Published in final edited form as:
Am J Geriatr Psychiatry. 2006 October ; 14(10): 812–822.

Structural Neuroimaging Research Methods in Geriatric Depression

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Abstract

Geriatric depression consists of complex and heterogeneous behaviors unlikely to be caused by a single brain lesion. However, there is evidence that abnormalities in specific brain structures and their interconnections confer vulnerability to the development of late-life depression. Structural magnetic resonance imaging methods can be used to identify and quantify brain abnormalities predisposing to geriatric depression and in prediction of treatment response. This article reviews several techniques, including morphometric approaches, study of white matter hyperintensities, diffusion tensor imaging, magnetization transfer imaging, t2 relaxography, and spectroscopy, that have been used to examine these brain abnormalities with a focus on the type of information obtained by each method as well as each method's limitations. The authors argue that the available methods provide complementary information and that, when combined judiciously, can increase the knowledge gained from neuroimaging findings and conceptually advance the field of geriatric depression. (Am J Geriatr Psychiatry 2006; 14:812–822)

Keywords

Depression; neuroimaging; white matter; gray matter

Geriatric depression is a heterogeneous syndrome that likely has multiple determinants. Among these, abnormalities in specific brain structures likely confer morbid vulnerability that increases the propensity for development and chronicity of late-life depression.[1] Geriatric depression consists of complex and heterogeneous behaviors, however, that are unlikely to follow a simple lesion–syndrome relationship. The etiology of such brain abnormalities may be diverse and result from processes commonly occurring in older adults, including genetic influences and vascular, inflammatory, autoimmune, and endocrine processes.[2] Although imaging studies thus far have identified group differences between normal subjects and those with late-life depression that are not robust or distinctive enough to be used for diagnosis of individuals, recent advances in magnetic resonance imaging (MRI) techniques allow the in

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This study is supported by grant RO1 MH65653 (Alexopoulos), P30 MH68638 (Alexopoulos), by grant RO1 MH60662 (KOL), by K23 MH074818 (FGD), K23 MH067702 (CFM), R01 MH64783 (MJH), and by the Sanchez Foundation.

Dr. Alexopoulos has received research grants by Forest Pharmaceuticals, Inc., and Cephalon and participated in scientific advisory board meetings of Forest Pharmaceuticals. He has given lectures supported by Forest, Cephalon, Bristol Meyers, Janssen, Pfizer, and Lilly and has received support by Comprehensive Neuroscience, Inc. for the development of treatment guidelines in late-life psychiatric disorders.

vivo identification of the specific brain structure abnormalities that have the potential to further elucidate the role of brain structure abnormalities in the pathophysiology of geriatric depression and the mechanisms of treatment response. Because more than one brain abnormality may confer vulnerability to geriatric depression, structural neuroimaging studies need to have sharply focused hypotheses that take full advantage of the developing technology to clarify with greater specificity the location, type, and extent of abnormality. Effective use of such information can help constrain models of late-life depression.

We discuss the potential uses and limitations of both traditional and recently developed MRI approaches to the study of late-life depression. The review is limited to MRI studies because of: 1) the relative safety of MRI compared with computed tomography scans (i.e., no radiation is used in MRI scans); and 2) the optimization of new MRI techniques for examination of white matter (WM). Accordingly, we discuss morphometric volumetry studies as well as WM pathology and magnetic resonance spectroscopy (MRS) studies. These are summarized in Table 1. Representative data from each method discussed are presented in Figure 1. Because the terminology is evolving, we also provide a glossary (Table 2). The interested reader is referred to MR physics texts[3,4] for more detailed information.

VOLUMETRIC STUDIES

Manual Morphometry

The most common method to examine differences in brain morphometry in vivo is the use of T1-weighted images. Most morphometric studies have depended on manual measurements of regions of interest (ROI). These studies provide measures of the volume of specific brain areas and have the advantage that the boundaries used are typically guided by relevant neuroanatomic parameters. The reliability of such measures tends to be high, at least within a particular laboratory or among a small set of raters. ROI studies of geriatric depression suggest marked volume reductions in the brains of older depressives in multiple frontal, limbic, and subcortical regions, including the anterior cingulate gyrus, prefrontal cortices, the neostriatum, and the hippocampus.[5–9]

A number of methodological limitations must be considered when interpreting morphometry studies. First, bearing in mind that loss of neuronal bodies, decrease in neuronal size, and decreases in dendritic arborization are all potential sources of volume reductions on T1-weighted images, the specific neurohistologic processes that account for the observed volume reductions cannot be distinguished. Second, larger or smaller volumes of the same brain structure may be associated with different mechanisms related to late-life depression. For example, enlarged amygdala volume has been observed during the first depressive episode[10] and interpreted as a predisposing factor to depression. In contrast, reduced amygdala volumes in recurrent depression[11] may be a result of impaired neurogenesis during previous depressive episodes. Third, antidepressant medication itself may modulate regional brain volumes. For example, Lavretsky et al.[12] found that orbitofrontal gray matter volumes were larger in patients with geriatric depression treated with antidepressant medication compared with drug-naive patients, although these volumes were smaller than in age-matched controls.

A significant limitation of manual ROI morphometry is the lack of standard guidelines used for delineation of ROIs across laboratories. Thus, differences between studies may be influenced by differences between research groups in the neuroanatomic boundaries used to identify ROIs. Manual ROI measurements also are time-consuming. The ROI often is drawn on every slice of an MR image, and the time necessary to establish inter- and intrarater reliability can be prohibitive. For these reasons, some investigators have begun to champion an atlas-based approach in which an ROI is derived in standard space and warped back to the individual’s brain space. An advantage of this method is that only one ROI needs to be drawn

for the entire sample. This method is ideal for hypothesis-driven approaches in which the region (s) of interest are chosen with regard to the literature but is not applicable in cases in which hypothesis generation is the goal.

Voxel-Based Morphometry

Voxel-based morphometry (VBM)[13] is a newer analytic method in which anatomic (typically T1-weighted) scan data are coregistered into a standard space, for example, Talairach space, so that comparisons can be made at homologous locations across images. The images typically are segmented into gray matter, WM, and cerebrospinal fluid components before analysis. The findings from these studies are generally interpreted as differences in tissue density. The advantage of VBM is the ease with which it can be carried out as well as its ability to interrogate the entire brain at once, meaning that novel findings can be more easily detected.

One disadvantage of VBM is its relative insensitivity to complex relatively nonlocalized differences in brain structure.[14] Thus, VBM has been shown to be biased toward detection of very local differences in brain structure but biased against detecting more distributed differences across brain regions.

The issue of false-positive findings is nontrivial in VBM and all voxelwise measures. As the number of statistical tests increase, the chance of a false-positive (type I error) increases. Because the tests, computed at each voxel, are not statistically independent, Bonferroni correction (simple division of the nominal p value by the number of tests) is not appropriate. Several alternative strategies have emerged. Most of these involve setting a magnitude threshold, whereby a group difference must be significant at a specified p level. In addition, it is common to set an extent threshold, whereby a certain number of contiguous voxels (cluster) have to be significant at a given p value. Within this framework, Friston et al. have developed the Gaussian random fields[15] method to correct for multiple comparisons. Others suggest using the false discovery rate[16] that corrects for, at minimum, false-positives. More recently, Baudewig et al.[17] have advocated using staged p values. In this approach, a conservative seed p value is computed and a minimum cluster size is set. All other voxels in the cluster need meet only a conventional threshold.

The quality of intersubject image registration can significantly influence results obtained using VBM.[18] To empirically examine some of the methods of intrasubject image registration, we quantitatively compared our nonlinear registration, automated registration toolbox (ART19), with both SPM99 (available at www.fil.ion.ucl.ac.uk) and automated intersubject registration (AIR20), two commonly used intrasubject registration algorithms. We measured the influence of registration methods on both the initial and final location of 20 different landmarks. For almost every landmark, ART gave a smaller intersubject dispersion than either SPM99 or AIR.[21] This high-quality intersubject registration significantly influenced functional MRI results.[22] Given age-related increases in the variability of the shape of various structures (e.g., ventricles), it is important to use age-appropriate templates.

Finally, WM hyperintensities, which are prevalent in geriatric depression, may cause tissue to be misclassified during the segmentation process, leading to inaccuracies in VBM results.

Despite the aforementioned caveats, recent studies indicate that VBM is an effective tool for the detection of structural anomalies in geriatric depression. For example, in a VBM study, hippocampal and prefrontal volumes were smaller in depressed than nondepressed elderly subjects.[23] Furthermore, smaller hippocampal–entorhinal cortex volumes were associated with number of years since the first episode of major depression.

WHITE MATTER PATHOLOGY

White Matter Hyperintensities

The most common method to study WM neuropathology on MRI has been the examination of WM hyperintensities (WMH). These hyperintensities are typically observed in T2-weighted or fluid-attenuated inversion recovery sequences and are taken to indicate WM damage. WMH are more prevalent and severe in older depressed individuals than age-matched control subjects and mainly occur in subcortical regions and frontal WM projections.[24] Subcortical hyperintensities have been found to be associated with executive dysfunction.[25,26] Both executive dysfunction and subcortical hyperintensities have been shown to predict poor outcomes of geriatric depression.[27–30]

The methods of quantifying WMH are beset with some of the same limitations as morphometry studies. First, there are several WMH rating scales and these scales vary in scope, sensitivity, and reliability.[31] Second, postmortem studies of the histology of WMH suggest that such WM abnormalities reflect a number of pathologic processes; however, the methodology prevents a reliable discrimination among such mechanisms. Third, analysis of WMH does not allow identification of specific affected WM tracts. One hopes that the introduction of new MRI approaches (e.g., diffusion tensor, magnetization transfer) will help to achieve not only better differentiation between true WM lesions and spurious unidentified bright objects, but will also help to clarify the underlying pathologic causes of the WMH.

Diffusion Tensor Imaging—Diffusion tensor imaging (DTI) offers a promising new technique for the identification of cerebral networks critical to geriatric depression.[32] This method measures the self-diffusion of water. When no barriers to such diffusion are present, it occurs equally in all directions (i.e., it is isotropic). However, when barriers are present, diffusion tends to follow the long axis of those barriers (i.e., diffusion is anisotropic). DTI involves the acquisition of at least six images that are sensitive to diffusion in different directions as well as one reference image with no diffusion weighting. Diffusion anisotropy can be quantified using DTI by a number of different scalar metrics, including fractional anisotropy (FA). FA values range from 0 (perfectly isotropic diffusion) to 1 (the hypothetical case of an infinitely long, infinitesimally narrow tube).

The basis for anisotropic diffusion in brain appears to depend on cell membrane integrity and is modulated by myelin.[33,34] DTI is sensitive to WM pathology in a number of disorders, including multiple sclerosis,[35] schizophrenia,[36–38] and dyslexia.[39] It is also sensitive to the effects of aging.[40,41] Moreover, relationships between FA and function have been shown in a number of domains, including impulsivity,[42,43] cognitive function,[44–46] and psychopathologic symptomatology.[47]

Depressed elderly patients exhibit compromised integrity (reduced FA) of the right superior frontal WM.[48] Furthermore, in a preliminary DTI study, reduced FA of the WM lateral to the anterior cingulate gyrus was associated with poor response to citalopram in depressed older patients.[49] In a study of 51 patients, we found significant associations between FA and the executive aspects of the Stroop in multiple frontostriatal–limbic regions, including WM lateral to the anterior and posterior cingulate cortex, and WM in prefrontal, insular, and parahippocampal regions. Moreover, systolic blood pressure is inversely associated with FA at the WM of the anterior cingulate and basal ganglia, especially in patients with executive dysfunction (based on performance on the Stroop Color-Word task). These correlations were less extensive in patients without such executive dysfunction.[50] The association of systolic blood pressure with reduced FA in corticostriatal–limbic regions is consistent with the vascular depression model.[51,52]

It has been suggested that diffusivity perpendicular to (radial diffusivity [D_{RA}]) and parallel to (axial diffusivity [D_{AX}]) the direction of principal diffusion may be sensitive to different neural pathology. For example, increased D_{RA} has been attributed to compromised myelin. The knockout mouse *shiverer*, which lacks myelin basic protein, shows reduced diffusion anisotropy and increased D_{RA} with no change in D_{AX}.[53] Decreased D_{AX} has been associated with axonal degeneration. Mice with retinal ischemia show axonal degeneration followed by demyelination. DTI scans of these animals showed decreased D_{AX} followed by increased D_{RA}, consistent with axonal loss followed by demyelination in the same animals.[54] These measures might prove helpful in clarifying the relative roles of myelin and axonal integrity in WM changes in geriatric depression.

A potentially promising application of DTI is fiber tractography,[55,56] in which directional information from the diffusion tensor can be used to map out putative fiber tracts. This application should ultimately provide information on regional connectivity and has been suggested as a method to generate regions of interest. Only recently have quantitative methods been developed to evaluate tractography.[57,58] It would be useful to examine the extent to which tracts differ in individuals who are predisposed to geriatric depression relative to those who are not.

There are a number of limitations to DTI. For instance, a number of studies have used small samples and methods for analysis of the data are not well standardized. In addition, most, but not all,[59] DTI scanning sequences use a rapid imaging technique called echoplanar imaging. This technique is affected by magnetic susceptibility effects that occur, for example, at barriers between tissue and air or between tissue and bone, e.g., near the nasal sinuses. These susceptibility effects worsen at higher magnetic fields and can lead to distortion of images or, in extreme cases, loss of information.

A number of interpretation issues also remain. Many authors have characterized DTI as a measure of WM, whereas in reality, it is only a method to measure anisotropic diffusion. Some[34] have argued that DTI primarily measures axonal membrane integrity with myelin playing a modulatory role. A consideration of tensor components such as D_{RA} and D_{AX} may prove informative in this regard. Another important issue is the influence on DTI measurements of regions in which fibers with different orientations cross. A related issue is that most DTI studies have used low spatial resolutions, which can lead to partial volume effects in which fibers of varying orientations will be included in a given image voxel that could be separated with better spatial resolution. Some have proposed using high angular diffusion imaging to address this problem,[60] but it is unclear whether such methods can unambiguously separate crossing fibers at the voxel level. Low spatial resolution also plagues tractography because the resolution can be several orders of magnitude coarser than the fiber maps produced by tractography programs.

Intersubject image registration is an important concern for voxelwise DTI analysis for two reasons: first, coregistration of images of different modalities (e.g., T2-weighted to T1-weighted) is of questionable validity on the fine anatomic level. Second, the directional aspects of the tensor need to be registered individually.[61,62] Note that this second problem is not relevant if only scalar measures such as FA are of concern.

The optimal solution to the first problem is to register images of the same modality. For example, in our studies,[38,43,63] a T1-weighted image is registered to a T1-weighted template using a nonlinear registration algorithm. Then, the T2-weighted image is linearly registered to the registered T1-weighted image. Finally, the unweighted diffusion tensor image (which is T2-weighted) is nonlinearly matched to the T2-weighted image. This last step corrects for susceptibility-induced distortion. These three steps are combined into one transformation step

to minimize interpolation errors. This transformation can then be applied to FA maps as well as coregistered maps of other modalities. The result is highly accurate and precise intrasubject registrations of the image maps, which affords a greater ability to integrate results across imaging modalities.

The second problem arises because the transformation described in the preceding paragraph only deals with scalar measures. The approach described here can be applied to each directional component of the diffusion tensor, thereby yielding high-quality transformations of directional aspects of DTI.

Magnetization Transfer Imaging—Magnetization transfer imaging (MTI[64]) offers another method to assess the role of WM in geriatric depression. MTI provides contrast based on the interaction of the normally observed tissue water signal with protons contained in large macromolecules (including myelin) in tissue. The latter are invisible in standard MR sequences because of their very short T2 relaxation properties, but nevertheless can have an indirect effect on free water signal if the magnetization of water bound to the macromolecules is prepared by a special saturation pulse with large-frequency offset. In this imaging modality, two sequences are used, one of which is essentially proton density-weighted. In the other sequence, an off-resonance pulse is prepended to the original sequence, which eliminates the signal due to the protons associated with macromolecules, thereby lowering image contrast. The contrast difference between the two image sets is usually given by the magnetization transfer ratio (MTR). In a study comparing DTI with MT in multiple sclerosis,[65] normal-appearing periplaque regions (PWM) were compared with normal-appearing WM remote from the plaques. FA in the PWM regions was significantly lower than in remote regions. However, magnetization transfer ratio did not detect a significant difference between the two regions. The authors concluded that MT is sensitive to demyelination and axonal degeneration, which is present in and near lesions, but less sensitive to inflammation and edema, which is present in less affected regions, whereas FA is more sensitive to these processes. This result suggests that MTR and FA can provide complementary information in WM. Recently, however, Kubicki et al.[66] found substantial correlations between MT and FA in patients with schizophrenia. Thus, the nature of the relationship between FA and MT remains unclear.

Kumar and colleagues[67] demonstrated the usefulness of MT in the study of WM abnormalities in geriatric depression. In a preliminary study, they examined MT in eight patients with late-life depression and eight nondepressed comparison subjects. They found that, relative to age-matched control subjects, older depressed patients have lower MTRs in the genu and splenium of the corpus callosum, the neostriatum, and the occipital WM.

MTR is not a quantitative measure because the reduction in signal intensity on the scan with the saturated pulse is measured *relative* to the reference scan. The MTR gives rise to a single value and has been shown to be sensitive to scanner and sequence differences. Recently, quantitative magnetic transfer imaging has been implemented in humans.[68,69] Although these methods, which involves acquisition of numerous scans with varying saturation pulse frequencies and strengths, are time-consuming, they do yield quantitative estimates of magnetization transfer effects. Their value in geriatric depression has yet, to our knowledge, to be demonstrated, although the implementation of this method represents a potentially important research direction.

T2 Relaxography—More recently, T2 relaxography (T2R[70]) has been used to examine WM function. In this imaging modality, T2 signal characteristics are determined at multiple echo times. The T2 relaxation times (typically less than 50 msec) are attributed to water in myelin layers. Intermediate relaxation times (typically 50–200 msec) are attributed to intracellular water, whereas the longest relaxation times (typically greater than 200 msec) are attributed to

extracellular water. In T2R, a myelin fraction (MF) is computed as the signal at the shorter echo times (TE <50 ms) divided by the total signal at all echo times. Flynn et al.[71] found reduced MF in patients with schizophrenia. This method could be useful in geriatric depression such that decreased MF could be taken to suggest a reduction in myelin. A drawback of this method is that until recently, only a single imaging slice could be acquired in a reasonable amount of imaging time as a result of pulse sequence limitations. Vidarsson and colleagues[72] have suggested modifications to the T2R protocol to allow for the collection of multiple image slices in a reasonable scanning time. To our knowledge, this is the only published study using this promising new method; however, it is likely that its use will increase in the near future.

Magnetic Resonance Spectroscopy—MRS provides important information on the neurochemical environment. Different molecules have unique MR spectra that can be quantified by taking the area under the signal curve. In most cases, the values are not absolute, so it is customary to take ratios of the measure of interest to some standard metabolite, for example, choline.

Most spectroscopy studies thus far have used single voxel acquisitions with a high number of signal repetitions to get adequate signal-to-noise ratio. Other studies use chemical shift imaging to obtain spectroscopy data on an image slice or set of slices.

One of the primary metabolites of interest, *N*-acetyl aspartate (NAA), is present only in neurons[73] and has been viewed as a marker for neuronal integrity. Kumar and colleagues[74] used MRS to examine biochemical abnormalities in left frontal WM and bilateral anterior cingulate gray matter of elderly depressed patients. They observed higher choline to creatine as well as myoinositol to creatine ratios in the white, but not gray, matter of patients relative to age-matched comparison subjects. Results from a follow-up MRS study suggested that cognitive performance was associated with levels of metabolites as measured by 2–D MRS in healthy control subjects but not in patients with geriatric depression.[75] These authors interpreted their results as indicating that cognitive performance in geriatric depression may be associated with biochemical changes in frontostriatal circuitry.

An issue that needs to be addressed in spectroscopic studies of pathologic populations is that the T2 signal, from which spectra are derived, can differ across groups. This makes it difficult to distinguish whether observed effects reflect differences in metabolite concentration or differences in the metabolite's microenvironment. One solution to this problem is to acquire full T2 spectra of the metabolite. This process would increase scan time by an order of magnitude or more, however. Recently, some have advocated for J-coupled spectroscopy, which examines the Fourier transform of the T2 spectrum.[76–78] An alternative is to use modified sequences, although these are more difficult to implement than conventional sequences.

Another issue concerns the effect of antidepressants on metabolite levels. For example, occipital GABA levels increase after treatment with serotonin specific reuptake inhibitors in depressed patients.[79] These issues need to be systematically studied in patients on or off antidepressant medication, although medication washout in patients raises ethical concerns. In some ways, the sensitivity of spectroscopic measurements makes it an ideal method with which to examine medication effects on brain metabolism, leading to the possibility of clinical trials of the brain metabolic efficacy of antidepressant agents in geriatric depression.

Synthetic Approaches

MT, DTI, T2R, and MRS scans have been analyzed using ROI approaches. In this case, ROIs are either drawn or placed in relevant regions. The ROIs assess relatively circumscribed areas

within anatomically meaningful structures, but they typically are measured on relatively low-resolution images. As a result, the anatomic specificity of such ROIs is limited. Moreover, the ROIs do not provide an assessment of changes throughout the brain. Thus, it is difficult to know from ROI-based methods how specific the findings are. As mentioned previously, a potentially useful approach, particularly with large data sets, is the use of atlas-based ROIs.

Another approach to such measurements is to use voxelwise analyses, which provide the advantage that the entire brain is sampled. However, because of large individual differences in brain structure, the validity of this method on a fine anatomic level is unclear. Nonetheless, many voxelwise studies using DTI have yielded results consistent with those found in ROI methods.[37,38] Important issues to consider include how much the data are smoothed to meet assumptions of statistical normality[80] as well as quality of intersubject image registration.[21,22]

A particular limitation across studies is the lack of consistent data acquisition and analytic strategies. In part, this occurs because of the rapid progress being made in neuroimaging. New imaging techniques are developed constantly, and different groups are working in different modalities. Nonetheless, this problem makes it difficult to compare results from different laboratories. There is a need for standardization of these strategies. This could drive multicenter studies that could address issues of 1) statistical power, 2) sample and disease heterogeneity, and 3) the reliability of methods across sites. Standardized methods also would permit the implementation of large clinical trials. The Biomedical Informatics Research Network (BIRN; www.nbirn.net) is an example of a group that is attempting such standardizations. They are currently in the process of creating DTI calibration data sets. Other data sets of this type will be welcome.

CONCLUSION

Although the etiology of geriatric depression is unknown, there is consensus that diverse processes (e.g., vascular lesions, impaired neurogenesis, inflammation, genetics), alone or in synergy, disrupt certain brain structures and confer vulnerability to depression.[2] Frontostriatal structures, the hippocampus, and the amygdala are structures whose functional disruption is thought to predispose to geriatric depression. WM pathology may interfere with functional communication among these structures and create vulnerability to geriatric depression. This model postulates that vulnerability to geriatric depression is not created by a single lesion or a failing of a single brain structure but by a state of disruption that can be created by diverse brain abnormalities. Accordingly, several models of predisposition to geriatric depression have been advanced, and each may account for a significant percentage of vulnerable patients.[1]

Central to testing hypotheses related to structurally based vulnerability to geriatric depression is the availability of neuroimaging techniques. The diversity of extant structural neuroimaging modalities allows assessment of various aspects of brain structures and WM regions implicated in geriatric depression. From the clinical point of view, structural neuroimaging has begun to identify subgroups of depressed elders resistant to traditional treatments. Understanding the underlying mechanisms can guide the development of novel therapeutic approaches.[2] The advances in technology, however, do not lessen the importance of rigorous study design. Hypothesis-specific decisions must be made about appropriate comparison groups or regions and must also consider how individual variation in lesion location, for example, might be obscured by averaging methods.

Each MR imaging approach is best suited to provide information about some aspects of brain structures but not others. However, the information derived from different imaging approaches can be complementary and lead to a coherent understanding of brain dysfunction contributing

to depression. For example, volumetric assessment demonstrated reduced caudate[9] and putamen[81] volumes in depression as well as components of frontolimbic pathways.[6] A recent study offered preliminary evidence of reduced magnetization transfer in the neostriatum of depressed elders suggesting demyelination and axonal degeneration.[67] T2 maps have shown a larger volume of WM hyperintensities in geriatric depressives compared with normal elders.[82] DTI studies documented microstructural abnormalities in WM of frontolimbic pathways. Both WM hyperintensities and microstructural abnormalities have been associated with executive dysfunction, and all three predict poor antidepressant response.[2,27–30,49,83–85] Therefore, although each approach offers limited information, converging findings support the hypothesis that frontolimbic integrity is critical for antidepressant response.

Clear hypotheses that consider the technical and interpretative strengths and limitations of the proposed methods can leverage the recent advances in structural imaging techniques despite existing technical and interpretive shortcomings. The richness of current structural neuroimaging methods allows the advancement of hypotheses that could not be conceived before these technical developments. Therefore, clear understanding of what structural neuroimaging can and cannot measure reliably, and the strategic use of such information, is central for the conceptual advancement of the field of geriatric depression.

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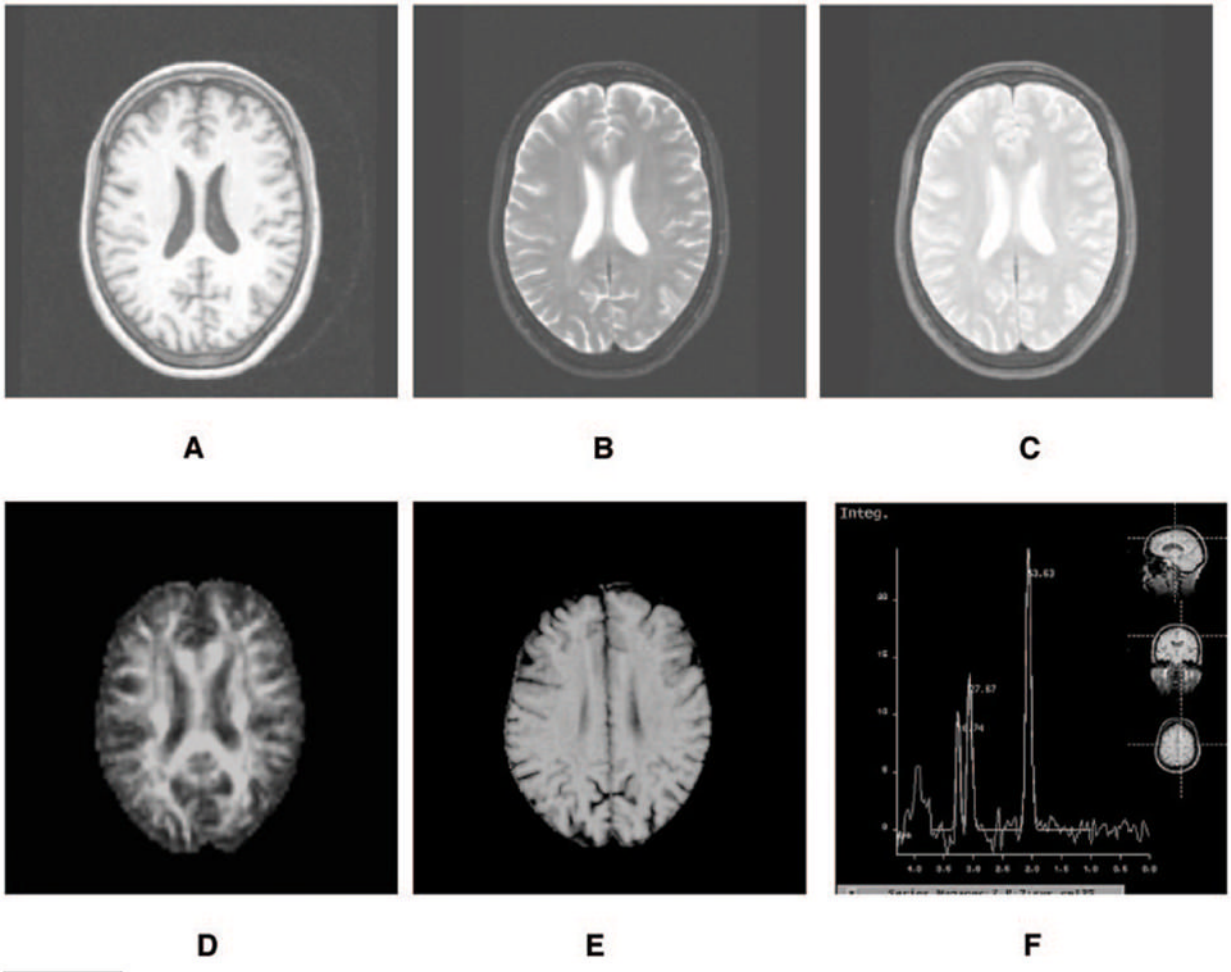

(F) The peak references are, from left to right, choline, creatine, and *N*-acetyl aspartate. The images to the right indicate voxel location (at crosshairs) in sagittal, coronal, and axial planes. Voxels are 8 mm^3.

FIGURE 1.
Images From (A) T1-Weighted, (B) T2-Weighted, (C) Proton Density-Weighted, (D) Fractional Anisotropy, (E) MTR, and (F) Spectroscopy Images

TABLE 1

Comparison of Magnetic Resonance Imaging (MRI) Methods for Assessing Structural Deficits in Geriatric Depression

Method	Strengths	Weaknesses	State of Development
MRI volumetry	Simple to implement	Time-consuming; laboratory-dependent	Commonly used
Voxelwise analyses	Highly automated	Depends highly on image registration quality	Relatively new
White matter hyperintensities	Simple to implement	Typically rated subjectively	Commonly used
DTI	Highly sensitive to pathology	Not specific as to pathology	Development of optimized sequences and analytic methods
MTR	Specific to macromolecules	Relatively low signal-to-noise ratio; not quantitative	Few studies
T2R	Specific to myelin	Time-consuming; does not yield whole brain information	Not applied to geriatric depression yet
MR spectroscopy	Chemically specific	Poor spatial and temporal resolution	Needs better multislice implementation

TABLE 2

Glossary of Magnetic Resonance Terms

Magnetic resonance image (MRI) sequences work by the application of radiofrequency (RF) pulses in the presence of a magnetic field. In proton MRI, the magnetic field serves to align a very small proportion of the protons (typically water) in the brain along the direction of that magnetic field. In the basic MR experiment, an RF pulse of an appropriate frequency perturbs the protons so that they are no longer aligned with the magnetic field. A typical RF pulse might perturb the protons perpendicular to the magnetic field. This is referred to as a 90° pulse. After the RF pulse(s) is applied, the protons return ("relax") to their original orientation, releasing energy in the process. The signal from this relaxation process serves as the basis of MRI.

- Relaxation: the return of the protons stimulated by the pulse sequence to their normal state. Relaxation occurs both along the predominant magnetic field (T1 processes) and perpendicular to that field (T2 processes).
- Relaxation time: the time for the signal to return to 63% of its original strength (for T1) and or to decrease to 37% of its strength (for T2).
- T1-weighted image: an imaging sequence typically used for anatomic scans. On these images, gray matter appears gray, white matter appears bright, and cerebrospinal fluid appears dark.
- T2-weighted image: an imaging sequence typically used to examine white matter hyperintensities. On these images, gray matter appears gray, white matter appears dark, and cerebrospinal fluid appears bright as do white matter hyperintensities.
- Proton density-weighted image: an imaging sequence typically used to detect white matter pathology. On these images, gray matter appears gray, white matter appears darker, and cerebrospinal fluid appears bright.
- Saturation pulse: an RF pulse that nulls the signal of a certain population of protons.
- Off-resonance pulse: an RF pulse that is at other than the appropriate (resonant) frequency.
- Frequency offset: the degree to which the off-resonance pulse differs from the resonant frequency.
- Echo time: the time between the application of the initial RF pulse and the recording of the MR signal.
- Fourier transform: a decomposition of a continuous signal into cosine and sine functions.
- J-coupled spectroscopy: a form of spectroscopy in which the Fourier transform of the T2 spectrum is estimated for a metabolite.
- Standard space: an anatomic space in which brain landmarks are located at standard points. In most cases, the anterior commissure is set as the zero point for each of the three Cartesian (x, y, z) spatial coordinates.