

## Brain Imaging in Affective Disorders: More Questions About Causes Versus Effects

**B**rain imaging is a powerful tool to explore various aspects of brain function or structure in psychiatric patients. In this issue, two interesting articles report on imaging results in patients with major depression or bipolar disorder. They add to an expanding literature on the nature of underlying functional abnormalities or structural effects of major psychiatric disorders.

Positron emission tomography (PET) was employed in the article by Liotti et al. This technique commonly utilizes radioactive [ $^{15}\text{O}$ ]H $_2$ O to explore rapid changes in cerebral blood flow or  $^{18}\text{F}$ -deoxyglucose to measure glucose metabolism, both of which reflect general levels of activity. The technique can also utilize radioligands to explore receptors or effects of specific pharmacological agents.

In the Liotti et al. study, [ $^{15}\text{O}$ ]H $_2$ O PET was employed to explore cerebral blood flow as a window on functional area activity in response to transiently recalling sad autobiographical events in 10 subjects with remitted major depression (nine were receiving maintenance antidepressant medication), seven subjects experiencing an acute major depressive episode (all but one were medication free), and eight healthy comparison subjects. All subjects were female.

Both depressed patient groups demonstrated increases in activity in the lateral inferior frontal cortex and dorsal anterior cingulate and deactivation in the medial orbitofrontal cortex, anterior thalamus, and occipital cortex. In contrast, healthy comparison subjects did not demonstrate these changes but had activation of the ventral subgenual anterior cingulate and the left parahippocampal gyrus in addition to deactivation of right dorsolateral prefrontal cortex. Several regional cerebral blood flow (rCBF) changes were seen across all groups (e.g., increases in insular cortex, cerebellar vermis, and motor cortex), suggesting a possible common circuit for sadness induction (1).

This study points to altered activation of specific brain regions in depressed patients experiencing sadness and to possible altered regional brain activity as a trait marker for depression. Several of these regions with altered activity with transient sadness, including those with commonalities and dissociations between groups, have been implicated in studies of depressed patients relative to healthy comparison subjects. What is so important here is that the pattern is evident in these subjects with major depressive disorder even when their illness is in remission. These findings add to an ever-expanding database in which the prefrontal cortex and anterior cingulate merit particular attention in our efforts to understand why some individuals are vulnerable to the disorder.

In the July issue of the *Journal*, Lockwood and colleagues (2) presented interesting data on the effects of aging on the prefrontal cortex, with a particular effect seen in elderly depressive subjects. Mayberg et al. (3) and Drevets et al. (4) have previously reported on several occasions structural and functional alterations in prefrontal subgenual regions, and further confirming data have come from Ongur et al. (5), who used neuropathological techniques. Yet, we still do not know for sure if these areas are altered premorbidly or whether alterations represent the disease process.

The issue of disease process versus premorbid vulnerability is, in part, addressed in an article by Strakowski et al., who used structural magnetic resonance imaging (MRI)

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to study ventricular and brain size in patients with first-episode versus multiple-episode bipolar disorder. This MRI technique explores brain structure rather than activity and function. As such, activity or efficiency of processes can only be, at best, inferred. This study builds on a database of schizophrenia research in which disease progression has been associated with ventricular enlargement over time, suggesting that schizophrenia may actually involve progressive brain atrophy. In the Strakowski et al. study, lateral ventricular size was significantly greater in patients with multiple-episode bipolar disorder than in those experiencing their first bipolar episode or in healthy comparison subjects, although all three groups were of similar age. Differences in ventricular size did not appear to be due to overall small cerebral tissue volume. The authors note that glial tissue loss has been described in other studies of bipolar disorder (6), and they raise the possibility of white matter loss in the disorder. Indeed, this area has been largely overlooked in previous studies, in part, for technical reasons. However, recent advances in diffusion tensor imaging may allow for quantifying volumes of white matter connecting tracts. This area makes intuitive sense, since abnormal connections may ultimately tell us much about abnormal behavior.

The Strakowski et al. study also notes smaller hippocampal volume in patients experiencing their first bipolar episode than in patients with multiple-episode bipolar disorder or comparison subjects. The smaller hippocampal volume fits another report in the July issue of the *Journal* (7) in which a significantly smaller hippocampus was observed in subjects experiencing their first depressive episode. In the Strakowski et al. study, the smaller hippocampal volume was of marginal significance and was not observed in patients with multiple-episode bipolar disorder, so it is difficult to fully interpret these results. Still, they do suggest that a smaller hippocampus may be a risk factor for developing psychopathology (7, 8).

The Strakowski et al. study points out the need for longitudinal studies in patient cohorts to really understand disease processes. Cross-sectional studies are informative, but without following patients and studying them repeatedly, we may be making understandable misinterpretations. The recent papers on the genetics of hippocampal volume have questioned whether depression itself causes tissue volume loss (8). These questions will best be answered by prospective studies of cohorts of patients and comparison subjects to determine whether age or disease process, or both, may contribute to changes in structural volumes.

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