COMMENTARY

Is Impaired Neurogenesis Relevant to the Affective Symptoms of Depression?

Readers of this journal are likely to agree with three statements. First, it is impossible to think effectively about depression outside the context of biology. Second, it is impossible to think effectively about depression as only being a matter of biology (see Caspi et al 2003 for a brilliant demonstration of this). Finally, despite the vast quantities of excellent research on which those two conclusions rest, we remain woefully inadequate at effectively treating depression in vast numbers of its sufferers.

Because of this, a new, exciting hypothesis that promises to transform how we think about the causes and treatment of depression is obviously welcome. The notion that depression can arise from impaired hippocampal neurogenesis and that an array of antidepressants ultimately work by stimulating such neurogenesis is one such exciting hypothesis (with both parts of that idea henceforth collectively referred to as the "neurogenesis" hypothesis).

Does the bulk of evidence support or go against this hypothesis? As seen in the two preceding reviews by leaders in this field, the answer to this question is not at all clear, because the relevant literature is sparse and subject to some markedly differing interpretations. Thus, it seems useful to summarize what is known at this point, what are the key assumptions and criticisms surrounding the interpretations of each set of findings, and what new experiments are most needed. I begin with three of the more peripheral or distal questions that arise from this hypothesis.

Does the Time Course of Neurogenesis Help to Explain the Time-Course Paradox of Antidepressant Action?

The seemingly clear mechanisms of action of selective serotonin reuptake inhibitors (SSRIs), tricyclics, and monoamine oxidase (MAO) inhibitors are greatly complicated by the fact that although the drugs have relatively rapid effects upon monoamine signaling, the latency until they are clinically efficacious is far longer. This has prompted models focusing on the more prolonged consequences of their direct monoamine effects (e.g., receptor downregulation and interactions with presynaptic autoreceptors).

Although these models are perfectly plausible, they are complex and rely on many assumptions. Thus, the possibility that these antidepressants are effective, instead, by stimulating neurogenesis, immediately begs the question of whether the time course of such neurogenesis fits with the delayed time course of clinical efficacy.

At present, an array of studies suggests this to be the case (although these studies have not always demonstrated that these new neurons have formed functional synapses during that time). Were this not so, this would be strong evidence against the neurogenesis hypothesis of depression. Instead, the clear and well-replicated finding that the time course does fit constitutes indirect, correlative support.

Does the Idea That Impaired Hippocampal Neurogenesis Gives Rise to the Affective Symptoms of Depression "Make Sense"?

Major depression is often accompanied by problems with declarative learning and memory (Austin et al 2001), a province of the hippocampus, and virtually all participants in this debate agree that impaired hippocampal neurogenesis during depression could help explain the cognitive deficits of the disease. This consensus would be somewhat controversial in some quarters. This is because the adult neurogenesis field is wrestling with the issues of whether new hippocampal neurons actually function and, if so, what those functions are; whether new neurons support even the "traditional" hippocampal roles in declarative memory is a highly contentious topic (Rakic 2002; Shors et al 2001). But the neurogenesis hypothesis is more expansive, in that is posits that hippocampal neurogenesis is also relevant to the defining *affective* symptoms of the disease. How plausible is this?

Advocates of this position have constructed some scenarios built around 1) the fact that the hippocampus communicates with many of the neuroanatomical "hot spots" of depression (the prefrontal and cingulated cortices and the amygdala); and 2) a sequence that can be summarized as follows: declarative memory deficits make it more difficult to accurately perceive cause and effect; such inaccuracies make it difficult to detect control and agency; this increases the likelihood of a globalized sense of helplessness, which is the cognitive foundation of depression.

There will obviously be considerable differences as to how much of a stretch this seems to those assessing the hypothesis. Is there a pattern as to who finds this plausible? There is the frequent phenomenon that neuroscientists who study brain region X tend toward the view that region X is the center of the neurobiological universe; however, in this case, in surveying opinions regarding this matter, I think I detect the opposite pattern, namely that the more expertise someone has about the hippocampus and its role in cognition, the less plausible they find this novel role for the hippocampus; I believe I fall into this camp. At present, teleology does not strike me as providing particularly strong support for the hypothesis.

Do Stress and/or Glucocorticoids Inhibit Adult Neurogenesis in the Hippocampus? What Are the Morphometric Consequences of This?

In many ways, the biology and psychology of depression intersect with stress (to briefly summarize: major stressors precede many depressions; pathologic or pharmacologic excesses of glucocorticoids can cause depression; approximately half of depressives have some version of glucocorticoid excess; glucocorticoids and stress have many neurochemical and neuroanatomical effects that are commensurate with the biology of depression; and antiglucocorticoids can act as antidepressants [reviewed at length in Sapolsky 2000; Wolkowitz et al 1999]). Thus, a key issue is whether stress and/or glucocorticoids inhibit neurogenesis.

This is one of the best-replicated findings in the field. Stress and glucocorticoids are among the strongest, if not the strongest, inhibitors of hippocampal neurogenesis; both parties in the preceding debate are in agreement about this. Were this not to be the case, this would weigh strongly against the neurogenesis hypothesis. Instead, the solid evidence of such inhibition constitutes indirect, correlative support for the hypothesis. As pointed out by the authors, it is critical that the difficult studies be carried out to determine whether human depression is associated with decreased rates of neurogenesis.

This segues to a related issue, namely whether stress- or

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glucocorticoid-induced inhibition of neurogenesis can ever be of sufficient magnitude to cause an overall decrease in hippocampal volume. This question is prompted by the now well-replicated finding that prolonged major depression can be associated with a selective loss of hippocampal volume (reviewed in Sapolsky 2000). This finding is weakened somewhat by the fact that it has not yet been shown that volume loss only occurs in hypercortisolemic depressives (amid indirect evidence for this [Sheline et al 1996]). Nonetheless, such volume loss is commensurate with a huge preclinical literature showing how stress and glucocorticoids can preferentially damage the hippocampus. A number of investigators in the adult neurogenesis field have generated estimates regarding the rate of neurogenesis, suggesting that a substantial percentage of the dentate gyrus (the site of hippocampal neurogenesis in the adult) might be replaced with new neurons over the course of the lifetime (Gould and Gross 2002). The following should be considered, however: 1) these are thought to be fairly soft estimates by many in the field (Rakic 2002); 2) it is not yet known whether the hippocampal volume loss in human depression is preferentially centered in the dentate (which would support the neurogenesis hypothesis); 3) it is not known whether the volume loss involves a paucity of neurons (which would also support the neurogenesis hypothesis) or an atrophy of neuronal processes (which can be a consequence of stress or glucocorticoid exposure); and 4) if there is indeed a depletion of neurons, it is not known whether it is due to the failure of new neurons to be born (supporting the neurogenesis hypothesis) or due to the death of preexisting neurons (for which there is some precedent).

Thus, although it is well established that stress and glucocorticoids inhibit hippocampal neurogenesis in nonhuman species, it is not yet known whether the same occurs in human depression or whether any such inhibition could give rise to the hippocampal volume loss in many cases of depression. It should be noted, however, that the hypothesis does not require that neurogenesis be relevant to total hippocampal volume, just that it be relevant to the affective symptoms of depression.

To summarize this section, the ability of stress to inhibit neurogenesis and the time course of antidepressant-induced neurogenesis offer indirect support for the hypothesis, although the notion of hippocampal neurogenesis being relevant to the affective symptoms of depression seems like a stretch to many. We now turn to what strike me as more central, proximal questions related to the neurogenesis hypothesis. As can be seen, studies addressing these questions have generated some very clear data with some very conflicting interpretations. The first question is a dual one and is related to the first half of the neurogenesis hypothesis (i.e., the role of impaired neurogenesis in the emergence of depression).

Can Depression Occur Without Impaired Hippocampal Neurogenesis? Can Impaired Hippocampal Neurogenesis Occur Without Depression?

In considering the first question, Henn, Vollmayr, and colleagues showed that bromodeoxyuridine labeling in the hippocampus did not differ between rats who were learned helpless and those who were resistant to such helplessness (Vollmayr et al 2003).

Data regarding the second issue has come from Duman, Henn, and Vollmayr and, pleasingly, there seems to be consensus on this issue. In three studies, hippocampal neurogenesis was decreased substantially (40%–90%) and, importantly, by three different means (restraint stress, an active avoidance task, and selective irradiation of the hippocampus). In all three studies, this did not produce "depression" in the models used (Malberg and Duman 2003; Santarelli et al 2003; Vollmayr et al 2003). In the case of the irradiation study, Duman (one of the co-authors) suggests that a longer duration of impaired neurogenesis is needed to produce depression.

As is obligatory in this business, one must immediately question whether the behavioral consequences of stress in a rodent can ever be synonymous with human depression and whether the tests used are appropriate for assessing such putative rodent "depression." Two of the studies used variants on the learned helplessness tests that are arguably the gold standard for rodent models of depression, whereas one used a rather different test (which will be discussed below).

Amid the differing tests and the questions that can be raised about them, the consensus in the findings is impressive. At this point, it seems as if an acute impairment of neurogenesis is neither necessary nor sufficient to generate rodent models of depression.

We now turn to two critical questions related to the second half of the neurogenesis hypothesis, namely whether antidepressants are effective only insofar as they stimulate neurogenesis.

Do All Antidepressant Drugs or Therapies Stimulate Hippocampal Neurogenesis?

It is clear that the neurogenesis hypothesis would be gravely weakened if it turned out that some effective antidepressant therapy failed to stimulate adult neurogenesis. At present, there have been an impressive number of studies showing such stimulation in preclinical models. Antidepressant drugs that have this effect include SSRIs, tricyclics, MAO inhibitors, and tianeptine (the final drug is controversial, insofar as it is in use in Europe but not in the United States and because its mechanism of action seems to be virtually opposite to that of SSRIs). Moreover, neurogenesis is stimulated by lithium (which, despite the uneducated assumption of this nonpsychiatrist that it only works against the manic phase of bipolar disorder, can stabilize depression and potentiate the effects of other antidepressants [Bauer et al 2003; Fawcett 2003]) and by electroconvulsive therapy.

Thus, an impressively large and varied array of antidepressants has been shown to stimulate neurogenesis in clear and replicated studies; however, the hypothesis requires that there be no exceptions to this pattern, and a potentially key exception comes with two reports (in rats and monkeys) that transcranial magnetic stimulation (TMS) fails to stimulate hippocampal neurogenesis (though still having salutary effects commensurate with antidepressant action).

This should seem a fatal blow for the neurogenesis hypothesis, particularly given the demonstration in two species, including one phylogenetically close to humans (Czeh et al 2001; Scalia et al, unpublished data). The responses to this by advocates of the hypothesis are twofold: first, TMS is one of the newest of mainstream antidepressant therapies and thus is not enthusiastically accepted in many circles (i.e., many have argued that it is not sufficiently effective). Second, TMS is typically applied to the frontal cortex in humans, and even if it is a highly effective therapy, it is intrinsically problematic to study TMS in rats, because rats have little frontal cortex; countering this, of course, is the study using Old World primates, who are considerably more frontally well-endowed (Scalia et al, unpublished data).

Amid the impressive array of antidepressants that stimulate neurogenesis, TMS could represent a fatal blow to the hypothesis. It does not yet, and intensive research regarding TMS and neurogenesis is needed, dovetailing on the broader body of research needed regarding the antidepressant efficacy of TMS.

If You Block the Ability of an Antidepressant to Stimulate Neurogenesis, Is It No Longer Capable of Relieving Depressive Symptoms?

A demonstration that antidepressant efficacy requires enhanced neurogenesis would be the strongest possible support for the hypothesis, and such support seemingly comes with the well-publicized *Science* article discussed at length in both the preceding reviews (Santarelli et al 2003). To reiterate, the authors established a rodent model of depression, one whose behavioral symptoms were relieved by antidepressant treatment. The authors then inhibited hippocampal neurogenesis with localized irradiation of the structure and showed that the antidepressants were no longer effective at correcting the rodent depression. This was a well-controlled study, in that the authors showed 1) that the irradiation did not alter neurogenesis in the subventricular zone (the other brain region in which adult neurogenesis occurs); 2) irradiation of other parts of the brain did not alter hippocampal neurogenesis or block antidepressant efficacy; and 3) that a number of standard electrophysiologic measures of hippocampal function were unchanged by the irradiation.

This seems like immensely strong, even irrefutable support for the neurogenesis hypothesis. Naturally, criticisms have been voiced. They have taken two forms. First, demonstrating that electrophysiologic parameters were spared by the irradiation is important but is insufficient to conclude that a change in neurogenesis rates is the only thing changed by the irradiation regime. A priori, it has struck many that it would be surprising if the effects of irradiation were so focal. The second concern, voiced by many in the field, is that the test purported by the investigators to be one of depression was, in fact, a test of anxiety (the willingness of a hungry rodent to overcome its aversion to bright light and enter a brightly lit room for food). This concern was raised by Henn and Vollmayr and seems quite legitimate. Addressing this issue, Duman offers something that is a bit of a tautology, namely that a behavior in a rodent qualifies as a depression if it is normalized by antidepressants. The wide range of clinical uses of SSRIs seems to counter this argument.

Thus, this difficult study has generated some of the strongest support for the neurogenesis hypothesis; however, it seems clear that more support in this realm is needed along the lines of 1) replication; 2) use of more traditional rodent tests of depression; 3) testing with a broader range of antidepressant drugs and treatments; and 4) broader documentation of what is preserved in the hippocampi of these animals, despite the radiation.

Conclusions

As stated, the neurogenesis hypothesis has two components. The first is that impaired neurogenesis plays a role in causing depression. Although there is only a small relevant body of literature examining the issue at this point, it seems fairly clear that this is not tenable. Insofar as rodents can be valid subjects in modeling depression, decreased neurogenesis and depression can be dissociated.

The second component of the hypothesis is that antidepressants work by normalizing the (putative) neurogenesis defect. Here the evidence is markedly conflicting. The demonstration in two reports that TMS does not stimulate neurogenesis should put that part of the hypothesis to rest; however, as seen, some question whether TMS is enough of an antidepressant therapy to merit such veto power. Conversely, the demonstration that selective hippocampal irradiation blocks antidepressant efficacy should establish that part of the hypothesis on very strong footing; however, as seen, numerous caveats have been raised regarding that single study.

It is obligatory at this point to say that more research is needed, and that is indeed the case. The relevance of various animal models to human depression must be tested further. The arduous studies must be carried out examining the cellular basis of the hippocampal volume loss in human depressives. And further tests of this hypothesis must tackle the separate components of the neurogenesis phenomenon, namely the birth, differentiation and survival of new cells.

If the neurogenesis hypothesis withers for lack of any further supporting evidence, it will still have served a useful role. This is because of the status of adult neurogenesis as, arguably, the hottest topic in neuroscience. As a result of the spotlight being cast on neurogenesis, some light of attention will also be shone on the desperate need to develop new classes of antidepressants.

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Austin M, Mitchell P, Goodwin G (2001): Cognitive deficits in depression. *Br J Psychiatry* 178:200–211.

Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfmer S (2003): Lithium augmentation therapy in refractory depression— update 2002. *Eur Arch Psychiatry Clin Neurosci* 253:132–139.

Caspi A, Sugden K, Moffitt T, Taylor A, Craig I, Harrington H, et al (2003): Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science* 301:386–390.

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, et al (2001): Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci U S A* 98:12796–12801.

Fawcett J (2003): Lithium combinations in acute and maintenance treatment of unipolar and bipolar depression. *J Clin Psychiatry* 64:32–37.

Gould E, Gross C (2002): Neurogenesis in adult mammals: Some progress and problems. *J Neurosci* 22:619–623.

Malberg J, Duman R (2003): Cell proliferation in adult hippocampus is decreased by inescapable stress: Reversal by fluoxetine treatment. *Neuropsychopharm* 28:1562–1571.

Rakic P (2002): Neurogenesis in adult primate neocortex: An evaluation of the evidence. *Nat Rev Neurosci* 3:65–71.

Santarelli L, Saxe M, Gross C, Surget A, Basttaglia F, Dulawa S, et al (2003): Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301:805–809.

Sapolsky R (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 57:925–934.

Sheline Y, Wany P, Gado M, Csernansky J, Vannier M (1996): Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci U S A* 93:3908–3913.

Shors T, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001): Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410:372–376.

Vollmayr B, Simonis C, Weber S, Gass P, Henn F (2003): Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. *Biol Psychiatry* 54:1035–1040.

Wolkowitz O, Reus V, Chan T, Manfredi F, Raum W, Johnson R, Canick J (1999): Antiglucocorticoid treatment of depression: Double-blind ketoconazole. *Biol Psychiatry* 45:1070–1076.