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EDITORIAL

Functional Brain Imaging in the Elderly

Alzheimer's disease (AD) and late-life depression (LLD) are usually thought of as discrete brain disorders. Unfortunately, as with many clinical syndromes, there can be considerable overlap in their presentation. Depressive disorders occur in 10%–20% of patients with AD (*1*), and some patients with LLD have cognitive deficits that reach clinically meaningful proportions (*2*) and may resolve with effective treatment of the underlying mood disorder (*3*). It is not surprising then that clinical diagnoses are not always reliable. One reviewer noted that 8% of British patients who were initially diagnosed with dementia were subsequently determined to have major depression (*4*).

For planning a therapeutic regimen, an accurate diagnostic assessment is critical. LLD is responsive to both antidepressant medication and electroconvulsive therapy (ECT) (*5*). However, medication side effects are common in the elderly, who often have comorbid medical conditions, and medication-induced cognitive decline is especially likely in patients with dementia. ECT also generally worsens cognitive deficits, at least acutely, in all patients (*6*). A range of different treatment strategies has been proposed for patients with AD and several promising new agents are now being assessed in clinical trials (*7*). These medications also have side effects and their benefits are unlikely to be shared by patients with LLD.

Although progress in defining the pathophysiology of psychiatric disorders in the elderly has been slow, the available evidence clearly suggests that both LLD and AD are associated with derangements in brain structure and function. Structural brain imaging studies have shown that both disorders are associated with increased rates of cerebral infarction, cortical atrophy and leukoencephalopathy (*8*). Similarly, functional brain imaging studies suggest that *global* cortical blood flow is decreased to a similar degree in patients with LLD or AD (*9,10*). Therefore, the development of brain imaging techniques with diagnostic utility for LLD and AD is likely to depend upon an assessment of alterations in *regional* brain metabolism either at rest or in response to pharmacologic challenge or neuropsychologic tasks.

In this issue of the *Journal*, Sackeim et al. (*11*) report an analysis of patterns of regional cerebral blood flow, determined using the ^{133}Xe inhalation technique, in large groups of well-matched patients with LLD and AD. A Scaled Subprofile Model (SSM), which was initially developed to identify abnormal functional networks in clinical brain images (*12*), was used to distinguish patient groups according to distinct topographic pro-

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files of regional perfusion abnormalities. Patients with LLD demonstrated cerebral blood flow (CBF) abnormalities in a network comprising selective frontal, central, superior temporal and anterior parietal brain regions. In contrast, patients with AD demonstrated abnormal CBF in four regional networks, with cognitive impairment correlating most closely with disrupted parietotemporal topography.

Unfortunately, whereas analysis of the four topographic structures tested was useful for the identification of group differences between patients with LLD and AD, only 67% of individual patients were correctly identified using these parameters. Nonetheless, the results presented in this report represent an important initial step toward the development of reliable techniques for the assessment of disease-specific patterns of altered CBF. These results are even more remarkable in light of the fact that the ^{133}Xe inhalation technique only provides information on cortical perfusion with relatively limited spatial resolution. SPECT and PET techniques, which provide higher spatial resolution and can also image subcortical activity, represent promising complementary approaches and have recently been used to demonstrate findings that are in good agreement with the work presented in this report. Dolan et al. (*13*) employed $^{15}O_2$ inhalation to make PET brain perfusion measurements of 33 older patients with major depression, 10 of whom demonstrated significant, and ultimately reversible, cognitive impairment. Depressed patients had decreased regional CBF in the left and right dorsolateral prefrontal cortex, the left anterior cingulate gyrus and the right insula relative to normal controls. Those patients with depression and cognitive deficits had decreased left medial prefrontal perfusion and increased perfusion of the cerebellar vermis in comparison to those depressed patients without cognitive impairment. Holman et al. (*14*) prospectively studied 52 patients with AD and 61 patients with other dementing illnesses using ^{99m}Tc-HMPAO SPECT. These investigators found that the presence of bilateral temporoparietal perfusion defects was strongly associated with a clinical diagnosis of AD.

Time and further study will be required to determine which abnormalities of regional brain activity are epiphenomenal and which identify subgroups of patients by pathophysiology and course, including treatment response. The latter distinction will prove increasingly important as more specific and effective treatments for LLD and AD become available.

Postmortem studies have clearly shown largely separate anatomic and biochemical abnormalities associated with LLD and AD. The problem has been differentiating these pathophysiologies during life. Toward this end, further studies on the clinical utility of functional brain imaging are clearly warranted. They can be expected to yield results as surprising and rewarding as those observed in dementia 100 yr ago by Alois Alzheimer using the state-of-the-art technology of his time.

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