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Structural Neuroimaging of Geriatric Depression

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Abstract

There is a large literature on the neuroanatomy of late-life depression which continues to grow with the discovery of novel structural imaging techniques along with innovative methods to analyze the images. Such advances have helped identify specific areas as well characteristic lesions in the brain and changes in the chemical composition in these regions that might be important in the pathophysiology of this complex disease. In this article we review the relevant findings by each structural neuroimaging technique. When validated across many studies, such findings can serve as neuroanatomic markers that can help generate rational hypotheses for future studies to further our understanding of geriatric depression.

Keywords

Geriatric depression; late life depression; neuroimaging; MRI; white matter hyperintensities; magnetic resonance spectroscopy

Introduction

Neuroimaging has been a powerful tool in our search to identify neuroanatomic markers that provide information about the diagnostic and prognostic status of elderly patients with depressive symptoms. After decades of research, we now know several regions in the brain that are implicated in depression such as the anterior cingulate, orbitofrontal cortex and the hippocampus. Successes in delineating the neural circuits in depression have closely paralleled progress in neuroimaging techniques and advances in image analysis. Such non-invasive methods are critical as access to the tissue of interest, the brain, is otherwise impossible except in post-mortem samples.

Magnetic resonance (MR) or nuclear magnetic resonance occurs when protons in the nuclei of certain atoms (usually hydrogen) are subjected to a static magnetic field and then, exposed to a second oscillating magnetic field (pulse). During the application of the pulse, the alignment of the protons within the static magnetic field is disturbed. Following the application of the pulse, the misaligned protons relax and return to their original alignment emitting energy signals in the process. The relaxation times of different tissues vary, forming the basis of magnetic resonance imaging (MRI).⁽¹⁾ MR based methods such as MR morphometry, diffusion tensor imaging and MR spectroscopy among others are used detect

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differences between the brains of depressed and non-depressed elderly. Readers interested in further details about individual methods, their strengths and weaknesses in the context of geriatric depression are referred to the excellent review by Hoptman et al.(1)

Several differences in the structure of the brain between depressed and non-depressed elderly have been found and replicated. In this review, we summarize some of the salient structural imaging findings in geriatric depression and their implications to the neurobiology of late life depression. First we discuss morphometric studies focusing on volumetric differences; then, we discuss the findings from studies that examine white matter pathology using different imaging techniques. Finally, we summarize the biochemical correlates of depression found by magnetic resonance spectroscopy.

Volumetric Differences in Specific Brain Structures

Volumetric studies examine differences in the volumes of different brain structures among patients with depression compared with those who are not depressed. This can be accomplished either by traditional morphometric studies which focus on a predetermined, specific structure, based on previous knowledge about pathophysiology or voxel based morphometry which is not biased towards any one structure and assesses anatomical differences throughout the brain.

Morphometric studies

Most morphometric studies have utilized T1- weighted images to compare the volumes of specific structures such as the hippocampus or a particular region in the frontal cortex. These areas are called regions of interest (ROI). This hypothesis driven approach has identified several volumetric differences between depressed and non-depressed elderly.

The hippocampus—The hippocampus is one of the most commonly studied structures in depression. Studies in late life depression have repeatedly demonstrated a reduction in hippocampal volume among the depressed. (2-7) Though some studies did find negative results,(8, 9) two recent meta-analyses of MRI studies have confirmed that there is indeed an association between depression and decreased hippocampal volume.(10, 11) It has been suggested that earlier negative findings may be due either to the inclusion of the amygdala along with the hippocampus (12) or lower resolution of images. (13) Further exploration of this association has revealed that age of onset of depression correlates negatively with hippocampal volume as patients with late-onset depression had smaller hippocampal volumes when compared to those with early onset depression and controls. (4) In a younger cohort of patients followed over 3 years, depressed participants exhibited greater decline in bilateral hippocampal volume. (14)

Evidence from animal studies indicates that the mechanism underlying decreased hippocampal volumes is stress induced decrease in cell proliferation in the hippocampal region. (15, 16) Further, administration of antidepressants has been shown to prevent such stress induced suppression of neurogenesis.(17) Hippocampal volume reduction has also been shown to correlate with serotonin transporter promoter region polymorphism (5-*HTTLPR*) where individuals who were homozygous for the L allele exhibited smaller hippocampal volumes. (18) A similar correlation with the val66met polymorphism of the brain derived neurotrophic factor (*BDNF*) gene has been found to be positive in younger adults (19) but was not replicated in an elderly sample. (20) Though decrease in hippocampal volume has been proposed as an endophenotypes for depression, it is by no means specific as similar decreases occur in mild cognitive impairment and Alzheimer's dementia which are common co-morbidities in older adults with depression.(21, 22)

The amygdala—The amygdala is an important structure in emotion regulation as it identifies and integrates the emotional salience with perception. Functional studies have demonstrated that patients with depression have increased reactivity of the amygdala to negative stimuli which can be reversed by antidepressant treatment. (23) However, findings from structural studies have been conflicting as studies in younger cohorts have shown an increase in volume during the first episode of depression but not in those with recurrent episodes; further, it did not correlate with age of onset, illness duration or severity of symptoms.(24) Earlier studies included both the amygdala and hippocampus together making the results hard to interpret.(8) A meta-analysis combining amygdala volumes in depression from 14 studies found that there was a significant heterogeneity among the studies and that there was no significant association between amygdala volume and depression.(10) There is some evidence that the differences in volume might be heritable thereby making it harder to detect differences between depressed and non-depressed samples(25).

The striatum—Decreased volumes of the caudate (26) and putamen(27) which are important structures in the corticostriatal circuit were observed in depressed samples. This was later replicated in depressed elderly (28, 29) supporting the role of subcortical structures in geriatric depression. Another study found that a decrease in caudate volume predicted psychomotor slowing in older adults with depression. (30) Some studies did not find the above mentioned differences in basal ganglia volumes, however, this may have been due to differences in sample selection as the patients were younger (31) and free of medical comorbidities, specifically, cardiovascular risk.(32)

The anterior cingulate cortex (ACC)—Though the entire cingulate cortex was initially thought to be involved with emotion and behavior, the more recent understanding is that the ACC is important in emotion while the posterior part is more important in visuospatial function and memory. (33) The ACC is further subdivided into ‘affect’ and ‘cognition’ subdivisions (33) both of which are implicated in geriatric depression.(34) Some of the functions of the ACC salient to depression include conditioned emotional learning, vocalizations associated with expressing internal states, assessment of motivational content and assigning emotional valence to stimuli.(33)

In a meta-analysis of several structures involved in depression, the ACC had the largest effect, with depressed individuals having smaller ACC volumes.(10) Though not specific to elderly samples, some studies have demonstrated decreased volumes of the ACC in depressed individuals (35, 36) while others failed to do so. (37, 38) Another study that limited its sample to the elderly found significant bilateral reductions in gray matter volume in the ACC.(39)

Orbitofrontal cortex (OFC)—The OFC functions as part of a network which includes the hippocampus, amygdala and basal ganglia. It is involved in integrating sensory experiences and in emotional and reward related learning and decision making.(40) In elderly samples, compared with nondepressed subjects, depressed cohorts exhibit smaller OFC volumes.(39, 41, 42) There have been similar findings in younger adults (37, 43) though negative results have also been reported. (44) The decreased OFC volume in the depressed is consistent with postmortem findings which show a reduction in the density of pyramidal neurons in this region in the depressed.(45)

In a study that examined the functional implications of the OFC in depressed elderly, decreased left OFC volume was associated with poorer performance on the Benton Visual Retention Test (BVRT). (46) The BVRT measures perception of spatial relations and memory for newly learned material. Depressed elderly with smaller left OFC volumes made

more preservative errors and scored lower on the overall test.(46) Further, smaller medial orbitofrontal gyri volumes was found to be associated with impairment in both basic as well as instrumental activities of daily living.(47) Though no causal inferences can be made from either of the above cross sectional studies, they do expand our current understanding of the mechanisms that underlie cognitive dysfunction and functional impairment in depression.

Voxel Based Morphometry

Voxel based morphometry (VBM) is a highly automated method with a hypothesis free approach, not requiring *a priori* assumptions about the relevance of specific brain regions. VBM consists of the following four steps: spatial normalization which transforms all the subjects' data into the same stereotactic space; partitioning the spatially normalized images into segments such as gray matter, white matter and CSF; preprocessing the gray matter segment to make enable further voxel-by-voxel analysis to be comparable to the ROI approach; and, comparing the segment of interest such as the gray matter between the groups voxel-by-voxel.(48) VBM is a more recently described method compared to the ROI approach and the literature in geriatric depression using this technique is still in its early stages. Results from recent studies using this technique are encouraging in that the regions that have been identified are by often those that have been identified by previous structural and functional studies. As the literature from VBM is not as voluminous as that from traditional morphometric methods, results about different brain structures are presented together in this section.

In a study of 30 depressed and 47 non depressed elderly, depressed patients were found to have smaller right hippocampal volumes compared to control subjects and the volume of the hippocampal-entorhinal cortex was inversely associated with the duration since the first episode of depression. (49) In another study, VBM revealed decreases in the volume of the right rostral hippocampus, in the right amygdala and the medial orbito-frontal cortex bilaterally.(50) Additionally, the grey matter volume of both the right and left medial orbito-frontal cortex correlated negatively with scores on the geriatric depression scale.(50)

In-patients with late-onset depression were found to have smaller volumes in several regions of grey matter including the insula and the posterior cingulate region and white matter including the subcallosal cingulate cortex, floor of lateral ventricles, parahippocampal region, insula, and the cerebellum.(51) Compared with the depressed who did not attempt suicide, those who attempted suicide had decreased grey matter and white matter volume in the frontal, parietal, and temporal regions, and the insula, lentiform nucleus, midbrain, and the cerebellum. (51)

In a study that examined first-episode remitted geriatric depression, patients with remitted depression had smaller volumes of right superior frontal cortex, left postcentral cortex, and right middle temporal gyrus and larger left cingulate gyus volume compared with healthy control subjects.(52) In patients with remitted depression, the volume of the left cingulated gyrus correlated negatively with scores on the Rey Auditory Verbal Learning Test and delayed recall(52) providing further evidence that specific brain regions involved in depression might also be involved in cognitive impairment seen so often in the depressed elderly.

A limitation of the aforementioned studies is their small sample size which range from thirty-four (50) to seventy-seven.(49) Though many of the published studies have found significant associations, negative findings have also been reported (53) and larger sample sizes that could clarify these discrepancies are needed. False positives are an inherent problem in any technique where the number of comparisons is large and the sample size small; as in the case of VBM, however, several statistical methods to control for this have

been described. (48, 54) Another disadvantage that might be specific to geriatric depression is that this technique does not differentiate between vascular and degenerative causes of differences in regional brain volume. Despite the above limitations, early results are promising and VBM has the potential to identify new structural variations that could expand our current understanding of geriatric depression.

White Matter Pathology

White matter hyperintensities (WMH) are thought to be caused by small, silent cerebral infarctions. (55) Such silent cerebral infarctions were observed in 65.9% of patients with early or presenile-onset depression and 93.7% of those with late onset depression.(55) Early observations that older individuals with depression have a greater severity of clinically silent ischemic disease which were observable as hyperintense lesions on MRI scans(56) as well as clinical characteristics such as increased cognitive dysfunction(57) led to the advent of the “vascular depression hypothesis”.(58) White matter hyperintensities can be detected by various structural imaging methods including T2 weighted MRI scans, diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI).

Findings from T2 MRI studies

On T2-weighted MRI studies, the hyperintense signals are present in the white matter and can be classified into three major groups- periventricular hyperintensities (PVH), deep white matter hyperintensities (DWMH) and subcortical hyperintensities (SCH). Older depressed individuals have consistently been found to have more white matter hyperintensities than older healthy controls without depression.(59-63) Further, such lesions are more common in late-onset depression compared with early onset depression. (56) In a cohort of post stroke patients, those who developed post-stroke depression, were more likely to have severe DWMH (12.8% vs. 1.3%; $p=0.009$). (64)

Beyond just diagnosis and classification, white matter hyperintensities have been shown to be important in the course of illness and outcome of depression as subcortical white matter lesions were associated with occurrence, persistence, worsening and severity of depressive symptoms. (65, 66) Additionally, greater progression of white matter lesions was associated with poorer treatment outcomes as depressed elderly who had greater WMH volume did not achieve or sustain remission when compared to depressed elderly who had lower WMH volume.(67) Even in the absence of overt cerebrovascular disease, time to relapse was shorter in those who had severe deep white matter lesions.(68)

White matter hyperintensities have also been shown to predict response to antidepressant treatment. WMH burden predicted MADRS scores over a 12-week course of sertraline. Further, WMH correlated with neuropsychological testing measures which also predicted depression outcome with treatment, and both these variables correlated with the Framingham vascular risk factor scores, supporting the vascular depression hypothesis.(69) In another study, patients with depression who failed to remit after a 12-week controlled trial of escitalopram had greater MRI signal hyperintensity burden compared to those who remitted as well as elderly comparisons but, there was no difference in signal hyperintensity burden between those who remitted and elderly control subjects.(70)

Based on the evidence that vascular depression can confer risk for adverse outcomes and is produced by a pathology that separates it from other forms of depression, it has been argued that “subcortical ischemic depression” be considered as a unique and valid diagnosis corresponding to the “vascular depression” hypothesis.(71) In a more recent study replicated in two independent clinical samples, deep white matter hyperintensities was found to be the

most accurate marker for classifying depression into vascular vs. non-vascular depression. (72)

Diffusion tensor neuroimaging

Diffusion tensor imaging is an MRI based method that measures the self-diffusion of water which can be isotropic, when it occurs equally in all directions when no barriers are present, and anisotropic when the diffusion of water tends to follow along external barriers.(1) White matter tracts in the brain form organized barriers along which water can diffuse making the flow anisotropic. When such tracts are disrupted, the diffusion will be less anisotropic. Fractional anisotropy (FA) is a common measure used to characterize the integrity of the neural circuit. Using measures such as FA and apparent diffusion coefficient, DTI can help further our understanding of white matter pathology in geriatric depression by enabling researchers to locate and quantify the structure and orientation of cerebral white matter tracts.

In one of the earlier studies, regions with hyperintensities in the depressed elderly showed increase apparent diffusion coefficient and decreased fractional anisotropy when compared with normal regions though there was no significant difference in diffusion characteristics between the depressed and non depressed. (73) A more recent study showed significantly lower fractional anisotropy in the right superior frontal gyrus white matter of depressed patients. (74) Another study of one hundred and six depressed and eighty-four non depressed elderly participants found that depressed patients had significantly lower fractional anisotropy in the white matter lateral to the right anterior cingulate cortex, bilateral superior frontal gyri and the left middle frontal gyrus.(75) Such findings have been replicated in different populations: in a Chinese sample, late life-depression was associated with decrease fractional anisotropy in the frontal (superior and middle frontal gyrus), and temporal (right parahippocampal gyrus) regions.(76)

Diffusion anisotropy was lower in several regions of the brain including right superior frontal gyrus, left inferior frontal gyrus, left middle temporal gyrus, right inferior parietal lobule, right middle occipital gyrus, left lingual gyrus, right putamen and right caudate in patients with first-episode remitted geriatric depression.(77) Though most studies have concentrated on DTI imaging of white matter pathology, a recent study used DTI to examine the integrity of normal appearing white matter and found that depressed elderly had widespread abnormalities in DTI measures in the prefrontal region. (78) These studies strengthen the evidence for the possibility that decreased fractional anisotropy could affect the connectivity of the dorsolateral prefrontal circuit and the anterior cingulate circuit resulting in disconnection of cortical and subcortical structures, thereby resulting in depression. Further, decreased integrity of white matter tracts are also associated with decreased executive function, commonly seen in late life depression.(79)

Such microstructural abnormalities have also been shown to be associated with the severity of depressive symptoms and the likelihood of remission with treatment. Higher FA values in a region 8mm below the anterior commissure-posterior commissure line correlated with lower Hamilton Depression Rating Scale scores.(80) In another study, increased FA the region 15 mm above the anterior commissure-posterior commissure plane was associated with low remission after treatment with citalopram.(81) Similarly, failure to remit with sertraline was associated with increased FA in the superior frontal gyri and anterior cingulate cortices bilaterally. (82) In another study of depression treatment, depressed patients who had decreased FA compared to non-depressed showed an increase in frontal FA after electroconvulsive treatment.(83)

Magnetization Transfer Imaging

Magnetization Transfer MRI (MT-MRI) is another MRI based method used to examine biophysical properties of brain tissue. MT- MRI utilizes the two types of water molecules present in biological tissues, free water and water bound to molecules. Proton MRI detects signal from mobile protons or free water which have longer T2 relaxation times. The T2 relaxation times of protons associated with macromolecules are too short to be detected by conventional MRI. However, coupling between the bound and free protons allows the bound protons to influence the spin state of the mobile ones. MT imaging requires two image acquisitions where the first is similar to an MRI study. The second, which is the magnetization transfer acquisition, is acquired by first saturating the bound water by an off resonance radiofrequency pulse which negates the potential for the bound water to create a signal which then creates a signal reduction relative to the first image. The difference in signal intensity between the two images is the magnetization transfer ratio (MTR).(1, 84, 85)

One of the earliest studies using MTR in late-life depression found that older depressed patients had lower MTRs in the genu and splenium of the corpus callosum, the neostriatum, and the occipital WM.(84) Of note, all of these differences were in normal appearing white matter tracts which were free of hyperintense lesions.(84) In a more recent study with a larger sample size of fifty-five older patients with depression and twenty -four comparison subjects, depressed patients had lowed MTRs in multiple left hemisphere frontostriatal and limbic regions, including white matter lateral to the lentiform nuclei, dorsolateral and dorsomedial prefrontal, dorsal anterior cingulate, subcallosal, periamygdalar, insular, and posterior cingulate regions, complementing previous findings from volumetric and DTI studies.(86)

Magnetic Resonance Spectroscopy and biochemical Correlates of Depression

Magnetic Resonance Spectroscopy (MRS) is another non-invasive imaging method which unlike all the other techniques described above, characterizes chemical and cellular features in vivo. In the brain, concentrations and mobility of low molecular weight chemicals can be measured as spectral peaks which can then be used to identify abnormalities in brain regions that appear normal in MRI. (87) The measurements are usually not absolute and are presented as the ratio of the measure of interest to a standard metabolite such as creatine. (1)

In a preliminary study of twenty elderly patients with depression and 18 comparison subjects, myo-Inositol (mI)/creatine (Cr) and choline (Cho)/Cr ratios were significantly higher in the frontal white matter in the depressed group.(88) A subsequent study explored the relationship between these metabolites in a voxel in the dorsolateral cortex, and cognitive function in the elderly. Among nondepressed subjects, cognition positively correlated with Cho/Cr and mI/Cr and negatively correlated with phosphocholine/Cr in four domains of verbal learning, recognition, recall, and hypothesis generation, whereas, depressed patients did not have consistent relationships between the metabolites.(89) Thus imaging studies have revealed both neuroanatomic as well as biochemical changes in the frontostriatal circuitry that may be associated with cognitive changes in depression.

In a more recent study, patients with late-life major depressive disorder had a significantly lower N-acetyl aspartate (NAA)/Cr ratio in the left frontal white matter, and higher Cho/Cr and mI/Cr ratios in the left basal ganglia when compared with the control subjects.(90) Further, the myo-Inositol correlated with global cognitive function. (90) In older patients whose depression responded to treatment, concentrations of total NAA, choline, and creatine were significantly decreased in the prefrontal cortex while, concentrations of NAA and myo-Inositol were significantly elevated in the left medial temporal lobe.(91) These authors concluded that reduced neuronal phospholipid, and energy metabolism in the prefrontal

cortex persists in clinically improved depression and that the elevated metabolites in the temporal lobe might be associated with glial cell changes in the amygdala.(91)

MRS of the brain before antidepressant treatment of post stroke depression, followed by a second MRS six months after, revealed changes in metabolites in various regions.(92) Before treatment, NAA/creatine ratios in the bilateral hippocampus and thalami were significantly lower in post stroke depression patients than in controls. Choline/creatine (Cho/Cr) ratios were significantly higher in the bilateral hippocampus and left thalamus in post stroke depression patients than in controls. Further, Hamilton Depression Rating Scale scores significantly correlated with the Cho/Cr ratios in the left and right hippocampus. After treatment, patients had significantly higher NAA/Cr ratios in the left hippocampus and bilateral thalami and significantly lower Cho/Cr ratios in bilateral hippocampus and left thalamus.(92) This longitudinal study sheds light on some of the biochemical changes that occur in the brain with antidepressant treatment. The authors postulate that these changes might be due to the neurotrophic effects of antidepressants.

Conclusions

This review has highlighted some of the important findings in geriatric depression from structural imaging. Depression is a complex disease with multiple etiologies as evidenced by the many structures involved and the different kinds of lesions that are associated with the illness. Evolution of imaging methods and the refinement of its techniques have enabled the identification and assessment of many potential biomarkers and endophenotypes in depression. The future of imaging research will be multimodal, in which identified structural variations will be used to inform and improve hypotheses for further testing and confirmation by other techniques. In the case of the orbitofrontal cortex, an initial neuroanatomic difference of decreased volume among the depressed (42) was then studied with cognitive neurological testing which found that this volumetric difference was associated with decreased performance in tests.(46) Further, lower OFC volumes were associated with functional disability.(47) Thus findings from imaging studies can then be explored using different research methods to interrogate the varied aspects of depression and the many negative outcomes it portends. When consistently replicated, such findings might serve as imaging phenotypes that can identify vulnerability and predict treatment efficacy. (93)

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