Neuroimaging Research in Geriatric Mental Health

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Neuroimaging Research in Geriatric Mental Health
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For my wife, Barbara Baumann, and children, Max, Simon, and Evelyn. You are my inspiration. Thank you. —H. A.

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Neuroimaging is playing an increasing role in the research and treatment of mental disorders in the elderly. In part this stems from the fact that aging itself is the greatest risk factor for the neuropathological processes of neurodegeneration and cerebrovascular disease, both of which result in structural and functional brain changes that can be visualized with modern neuroimaging methods. The goal of this edited book is to summarize the current state of the field. Experts in geriatric psychiatry, cognitive neuropsychology, neurology, neuroradiology, and MR physics have contributed. This “primer” can help provide a common reference to help unify the field of neuroimaging in geriatric mental health and promote the development of new ideas.

Our goals for the book are to summarize the current state of the field of neuroimaging research in geriatric psychiatry and to promote continued rapid advancement. The target audience is investigators new to the field who are interested in a comprehensive survey. We also aimed for this work to be accessible to interested clinical geriatric psychiatrists (who want a research update) and to serve as a useful reference for established researchers. A main motivation for this book is that we have periodically been approached by new researchers asking how to get started. We hope that this book may serve as a starting point for these new investigators.

H.J.A., C.F.R., & M.F.
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Neuroimaging Research in Geriatric Mental Health
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Introduction: Perspectives From the National Institutes of Health

JOVIER D. EVANS

The field of clinical mental health research, compared to other aspects of clinical medicine, has been plagued by a lack of corresponding breakthroughs in basic science and clinical pathophysiology. One of the greatest challenges for psychiatry in the postgenomic era is to “catch up” with the rest of clinical medicine with respect to diagnostic, prognostic, therapeutic, and preventive strategies based on the relevant biology, pathogenesis, and pathophysiology of the disorders of interest.

The National Institute of Mental Health (NIMH) is interested in supporting translational research efforts leading to new discoveries that will help cure mental illness. The mission of the institute is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. For this work to move forward, the institute must foster innovative thinking and ensure that a full array of novel scientific perspectives are used to further discovery in the evolving science of brain, behavior, and experience. In support of this mission, NIMH will generate research and promote research training to fulfill the following four objectives of its Strategic Plan (National Institute of Mental Health, 2008): (a) support basic, translational, and clinical research to gain a more complete understanding of the genetic, neurobiological, behavioral, environmental, and experiential factors that contribute to mental disorders; (b) chart the
course of mental disorders over the life span in order to understand ideal times and methods for intervention to preempt or treat mental disorders and hasten recovery; (c) improve existing approaches and devise new ones for the prevention, treatment, and cure of mental illness, allowing those who may suffer from these disorders to live full and productive lives; and (d) through research, evaluation, and collaboration, further develop the capacity of the institute to help close the gap between the development of new, research-tested interventions and their widespread use by those most in need.

The field of geriatric psychiatry is poised at the current time to move forward in these efforts and to develop work in the field of late-life mental disorders along more focused, mechanistic directions. In 2004, the NIMH established an organizational unit focused on aging-related research. In that reorganization, the Geriatrics Research Branch was placed within the Division of Adult Translational Research so as to focus on basic mechanisms and aspects of cognitive and affective neuroscience bearing on clinical issues of aging. In 2007, the Geriatrics Research Branch supported and published the proceedings from a workshop discussing new opportunities in late-life affective disorders that charted a course for future work (Smith, Gunning-Dixon, et al., 2007). One of the workshop’s recommendations was that these new imaging techniques should be harnessed to examine clinical questions around course, pathophysiology, treatment response, and mechanism.

This book serves as an important complement to these efforts in providing information about the use of innovative imaging tools and techniques to examine aspects of pathophysiology and mechanism in relation to disorders of aging. It explains basic concepts of neuroimaging and serves as a primer for investigators in this field. It includes chapters from leaders in the field of geriatric neuroimaging using functional, structural, and newer modalities to examine aspects of late-life mental disorders. The following chapters discuss basic elements of what is required to begin scientific investigation in this area.

Neurobiological approaches represent unique opportunities for the identification of mechanisms of pathophysiology and vulnerability that could potentially inform the development of intervention and prevention strategies. Such strategies may have relevance to the treatment of younger patients as well as to patients with depression secondary to other neuropsychiatric or medical illnesses (e.g., Alzheimer’s disease, Parkinson’s disease, cerebrovascular disease) and to the development of integrative conceptual models that could be applied to the study of
other neuropsychiatric disorders. Reaching a better understanding of the complex nature of geriatric mental disorders will require that the approach be both translational and integrative.

Ultimately, the use of these integrative translational methods will lead to the development of new mechanism-based treatment studies and proof-of-concept clinical trial designs in which responses to specific medications can be examined in a more focused manner. The results of these clinical trials and the ancillary genetic and neuroimaging studies will lead to important questions that will have to be “reversed” or back-translated to inform the design of future neurobiological studies for these disabling disorders. In addition, for hypothesis-driven, mechanistic research to evolve, continued interaction between investigators across disciplines (including geriatric psychiatry, genetics, neuropsychology, neuroimaging, and neuropathology) will be critical.

REFERENCES


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BASIC PRINCIPLES OF MRS

In vivo magnetic resonance spectroscopy (MRS) is a noninvasive technique that allows for the measurement of biochemicals in particular regions of the brain. It takes advantage of the chemical shift effect, which is seen when the same nuclei in different molecules respond differently to a magnetic field. Magnetic field strengths usually range from 1.5 Tesla (T) to 4 T in human studies. The chemical shift is typically measured in parts per million relative to the nuclear frequency and plotted on the horizontal axis of a spectrum, with the vertical axis displaying the amplitude or intensity of a peak (Figure 2.1). Each peak represents a metabolite of interest for a given nucleus.

Several signal-detection parameters determine the shape of a spectrum. One is the voxel size, which determines the region of tissue being studied and the concentration of metabolites being measured. Another important parameter is relaxation time, represented by T1 and T2. T1 is the time necessary for hydrogen nuclei to emit 63% of the energy from the stimulating pulse, while T2 is the time for 63% of the transverse energy pulse to be lost because of dephasing. These parameters affect signal strength, since long T1s and short T2s are typically found in intracellular molecules with high molecular weights and thus can lead
to weak signals. As a result, MRS is particularly useful for measuring low-molecular-weight molecules that are highly concentrated. Typical concentrations of metabolites detected by MRS are in the range of 4 to 10 mM. It is difficult to detect metabolites under 1 mM. These concentrations can be reported in absolute measures or as ratios to creatine concentrations, using creatine as an internal control.

**NUCLEAR ISOTOPES USED IN MRS**

**Phosphorus**

Phosphorus-31 ($^{31}$P) MRS can be used to measure the following metabolites: adenosine triphosphate (ATP), phosphomonoesters (phosphorylcholine, phosphorylethanolamine, and glycerophosphate), phosphodiesters (glycerylphosphorylethanolamine, glycerylphosphorylserine, and phlycerylphosphorylinositol), phosphocreatine, and inorganic phosphate. This is a useful isotope to measure to understand the bioenergetics of neuronal processes.

![Sample proton MRS spectrum. Each peak represents a different metabolite, with the area under the peak equivalent to the concentration of the metabolite.](image)
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**SUMMARY OF METABOLITES DETECTED USING PROTON MRS**

<table>
<thead>
<tr>
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<td>Myo-inositol</td>
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<td>Gamma-aminobutyric acid</td>
<td>Inhibitory neurotransmitter</td>
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**Proton**

Hydrogen or proton MRS is used to probe for the following neurochemicals: choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), myo-inositol (mI), glutamate/glutamine, and gamma aminobutyric acid (GABA) (Table 2.1). NAA is generally viewed as a marker of neuronal viability and may represent a measure of neuronal volume, number, and/or function. The choline signal represents a composite of choline-containing metabolites such as phosphocholine, glycerophosphocholine, and phosphatidylcholine. These metabolites are involved in cell membrane integrity. Myo-inositol is seen as a marker of gliosis and is a storage form of the inositol phosphate second-messenger system. Glutamate/glutamine and GABA are, respectively, the most ubiquitous excitatory and inhibitory neurotransmitters. Other less commonly used nuclei include carbon, lithium, fluorine, and sodium.

**NORMAL AGING**

Several studies have used MRS to study neurochemical changes associated with normal, healthy aging. Perhaps owing to methodological limitations, early studies using MRS to examine brain alterations associated with normal aging failed to find significant changes over time (Chang, Ernst, Poland, & Jenden, 1996; Saunders, Howe, van den Boogart, Griffiths, & Brown, 1999). However, in a study by Cohen and colleagues comparing brain uptake of choline using proton MRS
in younger subjects (mean age 32) and older subjects (mean age 73), it was shown that older subjects had decreased choline uptake (Cohen et al., 1995). In a 2000 study, Valenzuela and associates showed that frontal white matter NAA/Cr ratios were significantly correlated with cognitive tasks of executive function. A significant decline in frontal lobe NAA was shown in comparing subjects from ages 20 to 70, with an overall decrease of 12% (Brooks et al., 2001). This decline was interpreted as a decrease in neuronal volume, number, or function, as NAA is thought to be a marker of neuronal viability. These changes are not limited to frontal white matter, as demonstrated in a study that showed age-related decreases in NAA, NAA/Cho, and NAA/Cr ratios across 30 different voxels (Angelie et al., 2001). In a longitudinal study examining similar measures over a 3-year period, Ross and coworkers demonstrated that there were no significant changes in brain metabolites (with the exception of mI) or cognitive function over the period studied (Ross, Sachdev, Wen, & Brodaty, 2006). In a comprehensive review and meta-analysis of MRS studies in normal aging, the majority of studies showed no significant change in metabolites with age; however, the authors did note a trend toward an increase in frontal and parietal choline with increasing age and a trend toward increased parietal and occipital creatine with increasing age (Haga, Khor, Farrall, & Wardlaw, 2009).

**LATE-LIFE DEPRESSION**

Utilization of MRS to study the biochemical changes associated with major depression has yielded a number of findings over the past few years. These include increases in choline and myo-inositol and decreases in NAA and glutamate associated with major depression (Auer et al., 2000; Kumar et al., 2002; Rosenberg et al., 2005; Vythilingam et al., 2003). These metabolic changes associated with major depression seem to be clinically relevant, as demonstrated by studies of treatment effect. For example, an increase in amygdalar region NAA was seen in depressed patients who exhibited a positive response to electroconvulsive therapy (Michael et al., 2003a). In addition, concentrations of Glx (a composite of glutamate and glutamine) in the left dorsal lateral prefrontal cortex were negatively correlated with severity of depression and increased significantly after electroconvulsive treatment (Michael et al., 2003b). In a report examining the effect of antidepressant treatment, it was shown that decreased NAA levels in the anterior cingulate cortex
in depressed patients were reversed with venlafaxine treatment (Gonul et al., 2006).

Other brain regions have been studied as well using MRS in major depression. For example, in one study showing an increase in glutamate levels associated with major depression, the region of interest was in the occipital cortex (Sanacora et al., 2004). In addition, MRS of the mesial temporal lobe of depressed patients demonstrated significant increases in choline/Cr ratios as compared to controls (Mervaala et al., 2000).

**DEMENTIA AND COGNITIVE DISORDERS**

**Mild Cognitive Impairment (MCI)/Cognitively Impaired Nondemented (CIND)**

MRS studies in MCI have been used to distinguish MCI from normal aging as well as more advanced forms of cognitive dysfunction. An early study by Kantarci and coworkers examined regional metabolic changes associated with MCI. They found that increases in mI/Cr ratios in the posterior cingulate were unique to MCI patients and Alzheimer’s patients, while decreases in NAA/Cr and Cho/Cr seemed present only in patients with more progressive disease (Kantarci et al., 2000). Subsequent studies have shown a similar pattern of changes associated with MCI patients as compared to control subjects (Catani et al., 2001). Other regions have been shown to demonstrate metabolic perturbations restricted to MCI. For example, in their study, Ackl and associates found that hippocampal decreases in NAA occurred in both MCI and Alzheimer’s patients but that NAA changes in the parietal region seemed to occur only in more advanced patients (Ackl et al., 2005). MRS has been studied as a predictor of developing dementia in a number of studies. For example, CIND patients compared to controls have been shown to have reduced NAA in the medial temporal lobe, hippocampus, and neocortical gray matter. There was also a difference between stable CIND patients and CIND patients who developed dementia over 3.6 years of follow-up (Chao et al., 2005). In another study, changes in occipital NAA/Cr ratios predicted conversion to dementia with 100% sensitivity and 75% specificity (Modrego, Fayed, & Pina, 2005). Thus MRS has been a useful tool in determining those early metabolic profiles that distinguish MCI from more advanced dementia and those changes that predict the development of more advanced dementia.
Alzheimer’s Disease (AD)

There have been numerous studies using MRS to measure brain metabolites in AD. The most consistent finding is reduced NAA, a marker of neuronal viability, and increased myo-inositol. This has been demonstrated in a number of cross-sectional studies (Frederick, Satlin, Yurgelun-Todd, & Renshaw, 1997; Lazeyras et al., 1998; Parnetti et al., 1997; Shiino et al., 1993). These patterns also occur longitudinally, as demonstrated in a brief report from Adalsteinsson and colleagues. They showed that gray matter NAA levels (on average) declined 12.26% over the course of a year in AD patients, whereas controls had no significant change over the same period (Adalsteinsson, Sullivan, Kleinhans, Spielman, & Pfefferbaum, 2000). Metabolic alterations associated with AD have been associated with cognitive function as well. For example, NAA reductions in the left medial temporal lobe were associated with impairment in verbal memory, while myo-inositol increases in the right parietotemporal cortex were associated with impairment in visuoconstructural performance (Chantal, Labelle, Bouchard, Braun, & Boulanger, 2002).

There have been several studies looking at the effects of treatment of Alzheimer’s disease on brain metabolic profiles. In a study on donepezil, the authors found that patients receiving treatment demonstrated higher NAA concentrations compared to patients receiving placebo over a 24-week period (Krishnan et al., 2003). In a subsequent study, these types of changes were shown to be significantly correlated with cognitive improvement associated with donepezil treatment (Jessen et al., 2006). Rivastigmine has also been shown to positively affect the metabolic profile associated with AD. Patients treated with rivastigmine over a 4-month period exhibited significant increases in frontal cortex NAA/Cr ratio (Modrego, Pina, Fayed, & Diaz, 2006). Thus, with the evidence from these treatment effect studies, it appears that the metabolic alterations seen in AD are related to the underlying pathophysiology of the disease.

Vascular Dementia (VaD)

While there have been a number of studies trying to use MRS to distinguish AD from VaD (Herminghaus et al., 2003; Kattapong, Brooks, Wesley, Kodituwakku, & Rosenberg, 1996), there are more similarities than differences in the patterns of change. The main distinguishing fea-
ture of VaD is the subcortical predominance of metabolic alterations versus more cortical changes in AD. However, as with AD, patients with VaD have been shown to have decreased NAA as well as increased myo-inositol (Herminghaus et al., 2003).

**Frontotemporal Dementia (FTD)**

As expected with FTD, metabolic changes are associated with more frontal structures, as evidenced by a study showing decreased NAA in frontal areas compared to more posterior regional changes in AD patients (Mihara, Hattori, Abe, Sakoda, & Sawada, 2006). In a study comparing FTD patients with AD patients and controls, frontal lobe NAA and Glx concentrations were decreased in conjunction with increases in mI (Ernst, Chang, Melchor, & Mehringer, 1997). The NAA results have been replicated in a later study examining metabolites in the posterior cingulate cortex of FTD patients (Kizu, Yamada, Ito, & Nishimura, 2004).

**Lewy Body Dementia (LBD)**

There are a few studies using MRS to examine brain changes associated with LBD. One report that included 20 patients with LBD showed that choline/Cr ratios were significantly elevated compared to healthy controls (Kantarci et al., 2004). In another study, white matter changes were detected with significantly lower mean NAA/Cr, Glx/Cr, and choline/Cr ratios in LBD patients compared to controls (Molina et al., 2002).

**Summary**

Overall, the studies outlined above demonstrate a general pattern that applies to most of the neurodegenerative diseases. Dementia subtypes appear to differ only in terms of the neuroanatomical regions affected. In a number of areas, including gray and white matter and cortical and subcortical regions, NAA tends to be decreased compared to controls, while increases in myo-inositol and choline have been detected. This is thought to reflect the loss of neurons (with NAA), membrane breakdown (choline), and reactive gliosis (detected by myo-inositol) associated with these diseases.
STRENGTHS AND LIMITATIONS OF MRS

The major strength of MRS is that it allows for the measurement of specific metabolites in a particular region of the brain. Thus the selection of crucial brain regions plays a vital role in elucidating the pathophysiology underlying late-life mental illness. This is also a potential limitation, as many studies choose different brain regions to study the same illness; thus generalizability and broad interpretation across studies are difficult to achieve.

Another limitation is poor resolution of specific peaks. Often, GABA, glutamate, and glutamine peaks overlap, making it difficult to determine exact concentrations of these metabolites. One technique designed to surmount this limitation is two-dimensional magnetic resonance spectroscopy (2D-MRS).

2D MAGNETIC RESONANCE SPECTROSCOPY

Two-dimensional spectroscopy is a technique that allows for greater resolution. The advantage of 2D spectroscopy is that it allows for the detection of GABA, which is typically masked by the spectral peaks of other metabolites, such as N-acetyl aspartate and glutamate/glutamine. One of the first papers to apply 2D MRS techniques to brain chemistry was done by Thomas and colleagues, showing the feasibility of the 2D J-coupled point-resolved spectroscopy (JPRESS) technique in human subjects (Ryner, Sorenson, & Thomas, 1995). They were able to detect peaks representing NAA, glutamate/glutamine, and lactate in occipital cortex.

Two-dimensional J-resolved spectroscopy has been successfully applied to measure previously hard-to-detect levels of GABA (Jensen, Frederick, Wang, Brown, & Renshaw, 2005). This technique has also been used to measure gray matter/white matter differences. A study by Jensen and colleagues showed that GABA levels are significantly higher in gray matter than in white matter (Jensen, Frederick, & Renshaw, 2005).

Localized two-dimensional chemical shift correlated magnetic resonance spectroscopy (2D-COSY) is a method that presents certain advantages over the JPRESS and J-resolved techniques. This method was successfully used in the human brain in a study by Thomas and associates, where peaks for N-acetyl aspartate (NAA), glutamate/glutamine (Glx), myo-inositol (mI), creatine (Cr), choline, aspartate, GABA, taurine, glu-
tathione, threonine, and macromolecules were identified (Thomas et al., 2001). The authors demonstrated that 2D-COSY generates spectra with better resolution and less overlap of peaks. 2D-COSY has also been shown to be highly reliable and reproducible (Binesh, Yue, Fairbanks, & Thomas, 2002).

The advantage of this technique is that it allows for the detection of important metabolites that are difficult to measure by traditional MRS methods. Particularly, it allows for better resolution of aspartate and GABA, important neurotransmitters that have been implicated in mood disorders.

CONCLUSION

MRS is an important tool for the localized measurement of brain metabolites; it has been successfully applied to elucidating the nature of geriatric mental illness. Despite its limitations, the method continues to evolve more sophisticated techniques for the improved measurement of clinically important neurochemicals.

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