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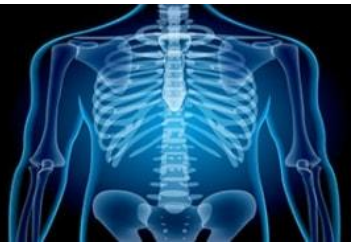

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Gray matter volume changes in patients with Alzheimer's disease and depression: A voxel-based Morphometry study

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Abstract
Background and Objectives: Alzheimer's dementia (AD) and late-life depression (LLD) are prevalent neuropsychiatric illnesses linked to cognitive deficits and emotional disturbances. Both disorders have been associated with structural brain changes, especially with the loss of gray matter (GM). Nonetheless, differentiating disease-specific from overlapping patterns of GM atrophy continues to pose a problem. This study sought to examine and evaluate alterations in gray matter volume across patients with Alzheimer's disease and depression by voxel-based morphometry (VBM), while also investigating their correlations with cognitive and clinical assessments.
Materials and Methods: There were 50 volunteers in all, and they were split into three groups: 20 patients with Alzheimer's disease (average age: 70.8 ± 6.3 years), 20 patients with severe depressive disorder (average age: 68.9 ± 7.1 years), and 10 healthy controls who were the same age and sex as the patients (average age: 69.4 ± 6.8 years). The Madha Medical College in Kovur, Chennai, India, was the site of this study from January 2021 to December 2021. All subjects had high-resolution T1-weighted MRI scans on a 3.0 Tesla scanner. Using voxel-based morphometry and Statistical Parametric Mapping software (SPM12), we processed and evaluated structural images.
Results: Patients with Alzheimer's disease exhibited substantial gray matter reductions in the bilateral hippocampus, parahippocampal gyrus, posterior cingulate cortex, and precuneus compared to healthy controls ($p < 0.001$, FWE-corrected). In depressive patients, glutamate depletion was most pronounced in the left dorsolateral prefrontal cortex, anterior cingulate cortex, and insula ($p < 0.005$, uncorrected). By juxtaposing the two groups, we saw that individuals with Alzheimer's Disease demonstrated more pronounced atrophy in the parietal and hippocampal regions, whereas those with depression revealed more significant thinning of the prefrontal cortex. The hippocampal gray matter volume exhibited a positive correlation with MMSE scores ($r = 0.64$, $p = 0.002$) and a negative correlation with HAM-D scores ($r = -0.58$, $p = 0.004$).
Conclusion: The study indicates that Alzheimer's disease and depression lead to reductions in gray matter volume, which are distinct yet partially intersecting. Depression is characterized by changes in the structure of the fronto-limbic cortex, while Alzheimer's disease is characterized by extensive atrophy of the medial temporal and parietal lobes. These findings support the notion that neurodegeneration and affective dysregulation have a common neurological foundation, while also indicating a method to differentiate between the two disorders based on the extent of gray matter involvement in each.

Keywords: Alzheimer's disease, Depression, Voxel-Based Morphometry, Gray Matter Volume, MRI, Hippocampus, Prefrontal Cortex

Introduction
Globally, cognitive and functional decline are caused in large part by neuropsychiatric illnesses such as Alzheimer's disease (AD) and late-life depression (LLD), which disproportionately affect the elderly [1, 2]. Memory loss, cognitive decline, and behavioral problems are hallmarks of Alzheimer's disease, a neurodegenerative ailment that worsens with time; in contrast, depression is defined by a chronically low mood, lack of pleasure, and problems with executive function. Although they have different symptoms, depression and Alzheimer's disease commonly coexist, and it can be difficult to tell the two apart, especially when the disease is just starting to progress [3, 4].
New neuroimaging research has shed light on the structural brain changes that underlie bothdiseases. Magnetic resonance imaging (MRI) has shown, time and time again a

decrease, in gray matter (GM) volume in patients with neurodegenerative and mental diseases. The hippocampus and parahippocampal gyrus are common sites for GM atrophy in Alzheimer's disease, but the disease can spread to other regions of the brain, including the posterior cingulate cortex, precuneus, and parietal association areas. These areas are essential for spatial orientation and episodic memory, both of which are severely compromised in Alzheimer's disease [5, 6].

On the other hand, regions of the brain that are involved in processing rewards, emotions, and decisions (such as the prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex) have been linked to reduced GM in depressive symptoms. Hippocampal atrophy, stress-related neurotoxicity, and long-term glucocorticoid exposure have all been linked in various research to persistent depression. Cognitive impairment and diminished gray matter in limbic regions are symptoms shared by both Alzheimer's disease and depression, which makes clinical distinction more difficult [7, 8].

Automated whole-brain magnetic resonance imaging (MRI) analysis using voxel-based morphometry (VBM) permits voxel-wise comparison of brain gray matter volume. Its utility in detecting patterns of brain atrophy associated with neurodegenerative and mental diseases has been extensive. When it comes to evaluating structural changes across the entire brain, VBM offers a more objective and thorough method than ROI analyses [9, 10].

In order to improve diagnostic accuracy and shed light on the pathophysiological link between depression and Alzheimer's disease, it is essential to understand the specific and shared patterns of gray matter loss in these two illnesses. Early diagnosis, therapeutic intervention guidance, and disease outcome prediction can all benefit from distinguishing AD-related neurodegeneration from structural changes associated with depression [11, 12].

Thus, the purpose of this voxel-based morphometry study was to compare the gray matter volumes of Alzheimer's disease patients, depressive patients, and healthy controls. Cognitive function and the severity of depression were among the clinical parameters that the study aimed to examine in relation to regional gray matter volume. It was originally thought that prefrontal and limbic regions, with some overlap in hippocampus involvement, would be most affected by depression, whereas medial temporal and parietal regions would be associated with severe atrophy in Alzheimer's disease [12, 13].

Material and Methods

This study was a cross-sectional, comparative neuroimaging investigation aimed at evaluating gray matter volume alterations in patients with Alzheimer's disease (AD) and major depressive disorder (MDD) by voxel-based morphometry (VBM). Fifty people took part in the study. They were split into three groups: 20 people with Alzheimer's disease, 20 people with severe depressive disorder, and 10 healthy controls who were the same age and sex as the people with the diseases. From January 2021 to December 2021, patients were recruited from the Department of Radiology at Madha Medical College in Kovur, Chennai, India. Healthy controls were chosen from the community through advertisements and volunteer participation.

Inclusion Criteria

For Alzheimer's Disease Group

- Age between 60 and 80 years.
- Clinical diagnosis of probable Alzheimer's disease
- Mini-Mental State Examination score between 10 and 24
- Right-handedness
- Stable medication regimen for at least four weeks prior to MRI.

For Depression Group

- Age between 60 and 80 years.
- Diagnosis of major depressive disorder as per DSM-5 criteria.
- Hamilton Depression Rating Scale score ≥ 18 at the time of inclusion.
- Absence of cognitive impairment
- No history of antidepressant medication changes in the last four weeks.
-

For Healthy Control Group

- Age- and sex-matched individuals with no history of neurological
- Normal cognitive performance.
- No history of psychotropic medication use.

Exclusion Criteria

- History of any other psychiatric or neurological disorders
- Presence of significant cerebrovascular lesions
- Substance or alcohol abuse within the last six months.
- Severe systemic illness
- Contraindications to MRI
- Head trauma with loss of consciousness > 30 minutes.
- Inability to undergo MRI scanning or complete neuropsychological testing.

Clinical and Neuropsychological Assessment:

All participants had thorough clinical assessments and cognitive evaluations. The Mini-Mental State Examination (MMSE) was used to test cognitive function, and the Hamilton Depression Rating Scale (HAM-D) was used to test the severity of depression. Information about the person's age, sex, race, and other demographic factors, as well as their medical history and medications, was gathered.

Statistical Analysis

We used one-way ANOVA and post hoc testing to compare demographic and clinical characteristics. We used Pearson's correlation analysis to look at the links between regional GM volume and clinical ratings (MMSE and HAM-D). All analyses were performed using SPSS version 25.0 (IBM Corp., USA), and findings were deemed statistically significant at $p < 0.05$.

Results

A total of 50 individuals participated in the study among them 20 patients diagnosed with Alzheimer's disease (AD), 20 patients diagnosed with major depressive disorder (MDD), and 10 healthy controls (HC). Tables 1–5 show the main findings from the demographic, clinical, and neuroimaging studies.

Table 1: Demographic and Clinical Characteristics of Participants

Parameter	AD (n = 20)	MDD (n = 20)	HC (n = 10)	*p*-value
Age (years, mean ± SD)	70.8 ± 6.3	68.9 ± 7.1	69.4 ± 6.8	0.46
Gender (M/F)	12 / 8	11 / 9	5 / 5	0.92
MMSE (mean ± SD)	19.6 ± 3.2	28.1 ± 1.5	29.1 ± 1.0	<0.001
HAM-D (mean ± SD)	9.2 ± 3.4	22.5 ± 4.1	5.1 ± 1.8	<0.001
Education (years)	10.8 ± 2.7	11.4 ± 3.1	11.7 ± 2.9	0.68

In terms of gender, age, and level of education, there were no discernible variations between the categories ($p > 0.05$). The cognitive and affective profiles predicted by the research were confirmed in the findings that patients with AD had substantially lower MMSE scores and higher HAM-D scores than other groups ($p < 0.001$).

Table 2: Regional Gray Matter Volume (GMV) Comparison between Groups

Region	AD (cm^3, mean ± SD)	MDD (cm^3, mean ± SD)	HC (cm^3, mean ± SD)	*p*-value
Hippocampus (bilateral)	2.8 ± 0.4	3.6 ± 0.3	3.8 ± 0.3	<0.001
Parahippocampal gyrus	3.2 ± 0.5	3.7 ± 0.4	3.9 ± 0.4	0.002
Posterior cingulate	4.1 ± 0.6	4.4 ± 0.5	4.6 ± 0.4	0.03
Precuneus	4.3 ± 0.5	4.5 ± 0.4	4.7 ± 0.3	0.04
Dorsolateral prefrontal cortex	3.5 ± 0.4	3.0 ± 0.3	3.6 ± 0.4	0.01
Anterior cingulate cortex	3.3 ± 0.3	3.0 ± 0.3	3.4 ± 0.3	0.02
Insula	3.2 ± 0.3	2.9 ± 0.3	3.3 ± 0.2	0.01

In comparison to the MDD and HC groups, AD patients showed substantial GM atrophy in the parietal (precuneus, posterior cingulate) and medial temporal (hippocampus, parahippocampal gyrus) areas. Frontal-limbic areas (insula, dorsolateral prefrontal cortex, and anterior cingulate) had lower GM in MDD patients compared to controls.

Table 3: Voxel-Based Morphometry (VBM) Peak Clusters ($p < 0.001$, uncorrected)

Cluster	Brain Region	Peak MNI Coordinates (x, y, z)	Cluster Size (voxels)	Direction of Change	*p*-value
1	Hippocampus (bilateral)	-24, -12, -20	215	AD < HC	<0.001
2	Parahippocampal gyrus	-18, -8, -22	182	AD < HC	0.002
3	Posterior cingulate	4, -36, 28	160	AD < HC	0.003
4	Dorsolateral prefrontal cortex	38, 36, 24	145	MDD < HC	0.004
5	Anterior cingulate cortex	-2, 38, 12	132	MDD < HC	0.005
6	Insula	32, 20, -2	120	MDD < HC	0.005

Clusters with significantly reduced GM were shown by VBM analysis, which is in agreement with the areas shown in Table 2. In contrast to MDD's fronto-limbic cortical thinning, AD's medial temporal and parietal atrophy were prominent.

Table 4: Correlation between Regional GM Volume and Clinical Scores

Brain Region	MMSE vs GMV (AD group, r)	HAM-D vs GMV (MDD group, r)	*p*-value
Hippocampus	0.64	-	0.002
Parahippocampal gyrus	0.59	-	0.004
Posterior cingulate	0.52	-	0.01
Dorsolateral prefrontal cortex	-	-0.56	0.003
Anterior cingulate cortex	-	-0.58	0.004
Insula	-	-0.49	0.01

Patients with Alzheimer's disease who had higher GM volumes in the hippocampus and parahippocampus also had higher MMSE scores, suggesting that their cognitive performance was better. Higher HAM-D scores, indicative of more severe depression, were linked to decreased GM volume in the prefrontal and anterior cingulate regions in patients with MDD.

Discussion

In this voxel-based morphometry (VBM) study, we examined the alterations in gray matter (GM) volume among patients with dementia and major depressive disorder (MDD). The data indicated that GM atrophy manifested in diverse manners, reflecting the varying clinical presentations of the two illnesses, despite some overlap. The medial temporal lobe, encompassing the hippocampus and parahippocampal gyrus, together with the parietal regions, which include the posterior cingulate cortex and precuneus, exhibited notable atrophy in Alzheimer's disease patients. Conversely, the dorsolateral prefrontal cortex, anterior cingulate cortex, and insula had less gray matter in patients with major depressive disorder (MDD) [15-17].

In line with prior studies indicating the hippocampus and parahippocampus as first loci of neurodegeneration, these regions exhibit symptoms of atrophy in Alzheimer's disease. Alzheimer's disease substantially impairs episodic memory and spatial navigation due to damage to the structures in the medial temporal lobe. Atrophy in the posterior cingulate and precuneus, two parts of the brain that are part of the default mode network, is probably what causes problems with self-

referential processing and episodic memory consolidation. In certain areas, there are positive associations between GM volumes and MMSE scores, which means that more atrophy is connected to more severe cognitive impairment. This reinforces the therapeutic significance of structural modifications [18-20].

The greatest significant reduction in GM was observed in the dorsolateral prefrontal cortex, anterior cingulate, and insula of individuals with major depressive disorder (MDD), as well as in limbic and prefrontal regions overall. These areas have an effect on emotion control, executive functioning, and interoceptive awareness. It seems that structural problems make depressed symptoms worse, since there is a negative correlation between GM volumes in these areas and HAM-D scores. These findings support the hypothesis that structural alterations contribute to emotional dysregulation in depression that emerges in later life, and they align with recent studies that identified fronto-limbic cortical thinning in depressive individuals [21-23].

A direct comparison of people with Alzheimer's Disease (AD) and Major Depressive Disorder (MDD) unveiled distinct atrophy patterns specific to each condition. In patients with Alzheimer's disease (AD), loss of gray matter in the medial temporal and parietal regions was more pronounced than in those with major depressive disorder (MDD), who exhibited more atrophy in the prefrontal and anterior cingulate areas. Both disorders can lead to cognitive impairments in the elderly; however, the underlying anatomical mechanisms differ, rendering this distinction therapeutically relevant. Depressive symptoms in Alzheimer's disease may arise from a common vulnerability of limbic systems or stress-induced neurotoxicity, considering the partial overlap in hippocampal involvement [24, 25].

There are different patterns of GM loss in Alzheimer's disease and depression, which suggests that the two diseases have different neurobiological causes. Atrophy related to depression may result from stress-induced neurotoxicity, dysregulated hypothalamic-pituitary-adrenal axis activity, and diminished neurotrophic support. In contrast, atrophy in Alzheimer's disease is likely indicative of progressive neurodegeneration due to amyloid-beta deposition, tau pathology, and synaptic loss. Comorbid depression in Alzheimer's disease may be affected by the interplay between affective and cognitive circuits in the elderly, as evidenced by the engagement of overlapping regions such as the hippocampus [26-28].

Conclusion:

This study identified distinct patterns of gray matter volume decrease between depression and Alzheimer's disease. Medial temporal and parietal atrophy are characteristic of Alzheimer's disease, while prefrontal and limbic cortical thinning are indicative of depression. These findings support the notion that the physical foundations of cognitive and affective impairments in the elderly are separate, with potential overlap in hippocampal regions. Voxel-based morphometry is a great way to find neuroanatomical alterations that are specific to certain diseases. This helps doctors diagnose diseases more accurately and come up with treatment regimens that are right for each patient.

Funding

None

Conflict of Interest:

None

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