is then used to visualize newborn cells. At a short time point after proliferation (2 hours after BrdU administration), BrdU-immunopositive cells (arrowheads) are often found in clusters and are localized to the subgranular zone (SGZ) between granule cell layer (GCL) and hilus. A diagram depicting the location of neural progenitor cells and maturing neurons is shown in the bottom panel. Approximately 80% of the newborn cells differentiate into neurons and the remaining cells differentiate into glia or have an undetermined phenotype. Cells destined to become neurons migrate into the granule cell layer, mature, and take on characteristics of adult granule cells. This includes extension of dendrites into the molecular layer (ML) and axons into the CA3 pyramidal cell layer via the mossy fiber pathway (mfp). Scale bar in upper panel represents 200 μ m.

Hippocampus and Depression

The hippocampus is a brain region most often associated with control of learning and memory; however, reduced volume of this brain region in depressed patients suggests that the hippocampus could also contribute to certain symptoms of depression. Cognitive dysfunction and altered control of the hypothalamic-pituitary-adrenal (HPA) axis could be explained in part by decreased function of the hippocampus. The hippocampus has also been implicated in anxiety as local infusions of anxiolytics or lesions of hippocampus produce anxiolytic responses in behavior in models of anxiety (Deacon et al 2002; Degroot and Treit 2002; File et al 2000; Menard and Treit 2001). In addition, the hippocampus provides inputs to other brain regions, including the prefrontal cortex, cingulate cortex, and amygdala that contributes heavily to altered mood and emotion in depression (Drevets 2001; Manji et al 2001). Based on these considerations, it is plausible to hypothesize that altered neurogenesis in hippocampus contributes directly to some, but not all aspects of depression, and could indirectly influence other symptoms of mood disorders including PTSD.

Stress Decreases Adult Neurogenesis

A key connection between neurogenesis and depression comes from studies of stress, which can precipitate or worsen depression (Brown et al 2003; Gold and Chrousos 2002) and is often used as a model in preclinical studies (Willner 1990). Stress produces a profound effect on neurogenesis, causing rapid and robust reductions in the proliferation of newborn neurons in adult brain (Table 1). Decreased neurogenesis has been reported with different types of stress and in different experimental animals, including intruder stress in marmosets (Gould et al 1998), subordination/psychosocial stress in tree shrews (Czeh et al 2001; Gould et al 1997; van der Hart et al 2002) and in rodents predator odor (Tanapat et al 2001), social defeat (Czeh et al 2002), chronic restraint (Pham et al 2003), footshock stress (Malberg and Duman 2003), and chronic mild stress (Alonso et al 2004). Prenatal stress also decreases neurogenesis in the adult hippocampus and is associated with reduced learning in rat (Lemaire et al 2000) and emotional behavior in rhesus monkeys (Coe et al 2003). In addition, inescapable stress leads to a reduction in neurogenesis that correlates with behavioral despair several days after exposure to stress in the learned helplessness model of depression (Malberg and Duman 2003). This correlation between decreased neurogenesis and behavioral despair at a time point well after exposure to stress indicates that the reduction in neurogenesis is not simply due to acute stress, and suggests that there is a relationship between reduced neurogenesis and the behavioral state of the animal.

The influence of the hypothalamic-pituitary-adrenal (HPA) axis on adult neurogenesis also provides a link with mood disorders. Activation of the HPA axis is one of the primary physiologic responses that prepares an animal physically and behaviorally to respond to stressful conditions. Approximately 50% of depressed patients exhibit dysfunctional regulation of this system, resulting in sustained elevation of cortisol, and lack of response to acute challenge with a synthetic glucocorticoid (i.e., nonresponders in the dexamethasone suppression test; Brown et al 2003; Gold and Chrousos 2002). Administration of adrenal-glucocorticoids to experimental animals decreases neurogenesis in the adult brain, mimicking the effects of stress (Cameron et al 1998; Gould et al 1992). The implication of these findings is that activation of the HPA axis and sustained elevation of glucocorticoids could lead to chronic inhibition of adult neurogenesis in the hippocampus. Because the hippocampus also provides negative feedback regulation of the HPA axis, it has been suggested that atrophy in depressed patients could lead to a recurrent and damaging cycle of HPA overactivation and sustained hippocampal atrophy (McEwen 1999; Sapolsky 2001).

Antidepressant Treatment Increases Adult Neurogenesis

Another important link between neurogenesis and mood disorders comes from studies of antidepressant drugs. In contrast to the effects of stress, antidepressant treatment increases neurogenesis in adult hippocampus (Table 1) (Czeh et al 2001; Madsen et al 2000; Malberg et al 2000; Manev et al 2001; Santarelli et al 2003). The induction of neurogenesis by antidepressants is dependent on chronic treatment, consistent with the time course for the therapeutic action of these medications. Upregulation of neurogenesis in the adult hippocampus occurs after chronic administration of different classes of antidepressants, including 5-HT and norepinephrine selective reuptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive seizures. This

Table 1. Influence of Stress or Antidepressant Treatment on Neurogenesis in Adult Hippocampus

Treatment	Effect	Species	Reference
Stress			
Social/subordination	Decrease	Marmoset	Gould et al 1998
Social/subordination	Decrease	Tree Shrews	Czeh et al 2001; Gould et al 1997; Van der Hart et al 2002
Social/subordination	Decrease	Rat	Czeh et al 2002
Predator odor	Decrease	Rat	Tanapat et al 2001
Restraint	Decrease	Rat	Pham et al 2003
Immobilization	Decrease	Rat	Vollmayr et al 2003
Footshock	Decrease	Rat	Malberg and Duman 2003
Footshock	Decrease	Rat	Vollmayr et al 2003
Chronic mild stress	Decrease	Mouse	Alonso et al 2004
Prenatal stress	Decrease	Rat	Lemaire et al 2000
Prenatal stress	Decrease	Rhesus	Coe et al 2003
Corticosterone	Decrease	Rat	Cameron et al 1998; Gould et al 1992
Adrenalectomy	Increase	Rat	Cameron and McKay 1999
Antidepressant Treatment			
Fluoxetine	Increase	Rat	Malberg et al 2000; Manev et al 2001
Fluoxetine	Increase	Mouse	Santarelli et al 2003
Imipramine	Increase	Mouse	Santarelli et al 2003
Tranylcypromine	Increase	Rat	Malberg et al 2000
ECS	Increase	Rat	Madsen et al 2000; Malberg et al 2000
Reboxetine	Increase	Rat	Malberg et al 2000
Rolipram	Increase	Rat	Nakagawa et al 2002a
TMS	No Effect	Rat	Czeh et al 2002
Estrogen	Increase	Rat	Tanapat et al 1999
DHEA	Increase	Rat	Karishma and Herbert 2002
Exercise/Running	Increase	Mouse	van Praag et al 1999
Antidepressant Blockade of Stress Effects			
Tianeptine	Blocks-Social	Tree Shrew	Czeh et al 2001
NK1-R antagonist	Blocks-Social	Tree Shrew	van der Hart et al 2002
Clorimipramine	Blocks-Social	Tree Shrew	van der Hart et al 2002
Fluoxetine	Blocks-Inescap	Rat	Malberg and Duman 2003
CRF-R1 antagonist	Blocks-Chr Mild	Mouse	Alonso et al 2004
AVP1b	Blocks-Chr Mild	Mouse	Alonso et al 2004
Fluoxetine	Blocks-Chr Mild	Mouse	Alonso et al 2004
Fluoxetine	Blocks-Mat Sep	Rat	Lee et al 2001

ECS, electroconvulsive seizures; TMS, transcranial magnetic stimulation; DHEA, dehydroepiandrosterone; NK1-R, neurokinin1-receptor; CRF-R1, corticotrophin releasing hormone receptor 1; AVP1b, arginine vasopressin receptor 1b; Inescap, inescapable footshock stress; Chr Mild, chronic mild stress; Mat Sep, maternal separation stress.

suggests that induction of adult neurogenesis may represent a common final target of different classes of antidepressants. Other treatments reported to have antidepressant effects and to increase neurogenesis include estrogen (Tanapat et al 1999), dehydroepiandrosterone (DHEA; Karishma and Herbert 2002), and exercise (van Praag et al 1999). One study has found that transcranial magnetic stimulation did not increase adult neurogenesis, although this treatment partially reversed the effects of social defeat on adult neurogenesis (Czeh et al 2002).

Antidepressant treatment influences at least two important aspects of adult neurogenesis, proliferation and survival of newborn neurons. Proliferation refers to the number of cells that are born in a given period of time and is typically analyzed within a short period (2 hours) after BrdU administration. This short time point is the approximate length of S phase of the cell cycle. The results of a study that directly analyzes cell proliferation at this early time indicates that antidepressants increase the rate of new cell birth (Malberg et al 2000).

After cell birth approximately half of the cells undergo a process of degeneration over the course of 3–4 weeks. Admin-

istration of antidepressants during this critical period increases the number of neurons that survive when determined at a 4-week time point (Nakagawa et al 2002a). Current studies are underway to determine whether antidepressants also increase the rate of neuronal maturation, which can be determined by the rate of growth of the processes (i.e., number and length of dendrites) of newborn neurons. The putative antidepressant, rolipram, has been shown to increase neuronal maturation (Fujioka et al 2004), as well as proliferation and survival (Nakagawa et al 2002a, 2002b). All of these effects would be expected to block or reverse the effects of stress, and possibly depression, on hippocampal atrophy.

Antidepressant Treatment Blocks the Effects of Stress on Adult Neurogenesis

Antidepressant treatment also blocks the effects of stress, or normalizes levels of neurogenesis, in adult hippocampus. This interaction has been observed with several types of stress models and antidepressant treatments (Table 1). Chronic administration

of an atypical antidepressant, tianeptine, blocks the effects of subordination stress on neurogenesis in the hippocampus of adult tree shrews (Czeh et al 2001). A similar effect has been observed after chronic administration of a neurokinin-1 receptor antagonist, a drug that has been shown to have antidepressant efficacy in clinical trials, or a tricyclic antidepressant (clomipramine; van der Hart et al 2002). These two elegant studies also demonstrate that the volume of the hippocampus is decreased by subordination stress and that antidepressant treatment reverses this atrophy. Downregulation of neurogenesis by social defeat is partially reversed by transcranial magnetic stimulation (Czeh et al 2002). A recent study found that chronic administration of either a corticotrophin releasing factor receptor-1 (CRF-R1) or arginine vasopressin receptor-1b (AVP1b) antagonist blocks the downregulation of neurogenesis caused by chronic mild stress (Alonso et al 2004). The influence of maternal separation stress on neurogenesis in young rats (14–21 days) is reversed by chronic fluoxetine administration (Lee et al 2001). We have found that the long-lasting decrease in neurogenesis that occurs after exposure to inescapable stress is reversed by antidepressant treatment, and this effect is accompanied by a reversal of the behavioral despair in the learned helplessness model of depression (Malberg and Duman 2003). The results of these studies demonstrate that antidepressant treatment not only influences neurogenesis in normal, unchallenged animals but can also block the effects of stress on neurogenesis in the adult brain.

Neurogenesis Is Necessary for the Action of Antidepressants in Behavioral Models

The ability of antidepressant treatment to increase neurogenesis in adult brain and to block the effects of stress provides strong evidence that adult neurogenesis may play a role in the treatment of depression and could possibly contribute to the illness itself; however, this data is only correlative and does not provide direct evidence that neurogenesis is a necessary cellular response for the treatment of mood disorders. The function of newborn neurons in adult brain has been difficult to assess experimentally because it is difficult to specifically block cell birth without influencing mature neurons and glia in the brain as well as nonneuronal cells in other tissues.

The function of newborn cells in hippocampus has been addressed in a recent study, however, that provides direct evidence that adult neurogenesis is necessary for an antidepressant response in behavioral models (Santarelli et al 2003). In this study, cell proliferation was blocked by exposure to irradiation that is focused on the hippocampus of adult mice. Irradiation decreases basal and blocks antidepressant induction of neurogenesis in the hippocampus and results in a corresponding blockade of the response to antidepressant treatment in two behavioral paradigms, novelty suppressed feeding and chronic unpredictable stress. In the novelty suppressed feeding paradigm, irradiation blocks the effect of antidepressant treatment on the latency to approach food pellets in the middle of an open field (i.e., antidepressants decrease the latency). In the chronic unpredictable stress model, irradiation blocks the effects of antidepressant treatment on the maintenance of the coat condition and grooming, which deteriorate with long-term stress. Important controls were also conducted in this study: irradiation did not influence neurogenesis in the subventricular zone, demonstrating the specificity of the irradiation treatment, and irradiation did not influence the functional properties of hippocampal neurons, determined by analysis of long-term potentiation.

These data provide strong support for the hypothesis that neurogenesis is required for antidepressant responses; nonetheless, there are a few points to consider. First, it is possible that other effects of irradiation, not decreased neurogenesis, account for the blockade of the behavioral responses to antidepressants. Second, the results do not demonstrate that blockade of neurogenesis leads to a more depressive condition in these behavioral models. Although irradiation dramatically reduces neurogenesis by 90% relative to sham-treated controls, there was no significant difference in the baseline behavior in either novelty suppressed feeding or chronic unpredictable stress (Santarelli et al 2003). This is consistent with another report that decreased neurogenesis is not correlated with behavior in the learned helplessness model of depression (Vollmayr et al 2003). These results indicate that neurogenesis may not be necessary for baseline responding in these behavioral models. Alternatively, mature neurons that are already present may be sufficient to support baseline behavioral responses. To test this hypothesis, the influence of more long-term blockade of neurogenesis on behavioral responding should be tested. Irradiation produces a long-lasting blockade of neurogenesis and animals could be examined at a longer time point to test this hypothesis. It is also possible that repeated or sustained downregulation of neurogenesis could contribute to recurrent depression or more severe cognitive deficits in older depressed patients, as discussed by Henn and colleagues (Vollmayr et al 2003).

In addition to their findings on irradiation, Santarelli et al (2003) found that antidepressant regulation of neurogenesis is blocked in 5-HT_{1A} null mutant mice and that there is a corresponding blockade of the behavioral response to a 5-HT selective reuptake inhibitor in the novelty suppressed feeding paradigm. This provides additional evidence that 5-HT_{1A} receptors mediate responding to 5-HT selective antidepressants and provides additional correlative data for neurogenesis in the behavioral actions of antidepressants.

Consideration of Time Course and Other Behavioral Models

The novelty suppressed feeding and chronic unpredictable stress models were chosen because the effect of antidepressants in these models is dependent on chronic treatment (i.e., 3 weeks), consistent with the time course for the therapeutic action of antidepressants. Although novelty suppressed feeding is usually considered a model of anxiety, the requirement for long-term antidepressant treatment validates the choice of this model. This is a critical point because it is likely that the function of newborn neurons may not be manifested for several weeks after birth, when the new neurons mature and make appropriate synaptic contacts.

The rapid response time to antidepressants is a limitation of other standard models of depression, such as forced swim and learned helplessness, that is, acute (1 day) or subchronic (~5 days) antidepressant treatments are effective in these paradigms. This raises a question regarding the validity of these paradigms to model the actions of long-term antidepressant treatment required for a therapeutic response, even though these models are widely used for drug testing and behavioral studies. Consequently, the rapid response makes it difficult to test the role of neurogenesis in the behavioral actions of antidepressants in the forced swim test and learned helplessness models. One possible explanation is that newborn neurons that have already been born before testing and are in the process of maturing are influenced by acute or subchronic antidepressant treatment (i.e., the survival or function, but not proliferation, of newborn neurons is regu-

lated and could be involved in the antidepressant response). Yet another consideration is that the depression–antidepressant paradigms are better models of general stress effects seen in a number of illnesses, most notably posttraumatic stress disorder.

Testing the Hypothesis: Analysis of Neurogenesis in the Brains of Depressed Patients

The results of studies in experimental animals provides evidence that neurogenesis could contribute to the alterations in hippocampal volume identified in brain imaging studies of depressed patients; however, to test this hypothesis directly, analysis of neurogenesis and cell number in hippocampus of depressed patients, on or off antidepressant medication, are required. Analysis of postmortem tissue from depressed patients and matched control subjects can provide this type of information. Total cell counts can be obtained by stereologic counting of neurons and glia. In addition, immunohistochemical studies using antibodies against cell cycle markers or immature newborn neurons can be used as a measure of cell proliferation in postmortem tissue. This type of analysis will indicate whether neurogenesis is reduced in depressed patients and whether antidepressant treatment blocks this effect or even increases adult neurogenesis in humans. It is also possible that a ligand or marker of neurogenesis for imaging studies in living patients will eventually be developed, although the low rate of neurogenesis in human brains will require a sensitive probe with extremely low background.

Further testing of this hypothesis will be possible as new approaches are developed to manipulate neurogenesis in the adult human brain. A major focus of current research efforts in the field is to identify the neurotrophic and growth factors and signaling pathways that control adult neurogenesis (see reviews by Duman et al 2001; Gage 2000). In this rapidly advancing field, it may be possible in the near future to deliver the appropriate combination of growth factors that support or promote neurogenesis in the human hippocampus. Alternatively, it may be possible to use pharmacologic approaches that target endogenous neurotransmitter signaling systems to stimulate expression of these growth factors in the hippocampus.

Conclusions

The studies cited and discussed in this review provide support for the hypothesis that regulation of neurogenesis in the adult hippocampus contributes to the treatment, and possibly the pathophysiology, of depression. Additional studies, in both experimental animals and in humans, are required to test this hypothesis. It is possible that neurogenesis in hippocampus underlies specific symptoms of depression but that alternate adaptive mechanisms in hippocampus as well as other limbic structures (i.e., amygdala and prefrontal cortex) are also required. This may include regulation of gene transcription and expression of neurotrophic factors that influence neuronal morphology in other ways (e.g., increased length and number of neuronal processes and/or synaptogenesis; Duman et al 2000; McEwen 1999). In either case, it is likely that these studies of cell birth and neuronal morphology, as well as brain imaging studies, will continue to demonstrate that structural as well as neurochemical alterations play a significant role in mood disorders.

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