

## Major Depression: Causes or Effects?

**T**his issue contains four articles that address a number of key aspects of the causes and effects of major depression. Three suggest that what we have often thought were effects may actually be causes of depression. As a whole, the articles point to a number of important questions that are worthy of further research.

Over the past few years, two major brain areas have been implicated in major depression—the prefrontal cortex/anterior cingulate and the hippocampus. The articles in this issue by Frodl et al. and by Lockwood et al. each point to abnormalities involving one of these areas. Lockwood et al. report on significant neuropsychological impairment in depressed patients, based on comparisons with healthy subjects. Elderly subjects demonstrated impairment in performance of tasks of executive function (suggestive of prefrontal/anterior cingulate dysfunction), and particular impairment was seen in elderly depressed subjects. These findings support a number of other observations involving the prefrontal region in depression (1, 2). Taken together, these data at first glance point to a major consequence or correlate of depression, namely marked cognitive dysfunction involving the prefrontal cortex/anterior cingulate, but also suggest that a performance decrement in the elderly involving this region could be a risk factor for becoming severely depressed.

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*“A smaller hippocampus could still reflect both a cause and an effect of major depression.”*

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Frodl et al. explored hippocampal volume in patients with first-episode major depression. Sheline et al. (3) and Bremner et al. (4) reported smaller hippocampal volumes in depressed patients than in healthy subjects. Further, Sheline et al. (3) reported that a smaller hippocampus was associated with greater lifetime duration of depression and suggested that excessive glucocorticoid activity could be a factor in this seeming atrophy. These findings extend Sapolsky's work with rats (5). The article by Frodl et al. raises serious questions regarding the significance and causes of smaller hippocampal volume. Indeed, the fact that the study involved first-episode patients suggests that a smaller hippocampus, particularly in men, is a risk factor for, rather than a consequence of, major depression.

These data fit nicely with findings from three other recent studies that all point to strong genetic influences on hippocampal volume. My colleagues and I (6) used a model involving paternal half-siblings among squirrel monkeys to explore the relative contributions of early life stress and genetics to hippocampal size in young adulthood. Paternal genetics—but not early stress—appeared to account for much of the variance in hippocampal size. Specific fathers appeared to sire offspring who had smaller hippocampi. These animals also demonstrated greater cortisol responses at the time of weaning, suggesting a risk factor for depression.

Two other studies of human twins by Sullivan et al. (7) and R.K. Pitman et al. (2001 personal communication and presentation at the 2001 annual meeting of the American College of Neuropsychopharmacology) have demonstrated rather convincingly that hippocampal size is largely genetically determined, although in the study by Sullivan et al. environment appeared to play a role in hippocampal size as well. In the study by Pitman et al., a smaller hippocampus appeared to be a risk factor for developing posttraumatic stress disorder.

Still, prospective longitudinal studies are needed to determine whether depression and other psychiatric disorders can result in a further diminution in hippocampal volume. Thus, a smaller hippocampus could still reflect both a cause and an effect of major depression.

The articles by Frodl et al. and Lockwood et al. emphasize two different regions, and little attention is paid in each article to the other region. It is, however, probable that both regions are involved and that activity in both of them and the connections between them helps explain both the somatic and cognitive symptoms of the disorder.

One possible common thread affecting both regions is excessive glucocorticoid activity. Administration of cortisol to healthy subjects results in dysfunction in both regions (8, 9). Frodl et al. note that although in rats high cortisol levels can relatively rapidly reduce hippocampal size, excessive glucocorticoids probably do not explain their hippocampal findings in the first-episode patients. On the basis of the time period involved, this seems sensible. However, they also cite the work of Sanchez et al. (10) in which type II glucocorticoid receptors were not appreciably found in the hippocampus of the rhesus monkey, although they were found heavily in the prefrontal cortex, as another reason for not invoking glucocorticoids. A human glucocorticoid receptor probe was used in that study. In contrast, Patel et al. (11), using specific probes for glucocorticoid receptors in the squirrel monkey, found glucocorticoid receptors in the hippocampus as well as in the frontal cortex. Thus, glucocorticoids could play a key role in the findings of both studies. A smaller hippocampus could be associated with higher glucocorticoid levels during stressful times, which could lead to cognitive dysfunction associated with effects in the prefrontal cortex/anterior cingulate and the hippocampus. In turn, excessive glucocorticoids could result in "atrophy" of specific brain regions. This area is worthy of further investigation and will require longitudinal study.

My colleagues and I have been studying prefrontal cortex/anterior cingulate and hippocampal function or activity in psychotic major depression, a subtype characterized by excessive activity of the hypothalamic-pituitary-adrenal axis. We have reported (12) that patients with psychotic major depression demonstrate impaired performance on both the color-word portion of the Stroop Color-Word Test and the Paragraph Recall Test (verbal memory). These data suggest impairment in both regions of interest; however, the deficit in performance on the Paragraph Recall Test was not in retention, suggesting that attention, response inhibition, and encoding could account for a large part of the deficit. In another study (13), we reported that patients with psychotic major depression demonstrated errors of commission but not omission on a word-list test, in line with problems of focus and encoding rather than in memory/recall per se. We are currently employing functional magnetic resonance imaging to tease apart these functions and brain regions and are using a specific antagonist for the low-affinity type II glucocorticoid receptor to assess whether blocking cortisol improves performance.

The article by Takeshita et al. is another seeming "effect" article and follows several recent articles pointing to an association between depression and a higher rate of mortality. The data are chilling: Takeshita et al. report that depressive symptoms are associated with a high mortality rate in otherwise healthy elderly subjects. The findings suggest that some aspect of the biology of depression is associated with early mortality. But what is this factor? This article does not provide an explanation, and further research is required to ferret out the cause for early mortality. Alterations in blood clotting and a high risk for arrhythmias are possible culprits that could lead to untoward consequences. They would, however, open the way for innovative interventions. For example, if depression is associated with high levels of circulating catecholamines and with arrhythmias, specific treatments could be aimed at preventing early mortality. It may be premature, however, to conclude that depression specifically leads to early mortality. Conceivably, a biological process might be at play that involves a number of somatic symptoms, some of which are depressive in nature, or there could be a biological process, such as a subtle cardiovascular dysfunction, that produces a depressive-like cast.

The study by Kendler et al. tested a hypothesis put forth previously by this group (14) on the multifactorial causes of depression. Using a twin cohort, they elegantly dissected out the roles of early experiences (e.g., childhood abuse), genetics, substance abuse,

etc., on early and later episodes of depression. The factors studied are those that we clinicians commonly see when treating depressed patients. This elegant pathway analysis might be strengthened if we had better candidate genes to add to the schematic, as well as baseline hippocampal volumes. Biology could play major roles in the seemingly psychosocial factors.

Taken together, these articles point to a number of possible causative factors as well as untoward consequences or correlates of major depression. Use of cross-sectional techniques can easily obfuscate what are truly causes and effects. Still, such research gives us important clues, and longitudinal studies can ultimately give us a better sense of the causes and effects of a troubling disorder in modern society.

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