Depression

The Brain Finally Gets Into the Act

Barry L. Jacobs

Princeton University

ABSTRACT—*The theory of clinical depression presented here integrates etiological factors, changes in specific structural and cellular substrates, ensuing symptomatology, and treatment and prevention. According to this theory, important etiological factors, such as stress, can suppress the production of new neurons in the adult human brain, thereby precipitating or maintaining a depressive episode. Most current treatments for depression are known to elevate brain serotonin neurotransmission, and such increases in serotonin have been shown to significantly augment the ongoing rate of neurogenesis, providing the neural substrate for new cognitions to be formed, and thereby facilitating recovery from the depressive episode. This theory also points to treatments that augment neurogenesis as new therapeutic opportunities.*

KEYWORDS—*serotonin; adult brain neurogenesis; stress; clinical depression*

When the history of mental illness is written, the 20th century will be remembered primarily not for its biomedical advances, but as the period when depression (along with the other major psychopathologies) was finally considered to be a disease and not a failure of character or a weakness of will. In part, this change is attributable to putting to rest, at least in the scientific community, the dogma of Cartesian duality of mind and body. Given that the mind is the manifestation of the brain, depression could be considered to be a somatic disorder, along with pathologies of the heart, kidney, and other organs.

HISTORICAL CONTEXT

This new perspective laid open the problem of depression to assault by investigators utilizing the modern biomedical armamentarium. Because of recent scientific advances at both the basic research and the clinical levels, it is the 21st century that will be remembered as the time when the major mental illnesses were finally understood at a deep, basic biological level, and when their treatments, and even prevention, were finally at hand.[1]

In the early years of modern biological psychiatry and psychology (1950s–1970s), neurobiological theories of depression focused on changes in patients such as elevated plasma levels of cortisol and corticosterone (hormones released from the upper portion of the adrenal gland), alterations in neurotransmitter-breakdown products found in the urine or cerebrospinal fluid, or lowered levels of neurotransmitters measured in plasma. In most of these cases, there was a heavy reliance on measures outside the central nervous system because of the general inaccessibility of brain measures. Thus, the search for the neural basis or pathophysiology of depression, in terms of either neurochemical or neuroanatomical-structural changes, came up largely empty.

More recently proposed neurobiological theories of depression attempt to directly relate precipitating events to changes in the brain, to classic symptomatology, and to coherent treatment strategies and even prevention. Such theories are especially attractive because they attempt to deal with the totality of the disease in a consistent and integrated manner. These theories go beyond simply pointing to "dysfunction in the left hemisphere" or "hypoactivity in the frontal lobes" and attempt to elucidate the neural and molecular mechanism underlying depression (Duman, Heninger, & Nestler, 1997; Jacobs, van Praag, & Gage, 2000; Manji, Drevets, & Charney, 2001). My colleagues and I have proposed one such theory, which focuses on the importance of neural changes in the brain for both the onset of and the recovery from depression (Jacobs et al., 2000).

NEUROPLASTICITY

One of the great conceptual leaps of modern neuroscience has been the notion of neuroplasticity. This is the idea that the adult brain can physically or morphologically change, not only in response to powerful toxins or trauma, but also in response to even subtle treatments or conditions. No less an intellect than the great Spanish neuroanatomist and Nobelist Ramon y Cajal believed that the morphology of the adult brain was essentially fixed. Scientists now know that even modest changes in the internal or external world can lead to structural changes in the brain. In fact, it is fair to say that the watchword for neuroscience in the past 20 to 30 years has become "plasticity."

Research in neuroplasticity has now shown that not only can neuronal morphology be altered, but also the actual number of neurons in the brain is not fixed. In the field of neurogenesis (the birth of new neurons), the work of Altman stands out as seminal. Altman was

[1]The importance of other aspects of psychiatric research in the past 50 years cannot be denied. This is the period in which psychopharmacology came into its own. In what many people consider a revolution, drugs were developed for the effective treatment of depression, bipolar illness, and schizophrenia.

Address correspondence to Barry L. Jacobs, Program in Neuroscience, Department of Psychology, Princeton University, Green Hall, Princeton, NJ 08544; e-mail: barryj@princeton.edu.

truly a scientist before his time (Altman & Das, 1965). In the early 1960s, he reported that two regions of the mammalian brain (most of his work was in rats), the olfactory bulb and the granule cell layer of dentate gyrus (DG; part of the hippocampal formation, which is a critical structure in the laying down of new cognitions), continue to generate new neurons in adulthood. In the context of the prevailing dogma of the immutability of the adult brain, this claim was heretical. And thus, not surprisingly, Altman's work was largely ignored and forgotten. It required more than 20 years for this topic to be reopened and reinvigorated. In the 1980s, Nottebohm reported that the overall size of certain regions of the bird brain, and the number of neurons in those areas, changed seasonally. Moreover, the increase in the number of brain cells appeared to coincide with the learning of new songs (Nottebohm, 1985). More than 10 years later, research groups led by Gould and Gage extended the concept of DG neurogenesis from birds and small mammals to monkeys, and eventually to humans (Erikssen et al., 1998; Gould, Cameron, Daniels, Wooley, & McEwen, 1994).

ADULT BRAIN NEUROGENESIS

Most neurons in the mammalian brain and spinal cord are generated during the pre- and perinatal periods of development. However, at least in the olfactory bulb, DG, and possibly some portions of the cerebral cortex areas, neurons continue to be born throughout life. These new neurons are derived primarily from progenitor cells that reside in the brain's subventricular zone, which lines the ventricles (fluid reservoirs of the brain), or in a layer of the hippocampal formation called the subgranular zone (lying immediately below the granule cell layer of the DG). Through a process that is as yet not well understood, a signal induces progenitor cells to enter the cell cycle and undergo mitosis (cell division). The entire process involves not only proliferation, but also migration and differentiation of brain cells. For the sake of economy, I use the terms proliferation and neurogenesis interchangeably because most new cells generated in the DG differentiate into neurons.

Our work in this field has focused on neurogenesis in the DG for several reasons: Neurogenesis occurs primarily in this structure, most studies of brain neurogenesis have been conducted on this region, this structure is known to play a critical role in brain information processing, and clinical evidence points to significant changes in the hippocampus in depression (as I discuss later). It is also well known that the hippocampus is linked to other brain structures, such as the amygdala, that play a more direct or central role in mood (affect).

STRESS

One of the cardinal features of depression is its recurrent nature. Some patients experience regular or periodic recurrence, whereas in other patients recurrence is aperiodic. It is tempting to speculate that such variation in mood might be attributable to the waning and waxing of some neural process in the brain.

In laboratory studies, the level of neurogenesis is quantified by treating animals with radioactive thymidine or bromodeoxyuridine (BrdU). These compounds are incorporated into the DNA of cells going through mitosis. Once these cells complete this process, their thymidine- or BrdU-labeled daughter cells in the brain can be identified and counted post mortem. A number of factors are known to positively and negatively influence neurogenesis in the DG. Stressors are the best known and most widely studied group of variables that strongly suppress DG neurogenesis. And almost always, this effect is attributable, in large part, to the release of hormones from the adrenal gland as part of the organism's general stress response. This fact was critical for our thinking, because stress and its related release of adrenal hormones are generally considered to be major etiological factors in clinical depression (Kendler, Karkowski, & Prescott, 1999).

SEROTONIN

The brain chemical most strongly associated with depression is serotonin (5-hydroxytryptamine). With the exception of psychotherapy, all effective treatments for depression are known to be directly or indirectly dependent on increasing brain serotonin. The best known of these are the eponymous SSRIs (serotonin-specific reuptake inhibitors), such as Paxil and Prozac. (These drugs act by preventing the serotonin that is released in the brain from being inactivated by being taken up by the brain cells that originally released it.) Thus, several years ago, we began to examine the effects of serotonin on cell proliferation in the DG of adult rats.

In our initial study, we found that the systemic administration of fenfluramine (which releases serotonin throughout the central nervous system) produced a powerful proliferative effect in the DG. We also found that this effect was completely prevented by prior administration of a drug that blocked serotonin's action at a specific site (5-HT_{1A} receptor; Radley & Jacobs, 2002). Such drugs also significantly reduced spontaneous, or basal, levels of brain-cell production, suggesting that serotonin plays a role in DG cell proliferation under normal, or naturalistic, conditions. This line of work has been confirmed and extended by Daszuta and her colleagues (Brezun & Daszuta, 1999).

Next, we conducted an experiment that has the most direct relevance to the present theme. Systemic administration of the antidepressant drug fluoxetine (which is also known by the brand name Prozac) for 3 weeks produced a 70% increase in DG cell proliferation above that of control animals (Jacobs & Fornal, 1999). Two recent studies have confirmed and extended our results (Malberg, Eisch, Nestler, & Duman, 2000; Manev, Uz, Smalheiser, & Manev, 2001). They demonstrated that short-term administration of antidepressant drugs did not augment proliferation, an important finding because these drugs show clinical efficacy only after 4 to 6 weeks of daily administration. Electroconvulsive shocks (a powerful antidepressant treatment) given to rats also result in increased proliferation (Madsen et al., 2000).

The theory that follows from these experimental results is simple. Chronic, unremitting stress (a major etiological factor in depression) suppresses brain neurogenesis either by acting on adrenal hormones or by suppressing serotonin neurotransmission. This suppression of neurogenesis occurs most prominently in the hippocampus, but other brain areas may also be involved, either directly or indirectly. Recovery occurs, at least in part, when serotonin neurotransmission is increased, especially if the 5-HT_{1A} receptor is activated, by any of a variety of methods (possibly including psychotherapy). Increased serotonin neurotransmission stimulates cell proliferation, and these recently born neurons provide the substrate for new cognitions to be formed.

This theory provides a ready explanation for the perplexing fact that antidepressant treatments typically require weeks to become effective.

It is known that it takes several weeks for newly generated cells in the DG to fully mature and become integrated into the existing brain circuitry.

THE HIPPOCAMPUS

If this theory is valid, the hippocampus should show a special relationship to depression. A number of different pieces of evidence link clinical depression to changes in the hippocampus (Jacobs et al., 2000). However, this is not to suggest that change in the hippocampus is the only change in the brain associated with depression, nor do we suggest that alterations in the hippocampus underlie all of the observable aspects of depression.

Further clinical evidence supports an important role for the hippocampus in depression.

- The brains of depressed patients have smaller hippocampi than the brains of control subjects.
- Patients with Cushing's Syndrome (elevated levels of adrenal hormones in plasma) have a high incidence of depression. Additionally, patients administered such hormones for other medical reasons frequently become depressed.
- Temporal lobe epilepsy, which involves massive cell loss in and around the hippocampus, is often accompanied by depression.

DISCUSSION AND FUTURE DIRECTIONS

This work is firmly based on research in the burgeoning field of neurogenesis, which is a facet of stem-cell research, a topic that recently has become highly publicized and politicized. This area holds promise for treating human disease because it suggests that dead or damaged brain cells can be replaced with new, healthy neurons. Probably the most obvious candidate for this type of intervention is Parkinson's disease, in which the primary deficit is the loss of a particular type of brain cell (dopamine neurons) in a specific brain area (substantia nigra).

What would be a true test of the present theory? The first issue would be to determine whether DG neurogenesis wanes when patients go into depressive episodes and waxes as they emerge from these episodes (either spontaneously or following some type of therapy). Investigating this issue would require the development of new brain-imaging techniques, with greater resolution and specificity for particular cell types than is currently possible. Even if a relation between DG neurogenesis and waxing and waning of depression is confirmed in clinical studies, and I believe it will be, these data would be only correlative. In order to determine if there is a causal relationship between alterations of DG neurogenesis and depression, there would be a need to experimentally manipulate cell proliferation. Would the efficacy of antidepressant therapies be blunted by drugs that suppress neurogenesis? There would be obvious ethical concerns associated with such studies.

Perhaps researchers will find new drugs that more directly target augmentation of neurogenesis, and their potency as antidepressants could be evaluated. Also, nonpharmacological therapies that are known to affect neurogenesis, such as exercise, could be more fully evaluated for their antidepressant efficacy. Does the birth and death of brain cells lie at the heart of all types of clinical depression, regardless of etiology? If cell loss is critical, is it always mediated by increased release of adrenal hormones? If not, what other neurochemicals could mediate these deleterious effects and thus also become candidates for novel pharmacotherapies?

How important to depression are changes in neurogenesis in brain regions other than the hippocampus? The hippocampus is thought to be more involved in cognition than in affect or mood. However, a major difficulty that may be at the heart of depression is the patients' inability to form new cognitions about their condition and the future, and their resulting tendency to remain mired in a depressed state. Also, as mentioned earlier, the hippocampus has important connections to brain structures directly involved in mood (affect). Finally, there is no reason to restrict the present theory exclusively to the hippocampus, because neurogenesis may be a more general phenomenon in the brain.

In sum, this theory is representative of a new generation of approaches to understanding psychopathology from a specific neural perspective. Etiological factors lead to identifiable neural changes in particular brain structures, which in turn produce distinct symptomatology. This perspective suggests that therapies targeted at reversing these neural dysfunctions will be effective in treating mental illness.

Recommended Reading

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