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Neuroimaging in geriatric psychiatry

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INTRODUCTION

Neuroimaging methods represent the interface between basic and clinical neuroscience (as shown in Figure 1). Advances in instrumentation, radiotracer chemistry, positron emission tomography (PET) and magnetic resonance (MR) imaging methodologies provide the opportunity to test mechanistic hypotheses generated from basic neuroscience studies in normal function and disease. In addition to translational research, neuroimaging allows ‘reverse’ translation by identifying putative mechanisms from clinical neuroscience research and using this information to inform the development of animal models or to perform basic studies to further understand the neurobiological mechanisms of a particular behavior. Such approaches have been applied to the study of neurodegenerative disorders, including Alzheimer’s dementia (AD), Parkinson’s, and Huntington’s disease. As reflected by the papers in this Neuroimaging Issue, depression is a major focus of neuroimaging in Geriatric Psychiatry. Over the past decade, the impact of geriatric depression on cognitive decline, disability, and mortality has been increasingly recognized (Lebowitz *et al.*, 1997; Alexopoulos, 2005) and has stimulated translational research in this area (Smith *et al.*, 2007). The papers in this issue represent unique observations regarding neural circuitry of geriatric depression and anxiety symptoms and of cognitive impairment associated with vulnerability to cognitive decline and AD and pave the way for novel treatment development.

BRAIN ENERGY METABOLISM AND CEREBRAL BLOOD FLOW IN GERIATRIC DEPRESSION AND ANXIETY

Incorporating neuroimaging into clinical trials may identify neurochemical and neuroanatomic differences between treatment responders and non-responders. Abnormalities identified through neuroimaging may serve as biomarkers and even inform treatment development by identifying mechanisms of treatment resistance. The study by Forester applies magnetic resonance spectroscopy (MRS) to understand changes in brain energy metabolism in geriatric depression and the effects of antidepressant (sertraline) treatment. The analysis of phosphorus metabolites in a whole brain volume revealed decreased total nucleoside triphosphate (NTP) and beta nucleoside triphosphate (bNTP) in geriatric depressed patients relative to controls and a decrease in NTP with sertraline treatment. In evaluating gray and white matter concentrations separately, prior to treatment, total NTP was

decreased in white but not gray matter and intracellular pH was higher in gray but not white matter. After treatment, pH levels normalized to control levels. Intracellular magnesium ion concentrations, phosphocreatinine, and membrane bound phospholipids were increased in gray matter but not white matter in the depressed patients relative to the controls. The altered cellular bioenergetics provides evidence of mitochondrial dysfunction in geriatric depression that is normalized by antidepressant treatment. These findings serve as the starting point of evaluation of the role of mitochondrial dysfunction in geriatric depression and provide further support for treatment development focused on this unique therapeutic mechanism.

Smith and colleagues report increased cortical glucose metabolism in brain regions with gray and white matter atrophic changes. These findings are consistent with resting state functional magnetic resonance imaging (fMRI) studies in young and older depressed patients demonstrating hyperactivity in regions of the 'default' network. As will be highlighted, several aspects of these observations are consistent with functional and structural MR findings presented in this issue. The analysis of the MR data in this study revealed more extensive white matter than gray matter changes. Moreover, glucose metabolism studies reveal more extensive correlations with depressive and anxiety symptoms than structural imaging investigations. There are several potential mechanisms that may explain the hypermetabolism identified by this study, including neuroinflammation, glutamate hyperactivity, beta amyloid deposition, and mitochondrial dysfunction. Each of these mechanisms can be further explored by multi-modality imaging in the same patient samples.

The neurobiological correlates of chronic, subthreshold depressive symptoms (SDS) are poorly understood. **Dodson** and colleagues report the effects of SDS on regional cerebral blood flow (rCBF) measured over a 9-year longitudinal follow-up interval in healthy control subjects enrolled in the Baltimore Longitudinal Study of Aging (BLSA). The cross sectional data revealed that greater SDS was associated with lower rCBF. A similar rCBF pattern was observed at 9- year follow-up, although reductions primarily in cortical regions were more extensive at follow-up (including left cingulate gyrus [BA 32] and inferior frontal gyri in the females and right medial frontal, left middle frontal, left inferior temporal, and left superior occipital gyri in the males). In addition, many of the regions affected cross-sectionally also showed longitudinal decreases associated with SDS. Males showed greater rCBF alterations in fronto-temporal regions than females. A consideration in interpreting these data is that about 15% of the subjects were taking antidepressant medications and would be considered treatment responders as they did not meet criteria for a major depressive episode at either time during the study. The contrast between the lower rCBF in this study and increased cerebral metabolism in the prior study by **Smith** and colleagues has several possible interpretations. A potential explanation might be that cerebral blood flow and metabolism are uncoupled in geriatric mood disorders. Alternatively, chronic subthreshold mood symptoms may have a different impact on the brain than episodes of major depression.

Andreescu and colleagues applied elegant fMRI activation paradigms and analytic methods to compare differences in activation of the cognitive control circuit in depressed elderly patients with and without comorbid anxiety. They employed a paradigm that selectively activates the cognitive control circuit involving threat monitoring, a core component of

anxiety disorders. The two patient groups did not differ significantly in task performance. A time series analysis method applied to the data demonstrated greater and sustained activation in dorsal anterior cingulate (BA 24), posterior cingulate (BA31), and prefrontal cortex (BA 6) in the anxious compared with the non-anxious subjects. These regions overlap with the regions showed to have a positive correlation between anxiety symptoms and cerebral glucose metabolism in the study by **Smith** and also include regions of the 'default network'. These observations are among the first to show functional neuroanatomic differences associated with anxiety in geriatric depression.

INTEGRATIVE METHODS TO EVALUATING STRUCTURAL PATHOLOGY IN GERIATRIC DEPRESSION: MR AND POST-MORTEM STUDIES

The study by **Gunning-Dixon** and colleagues adds another dimension to studies of diverse methodology suggesting that integrity of the anterior cingulate is critical for drug treatment response of geriatric depression. The study is another example of the integration of neuroimaging methods into clinical trials. The group evaluated the relationship of the volume of specific anterior cingulate regions to response of depressed elderly patient to escitalopram. Patients who remained symptomatic after 12 weeks of treatment had smaller volumes of the dorsal and rostral anterior cingulate gyrus, but no significant differences in the subgenual cingulate were observed. The differences observed in dorsal and rostral aspects of the cingulate rather than the subgenual cingulate are consistent with other reports in this issue, as well as other structural and functional neuroimaging studies in geriatric depressed patients.

The study by **Tamburo** and colleagues is an example of how shape analyses of MR imaging data may reveal subtle morphological abnormalities. Such abnormalities are particularly relevant to elderly patient studies in which the age related morphological changes might be difficult to distinguish from pathological conditions. In particular, MR studies of the amygdala in mood disorders across the lifespan have yielded controversial results. While the **Tamburo et al.** study found that depressed elderly patients had amygdala volumes comparable to those of controls, it observed bilateral changes in the shape of a region corresponding to the basolateral amygdala. As the basolateral amygdala is a component of the neural circuitry associated with affective and reward processing, stress responses and memory consolidation, this aspect of the amygdala may have a critical role in the neurobiology of geriatric depression.

The integration of genetics with neuroimaging is a powerful approach to understanding the functional significance of genetic polymorphisms involved in mood disorders, as well as the variability observed in neuroimaging measures among patients and controls. **Pan** and colleagues evaluated two genetic polymorphisms that have been implicated in depression, Catechol-O-Methyltransferase (COMT) and Methylenetetrahydrofolate reductase (MTHFR), relative to basal ganglia morphology measured with a volumetric MR method. The COMT polymorphism, that determines COMT activity has been implicated in depression, in antidepressant response, and in executive function. The MTHFR polymorphism is associated with differences in homocysteine levels, as well as depression risk.

The **Pan *et al.*** study did not observe an effect of either genetic polymorphism alone on basal ganglia volume. However, the combination of both genetic polymorphisms and putamen volume was shown to increase the susceptibility to depression, thus providing evidence for epigenetic interactions. As high homocysteine levels increase cerebrovascular risk and have a negative effect on monoamine concentrations, these factors may affect basal ganglia morphology and increase the risk for developing depression in late life. Such epigenetic interactions are critical to understanding some of the mechanisms contributing to specific syndromes of late-life depression.

The post-mortem study by **Otterloo** and colleagues is a product of the collaboration between a translational research center in geriatric mood disorders and one of the major post-mortem research laboratories focusing in depression. In contrast to the investigators' earlier finding of a loss of glutamatergic pyramidal neurons in the orbitofrontal cortex of depressed elderly patients, no cellular pathology was observed in the dorsolateral prefrontal cortex (BA 9). This post-mortem study points out that unlike the widespread cortical pathology observed even in the early stages of Alzheimer's dementia, the neuroanatomical changes observed in cognitively unimpaired depressed older adults are localized to specific neural circuits. The pathology in specific cortico–cortico, cortico–limbic, and striato–cortical circuits in geriatric depression represents a unique opportunity to study brain behavior relationships using complementary neuroimaging, genetic, neuropsychological, and pharmacologic methods. Post-mortem studies are critically needed for the interpretation of neuroimaging findings in geriatric depression, including the mechanisms underlying MR findings of gray or white matter loss, decreased white matter functional connectivity, altered cerebral glucose metabolism, molecular imaging findings of neurochemical alterations, or neuroinflammation. In addition, post-mortem data can inform the design of translational studies focusing on particular mechanisms.

NEUROANATOMIC CORRELATES OF COGNITIVE DYSFUNCTION IN THE EARLY STAGES OF COGNITIVE IMPAIRMENT AND AD

Two studies focus on one of the most important applications of neuroimaging and seek to identify the earliest neuroanatomic deficits in the course of memory impairment, subjective memory complaints, and amnesic mild cognitive impairment.

Rodda and colleagues report of the initial findings of the functional neural circuitry of subjective cognitive impairment (SCI). Volumetric changes have been reported in SCI. However, the functional neuroanatomic correlates and long-term consequences of this condition are poorly understood. While the SCI subjects and controls performed equally on an episodic memory task, SCI subjects showed greater fMRI activation responses in the left PFC (BA 6,9,44,46) compared to controls. In evaluating the within-group activation patterns, SCI showed a more extensive pattern of activation relative to controls including the left medial and prefrontal gyri, the left medial temporal, the left occipito-parietal, and the cerebellum (bilaterally). The increased activation response in SCI parallels fMRI findings of episodic memory in MCI, as well as individuals at genetic risk for AD (ApoE4 gene carriers). While many patients with geriatric depression report subjective cognitive

complaints, fMRI studies have shown blunted activation responses in patients relative to controls. These differences in activation distinguish geriatric depression and cognitive decline in MCI and AD.

What does a greater activation response actually mean in clinical and physiological terms? Do greater responses represent increased capacity of the brain to respond or a compensatory effect as is typically concluded in MR and PET studies? Is a greater activation response associated with slower disease onset or progression or a more favorable treatment response? Such issues can be best addressed by incorporating the neuroimaging paradigms into longitudinal study designs with comprehensive clinical and neuropsychological assessments.

Rami and colleagues studied the longitudinal course of gray matter degeneration in amnesic MCI (aMCI), prodromal AD, and probable AD. The investigators define Prodromal AD as a diagnostic category including individuals at higher risk for AD than aMCI. In addition to episodic memory impairment, the diagnosis of prodromal AD requires either evidence of activities of daily living impairment or a second domain of cognitive deficit. At baseline, the prodromal AD group compared to the aMCI group had greater loss of gray matter in left inferior frontal cortex, right parietal cortex, inferior temporal cortex, and hippocampus (bilaterally). The prodromal AD group differed from controls in these regions, as well as the anterior cingulate/medial frontal cortex. Within the 2-year follow-up interval, the prodromal AD group had a higher degree of conversion to AD than the aMCI group, as well as greater decline in tests of semantic fluency, similarities, confrontation naming (Boston Naming Test), and functional abilities. Extensive literature suggests that gray matter loss in the temporal cortex and hippocampus and impairment in episodic memory are associated with greater AD risk. The novel finding of the **Rami et al.** study is that low volume of frontal cortical regions and poor performance in cognitive functions requiring frontal integrity (eg., semantic fluency, confrontation naming, and abstract reasoning) are associated with conversion of prodromal AD into diagnosable AD.

The study by **Melrose** and colleagues complements the above findings and focuses on the functional neuroanatomy of deficits in confrontation naming, retrieval, and verbal fluency in AD patients. PET cerebral glucose metabolism measures were correlated with performance in a picture naming task (Boston Naming Test) and with the effect of phonemic cues, phonemic, and semantic fluency (letter and category naming). The patterns of correlations observed implicated the left inferior frontal gyrus in cued verbal memory. The anterior aspects of the left inferior frontal gyrus was involved in processing semantic information and the posterior aspect (in close proximity to the motor cortex and language production areas) involved in phonemic processing. The findings support the view that retrieval processing is localized in the frontal cortex and semantic knowledge processing is localized in the temporal cortex. The investigators conclude that frontal cortical dysfunction leads to naming impairment by disrupting the executive aspects of controlled retrieval. The results demonstrate that an established model of language processing can be evaluated in a neurodegenerative disorder characterized by extensive cortical pathology early in the disease course.

The study highlights the important role of executive function in AD with respect to language processing. Such an approach could be applied to study the normal aging process or MCI given the vulnerability of verbal naming and retrieval processes. Significant metabolic and perfusion deficits and amyloid deposition have been reported in the frontal cortex of MCI and AD patients, as well as in normal aging. However, their functional significance is poorly understood. Finally, the study highlights the point that not only impairment is associated with metabolic deficits but the ability to benefit from cues is associated with relative sparing of brain regions. The application of neuroimaging in this manner may have implications for determining which patients might benefit from rehabilitation strategies.

CONCLUSION

The papers in this issue identify several abnormalities of the neural circuitry and energy metabolism/blood flow in depression and anxiety symptoms, as well as the early stages of cognitive impairment and AD. As we have highlighted in this overview, a number of observations suggest that the neural circuitry of geriatric depression is different than that of younger patients. The papers also illustrate the value of integrating variety methodologies, including genetics, cognition, structural, and functional neuroimaging to understand the neurobiology of late life psychopathology. In the future, there will be unique opportunities for mechanistic studies, as the fields of the PET and MR molecular imaging continue to evolve, new, biologically meaningful genetics polymorphisms are discovered and more rigorous assessment methods of cognitive functions are developed.

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Neuroimaging as the Interface between Basic and Clinical Neuroscience

Figure 1.
Neuroimaging as the interface between basic and clinical neuroscience.