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Neuroimaging in Geriatric Psychiatry: Integrative Research as the Next Frontier

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The articles in this issue of the *Journal* represent asignificant advance in the application of neuroimaging methods to understand some of the most challenging questions regarding pathophysiology of late-life neuropsychiatric disorders. The articles are important examples of how neuroimaging methods, when combined with genetic or longitudinal methods or when integrated into a clinical trial can provide data relevant to neurobiologic mechanisms or biomarkers of clinical or cognitive outcomes. The neuroimaging field is always challenged by issues of clinical utility, given the complex and expensive procedures. The articles in the issue suggest the clinical utility for such issues as using imaging to predict cognitive decline and treatment response. Furthermore, the studies in this issue illustrate how studying geriatric populations provides a unique opportunity for mechanistic and biomarker studies that can then be applied to the study of younger neuropsychiatric patients.

A clearer picture of the neuroanatomic substrates underlying aspects of aging, cognition, and mood is emerging from the novel application of increasingly sophisticated neuroimaging tools. Studies have now advanced beyond finding simple cross-sectional assessments of anatomic differences between populations. A highlight of many of these studies is the use of longitudinal analyses to examine the dynamic nature of neuroimaging findings associated with disease progression and treatment response. In the article by Steffens and colleagues,[1] the authors addressed the question of whether hippocampal volume declines are associated with major depression and cognitive decline. The authors demonstrate in a large, well-characterized sample of patients and controls that cognitive decline is associated with hippocampal volume loss over a 2-year interval. Although the findings of cross-sectional studies of hippocampal volume loss in geriatric depression are controversial, the present study suggests that hippocampal volume loss may underlie cognitive decline in depression and dementia.

The important issue of whether genetic polymorphisms influence hippocampal volumes is the focus of two articles in the issue. The hippocampus is a crucial structure involved in the regulation of mood and cognition and thus holds particular relevance for geriatric

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depression. As mentioned, abnormalities in hippocampal shape and volume associated with major depression have been identified in some studies. Likewise, decreased serum levels of brain-derived neurotrophic factor (BDNF) have been associated with major depressive disorder in midlife.[2] The link between these two findings were initially examined in an article by Benjamin et al.,[3] where the authors found no effect of BDNF genotype on hippocampal volume. In this issue of the *Journal*, Kanellopoulos and colleagues[4] try to clarify how BDNF genotypes may play a role in hippocampal structural differences associated with geriatric major depression. In this study, the authors observed that the depressed *val/val* homozygotes had larger hippocampal volumes than nondepressed controls with the same genotype. The authors conclude that the val/val genotype may be neuroprotective in depressed patients. An important gene associated with dementia risk that is examined in the article by Sachs-Ericsson and colleagues[5] is apolipoprotein E (APOE). In this study, the authors demonstrate that the *APOE ε4* allele moderates the relationship between hippocampal volumes and cognitive decline in depressed elderly patients evaluated over 4 years. The *APOE ε4* allele influenced cognitive decline among subjects with smaller hippocampal volumes. Taken together, these two studies underscore the importance of considering genetic polymorphisms in interpreting hippocampal volume data and provide evidence of the neuroprotective and neurogenerative role of the BDNF val/val genotype and *APOE ε4* allele, respectively. The evaluation of such relationships in younger depressed samples would be of great interest to determine whether changes in hippocampus morphology earlier in life might predispose individuals to recurrent depression in late life and cognitive decline. Such patients could be followed and treated more intensively and would be candidates for neuroprotective interventions when such treatments become available.

In addition to using longitudinal analyses to examine correlates of cognitive decline, it is important to understand protective factors against cognitive decline. One of the key factors that are thought to be protective against cognitive decline is the notion of cognitive reserve. The important influence of white matter changes is explored in an article by Arenaza-Urquijo and colleagues,[6] who used diffusion tensor imaging to demonstrate the structural correlates of cognitive reserve in healthy elderly subjects, subjects with mild cognitive impairment, and subjects with dementia. The authors make the interesting observation that greater cognitive reserve is associated with more widespread decreases in fractional anisotropy in amnestic mild cognitive impairment (MCI) than in normal aging. As the authors have also investigated the relationship of cognitive reserve to the functional activation response, a logical next step for this work would be to determine whether increased activation responses associated with greater cognitive reserve are a compensatory response for alterations in brain structure. Understanding the neurobiology of cognitive reserve may inform the development of neuroprotective strategies.

White matter alterations have been observed in geriatric depression and have also been identified as putative biomarkers of clinical response. One of the first demonstrations of this idea was the discovery that severity of white matter hyperintensities predicted poor treatment response.[7] An article by Taylor and colleagues[8] continues this trend by using diffusion tensor imaging to examine longitudinal white matter functional integrity changes in depressed elderly subjects. Remission was associated with greater reduction in anterior

cingulate fractional anisotropy, while the nonremitted showed less evidence of decrease. As the authors suggest, this counterintuitive finding reminds us of the importance of studies designed to understand the mechanism underlying the changes in white matter as assessed by diffusion tensor imaging, particularly with respect to depression pathophysiology and antidepressant treatment.

Across the lifespan, positron emission tomography measures of cerebral glucose metabolism have consistently shown correlations with depressive symptomatology and biomarkers of antidepressant response. One of the initial observations in depressed patients in midlife was made by Mayberg and colleagues,[9] who found evidence of anterior cingulate hypermetabolism of depressed responders compared with nonresponders. Smith and colleagues[10] demonstrate that cerebral glucose metabolism in the resting state and the cerebral metabolic response to the first dose of an antidepressant (citalopram) is associated with clinical response after a 3-month clinical trial. These results are consistent with an earlier study published in the *Journal* that showed the ability of the metabolic response to one night of total sleep deprivation to predict antidepressant treatment outcome.[11] These observations suggest that the antidepressant response is associated with the adaptive capacity of the brain to respond to acute neurochemical alterations.

In summary, the articles in this issue of the *Journal* underscore how neuroimaging techniques are expanding our understanding of pathophysiology of geriatric mood and cognitive disorders, especially with respect to the clinical relevance of the neuroimaging measures. Ultimately, the use of neuroimaging to better understand the neuroanatomic and metabolic correlates of clinical features associated with aging, mood disorders, and cognitive dysfunction will be better served by the integration of the neuroimaging methods with clinical trials or longitudinal studies. The integration of neuroimaging and genetic measures is critical for an understanding of the intrasubject variability of the neuroimaging measures and for understanding the significance of genetic polymorphisms with respect to brain structural and functional in late-life neuropsychiatric disorders.

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