Differential Diagnosis of AD, PDD, and DLB Using Structural MRI Brain Imaging: An Unparalleled Precision

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As people grow older, Alzheimer's Disease (AD), Parkinson's Disease with Dementia (PDD), and Dementia with Lewy Bodies (DLB) become an increasing risk. While our healthcare industry is working to improve and innovate better diagnostic criteria, the diagnostic differentiation among these diseases remains substantially difficult due to overlapping clinical and neuropathological characteristics This review details the application and findings from Structural Magnetic Resonance Imaging (sMRI) studies differentiating AD, PDD, and DLB to provide deeper knowledge about the commonalities and contrasts among conditions, highlight the potential for the clinical application of promising MRI techniques, and emphasize necessary areas for future research. Today, sMRI stands at the forefront of a revolution in dementia diagnosis, offering a practicable, noninvasive, and efficient framework in distinguishing and differentiating among dementia types and providing a heartbeat of hope to millions suffering from dementia.

Keywords: Biomedical and Health Sciences, Dementia; Alzheimer's Disease, Parkinson's Disease with Dementia, Dementia with Lewy Bodies, Structural MRI

1 Introduction

1.1 Dementia Worldwide

Each year, 10 million new cases of dementia arise worldwide [1]. In fact, every 3.2 seconds, a person falls victim to the grasp of this spectrum of deadly diseases. The most common forms include Alzheimer's Disease (AD), Parkinson's Disease Dementia (PDD), and Dementia with Lewy Bodies (DLB). Worldwide, Alzheimer's accounts for 60-70% of cases, while DLB represents 15% of cases at autopsy, and Parkinson's affects nearly 10 million patients [1,2]. As one ages, the risk of progression to dementia in PD only increases and has been shown to affect over 70% of PD patients in an 8-year prospective longitudinal study, 6 times the rate in healthy control subjects [3].

1.2 Differential Diagnosis

The primary challenge in dementia research and clinical practice lies in accurately distinguishing between AD, PDD, and DLB. Due to significant overlaps in clinical and neuropsychological symptomology, differentiating AD, PDD, and DLB from each other is far from straightforward. Today, the clinical process of dementia diagnosis involves analyzing medical history, assessing physical and neurological function, and taking neuroimaging tests to reach a conclusive diagnosis. However, even among experts, diagnostic accuracy for Alzheimer's disease is 77% [4]. DLB is frequently misdiagnosed, with only one third of patients correctly identified due to its clinical similarity mainly with AD. One study has shown 61% of autopsy-confirmed AD and DLB cases were initially diagnosed as AD alone, and misdiagnosis rates between AD, PDD, and DLB can reach almost 50% [5]. That's because of a variety of reasons, primarily concerning pathological similarities among dementias. AD and DLB share clinical and pathological features that contribute to misdiagnoses especially at the onset of the pathology, such as cognitive decline, verbal initiation, language, emotion, and visuospatial awareness [6]. Neuropathologically, DLB and AD share the presence of amyloid plaques and neurofibrillary tangles (NFTs), which are hallmark features of AD. Up to 87% of DLB patients have a moderate to abundant amount of cortical amyloid plaques, or clumps. The sensitivity for diagnosing pure DLB is only about 32%, and it drops even lower to 12% when DLB coexists with AD. With such alarming statistics, it is clear that we must implement an improved diagnostic criteria for differential diagnosis as soon as possible [4,7].

DLB and PDD are often clinically hard to differentiate particularly in early stages, because they share many motor symptoms such as bradykinesia or slow movement, rigid muscles, and frequent tremors at the onset of the disease. They are both categorized under "synucleinopathy" characterized by the presence of "Lewy Bodies," or an accumulation of alpha-synuclein (α-syn) proteins. One factor that is distinguishable, though, is the timing of when the symptoms first arise. In PDD, cognitive decline happens after the motor difficulty symptoms arise, but

in DLB, cognitive impairment commonly happens with or even before motor difficulty symptoms occur[7]. Additionally, while both conditions share Lewy body pathology, patterns of α-syn protein clumps throughout the brain differ. For instance, while Lewy bodies are mostly confined to areas like the brainstem and substantia nigra for PDD, they can extend to the neocortex and limbic areas when it comes to DLB. Given the pathological similarities, disease-modifying treatment is more likely to succeed when started as early as possible. Thus, early diagnosis is a priority to mitigate the progression of PDD and DLB. However, since it is equally as important to examine the differentiation across all stages of the disease, this review aims to address differentiation of disease pathology in early to late stages.

AD, DLB, and PDD are still largely underdiagnosed conditions. It is therefore crucial to focus on neuroimaging tools that can help to clearly distinguish DLB from AD to improve differential diagnosis by providing additional information on brain changes. This paper aims to provide a thorough literature review on enhancing diagnostic accuracy of dementia such as AD, PDD, and DLB by utilizing various sMRI methods and approaches to identify differentiable neuroanatomical patterns of atrophy among these diseases. The current study makes use of systematic review and meta-analysis of pre-existing sMRI data to investigate neuroanatomical patterns within AD, PDD, and DLB. It will further explore the outcome of prior experiment results and evaluate the efficiency and potential of different methods of sMRI diagnosis. Knowing the pathological and clinical characteristics of the most frequent forms of dementia and exploring new sMRI diagnostic protocols is necessary in order to alleviate and minimize the detrimental impact of dementia on patients' lives.

1.3 Structural MRI

In this review, we will focus on Structural MRI (sMRI) neuroimaging and its ability to differentiate AD, PDD, and DLB. MRI involves the use of strong magnetic fields to change proton orientation in the body which can be excited using pulses of radiofrequency waves to emit energy that can be converted to signals from the atomic nuclei and applied to images as shown in Figure 1. The obtained image provides key details of the brain, such as Gray and White matter, Cerebrospinal Fluid (CSF), Cortical Thickness, Brain Atrophy, and Structural Integrity. Its post-processed images are particularly valuable in quantifying brain atrophy, specifically by mapping measurements of brain volume and cortical thickness. The process known as Volumetry measures the size of different brain regions while Cortical Thickness Analysis (CTA) involves analyzing the density of the brain's outer layer by calculating the distance between the inner and outermost edges of cerebral cortical gray matter.

As shown in Table 1, current quantitative sMRI studies reveal distinct brain atrophy patterns in AD. Early-stage AD features

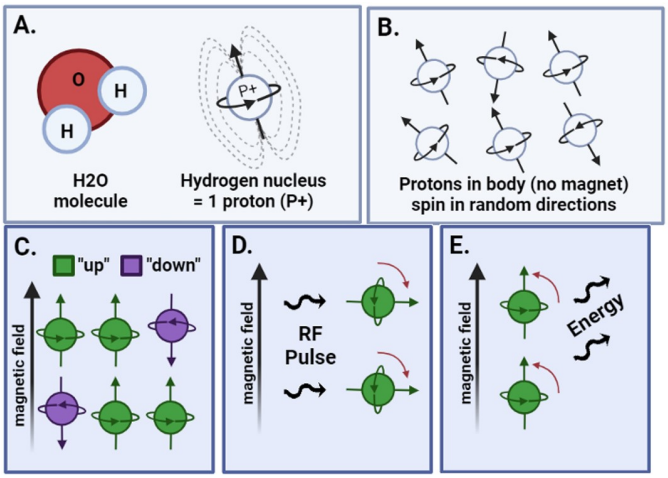

Fig. 1 MRI Mechanism. A. Hydrogen atoms of water molecules are involved, which each represent a proton with positive charge. B. Before the magnetic field is active, the protons in the body spin randomly. C. Protons align along their axis with magnetic field of the scanner. D. Turn on radiofrequency pulse; unpaired "up" protons rotate out of alignment. E. Turning off pulse makes protons realign with magnetic field, releasing energy that is measured. Created using BioRender

four morphometric subtypes, including hippocampal, predominant, and hippocampal-temporo-parietal atrophy patterns[8]. In addition, progression follows a pattern, with atrophy beginning in the hippocampus and amygdala, then spreading to the middle temporal gyrus and entorhinal cortex, followed by subcortical structures, and finally the frontal, cingulate, and parietal cortices. Thalamic volume loss indicates early cognitive decline in mild cognitive impairment (MCI) - a pre-diagnostic stage of AD while hippocampal and temporal atrophy are more evident in later stages[9]. The MRI-detected atrophy patterns along with AD stages are consistent with the pathological patterns of amyloid or NFTs deposition. Given these advantages, sMRI has notable limitations that is important to be acknowledged. For instance, sMRI typically isn't a stand-alone diagnostic tool in a clinical setting for dementia, but rather as a suggestive criterion for doctors to identify the atrophy patterns in the brain and match it with its corresponding disease type. Although it is effective at identifying and measuring specific patterns of brain atrophy, it lacks sensitivity due to early synaptic dysfunction or subtle cellular-level abnormalities that precede structural changes, and atrophy patterns may sometimes overlap across different diseases, meaning it might fall short in performance when detecting preclinical or earlier stages of dementia. Additionally, it is important to note the variability in sMRI protocols like different magnetic field strengths and scanner specific parameter setups – meaning the heterogeneity across different MRI applications could pose a challenge for consistent reproducibility and standardization of

findings[8]. Furthermore, despite the rise of Machine Learning applications into neuroimaging, implementation and translation of models into actual clinical practice remains difficult due to concerns over limited or biased dataset diversity and not sufficient accuracy rates, it will be hard for doctors with the correct expertise to navigate and trust the application of these models into real neuroimaging clinical data.

PDD is marked by distinct neuroanatomical patterns identified through sMRI. In early PD, increased iron content in the substantia nigra and striatum is indicated by higher R2* values[10]. As PD progresses to mild cognitive impairment, cortical thinning appears in areas related to memory, semantic processing, and visuospatial functions[11]. Finally, in PDD, usually developing several years after the onset of PD, more thinning occurs in the medial frontal, posterior cingulate, precuneus, and temporal regions, along with significant gray matter volume reductions in the hippocampus, thalamus, and anterior cingulate[12]. As PDD is often developed in late stage of PD, sMRI could identify the early sign of PD together with the atrophic patterns that are seen in cognitive impairment or dementia.

sMRI studies have also revealed distinct brain atrophy patterns in DLB as well. In DLB, patients show more thinning in the right anterior insula compared to pro-AD patients in early stages, who exhibit greater thinning in bilateral parietal and left parahippocampal gyri. As DLB progresses later on, cortical thinning occurs mainly in the right temporo-parietal junction, insula, cingulate, orbitofrontal, and lateral occipital cortices. DLB typically shows subcortical atrophy with relative preservation of the medial temporal lobe compared to AD[13]. In addition, visual assessment of medial temporal atrophy (MTA) at the MCI stage can help differentiate patients likely to progress to AD versus DLB or remain stable[9].

2 Results

2.1 Differentiating AD and PDD

AD and PDD present distinct neuroanatomical patterns. Recent attention has been given to machine learning AI models by implementing data classifiers into sMRI datasets, resulting in a fast, efficient, and accurate diagnosis. For example, Koikkalanien and colleagues in 2016 conducted a study differentiating AD and PDD using the volumetric and morphometric characteristics in sMRI scans[14]. They sorted T1-weighted sMRI data from 504 patients including AD, PDD, healthy controls, and some other dementias, training and testing data on a multi-class machine learning classifier to sort the data into 2 or more distinct classes, otherwise known as Multi-atlas segmentation. The final accuracy reached was 70.6%. Considering the limitations in dataset size, which could lead to lower accuracies during training and testing of the model, the relatively high accuracy of the multi-class machine learning classifier reveals how combining sMRI data with machine learning classifications holds potential for efficient and accurate differential diagnosis. The final accuracy of 70.6%, additionally, raises some concerns to its potential for clinical application as faulty misdiagnoses could risk the lives of patients. Future models should emphasize larger and more diverse datasets as well as a more robust imaging classification framework to improve the accuracy for clinical implementation.

Structural differences are a key component to consider when differentiating between the two diseases. A key detail that indicates these differences is the patterns of gray matter atrophy in the brain. Gray matter contains most of the brain's neuronal cell bodies – the spherical part of the neuron that contains the nucleus and connects to the dendrites – that bring information into the neuron and the axon, which sends information to other neurons for controlling all the functions of the cell. As dementia progresses, nerve cells in the brain die, visualized through volume loss or atrophy in the brain, disrupting their communication pathways and causing a decline in cognitive functions. Krajcovicova and colleagues in 2019 evaluated the use of gray matter atrophy biomarkers of sMRI images to differentiate AD and PDD, such as evaluating cortical thickness, Source-based morphometry (SBM), and Deformation-based morphometry (DBM), targeting specifically the hippocampus[15]. The review found that PDD, although showing more variability in its clinical presentation, had hippocampal atrophy far less severe than AD. The study concluded that the hippocampus-to-cortex ratio, a measure of hippocampal volume dictated by the amount of gray matter in the region compared to the volume of surrounding cortex, was the best biomarker quantifying the degree of hippocampal damage to differentiate between AD and PDD. Additionally, PDD patients were found with greater atrophy of subcortical regions, especially the basal ganglia, the pedunculopontine nucleus, and the basal forebrain, which are structures responsible for movement control. A limitation present in both Koikkalaninen et al. (2016) and Krajcovicova et al. (2019) is the utilization of their classifiers on single-time-point scans. It remains unclear whether the measured atrophy patterns from these scans reflect the acceleration of disease progression or the cause of variability or normal aging and whether the results could be applicable to long-term changes over time. A study by Novellino and colleagues using 3T-MRI hippocampal evaluation, or evaluating the whole brain as T1-weighted and diffusion tensor imaging, assessed the same hippocampal volume to cortex ratio in AD and PDD and found that AD patients exhibited greater volume reductions in hippocampal regions, which are critical for long-term memory[16]. Relating back to symptoms of cognitive impairment, we can see this is the case as Hippocampal atrophy can be seen even in early stages of AD, while in later stages for PDD as shown in Table 1. As the hippocampus is crucial for memory formation, we see that in AD and PDD stages with affected hippocampus regions correspond to memory losses as well. Frontal lobe degeneration and basal ganglia atrophy seen in PDD also

Table 1 Classifying AD, PDD, and DLB Characteristics

Dementia Type	Characteristics and Affected Regions	Corresponding Symptoms
AD	**Early Stage:** Hippocampal atrophy, mild cortical thinning. Affected regions: hippocampus, entorhinal cortex, temporal lobes. **Moderate Stage:** Widespread cortical thinning, atrophy spreads to parietal and frontal regions. Affected regions: parietal lobes, frontal cortex, posterior cingulate. **Late Stage:** Severe gray matter loss, hippocampal and temporal degeneration. Affected regions: hippocampus, amygdala, temporal lobes, parietal cortex [8,9].	**Early Stage:** Short-term memory issues, difficulty learning, disorientation. **Moderate Stage:** Language difficulties, impaired judgment, confusion, inability to perform complex tasks. **Late Stage:** Severe memory loss, inability to recognize family or friends, loss of motor control, need caregivers [8,9].
PDD	**Early Stage (PD):** Cortical thinning in motor areas, preserved cognition. Affected regions: substantia nigra, motor cortex, basal ganglia. **Moderate Stage:** Cognitive decline begins after motor symptoms, thinning in frontal cortex. Affected regions: frontal cortex, motor areas, hippocampus. **Late Stage:** Severe parietal and occipital thinning, relatively preserved medial temporal lobe compared to AD. Affected regions: hippocampus, frontal cortex, temporal lobes [11,12].	**Early Stage:** Motor symptoms, mild cognitive decline. **Moderate Stage:** Executive dysfunction, attention and memory issues, worsening motor symptoms. **Late Stage:** Severe motor dysfunction, marked memory loss, hallucinations, difficulty walking, speech difficulties [11,12].
DLB	**Early Stage:** Thinning in occipital and insular regions, minimal temporal lobe atrophy, early visuospatial deficits. Affected regions: occipital lobes, insula, parietal cortex. **Moderate Stage:** More pronounced parietal thinning, insular degeneration continues. Affected regions: parietal lobes, insula, posterior cingulate. **Late Stage:** Severe parietal and occipital thinning, worse than PDD, relatively preserved medial temporal lobe compared to AD. Affected regions: occipital lobes, parietal cortex, insula [13].	**Early Stage:** Visual hallucinations, fluctuating cognition, attention deficits, problems with depth perception. **Moderate Stage:** Worsening visuospatial issues, recurrent hallucinations, difficulty understanding spatial relationships. **Late Stage:** Increased hallucinations, motor symptoms similar to Parkinsonism, frequent falls [13].

correspond to the notable movement and coordination problems in later stages of the disease.

2.2 Differentiating AD and DLB

DLB, similar to PDD, has abnormal inclusion of Lewy Bodies, but also has similar symptoms of movement, tremor, and hallucination difficulties. Notably, AD and DLB have differing neuroanatomical patterns in that atrophy progresses throughout the brain in differing ways over time. AD has more of a wider, general pattern of atrophy that progresses from the hippocampus and amygdala to the remainder of the subcortical and cortical structures of the brain. On the other hand, DLB has more of a localized, regional pattern of atrophy that progresses from the right insula to the temporo-parietal junction to the insula to lateral occipital cortices, with relatively less atrophy in the medial temporal lobe. We can see this through the comparison between MRI images of a DLB patient and an AD patient in Figure 2.

Most sMRI studies that distinguish AD from DLB focus on comparing regional atrophy patterns in more prevalent homologous disease areas. Nemoto and colleagues in 2021 used a Convolutional Neural Network (CNN) framework to classify AD and DLB MRI images based on patterns of gray matter, using 280 patients consisting of 101 with DLB and 69 with AD. It is important to note the noticeable class imbalance between the two dementia groups, which may introduce a bias in the CNN framework towards the larger class. Consequently, performance metrics for DLB might be larger compared to AD detection. Although differences in atrophy were not significant,

DLB showcased somewhat less volume loss in areas like the temporal lobe and amygdala compared to AD patients, which are areas associated with memory processes. The hippocampus volume loss for DLB, similar to PDD, was also far less compared to AD[17]. AD patients also showed atrophy in the mid-anterior temporal, occipital, and subgenual cingulate cortex, areas that play important roles in memory and emotional regulation. On the other hand, DLB showed greater atrophy in subcortical areas that affect visuospatial processing. There was atrophy in the dorsal cingulate, posterior temporal, and lateral orbitofrontal regions. Atrophy in these visuospatial areas is linked to symptoms like hallucinations, visual disturbances, and impaired spatial awareness which are also seen commonly in the moderate to late stages of DLB.

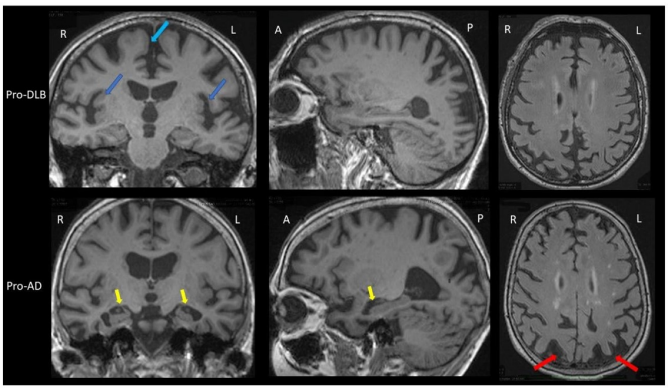

Fig. 2 Upper Part: Brain MRI of an 84-year-old prodromal DLB (Pro-DLB) patient. Lower Part: 84-year-old prodromal Alzheimer's (Pro-AD) patient. Arrows represent areas with gray and white matter degradation. Pro-DLB patient has greater insular atrophy, while the Pro-AD patient shows more pronounced hippocampal atrophy[7]

Computed structural abnormality index (STAND) maps that visualize regions of gray matter loss specific to each disease by comparing with control groups have also proved efficient across many studies. Vemuri and colleagues in 2009 developed a framework for differentiating AD, DLB, and Frontotemporal lobar degeneration (FTLD), another dementia that causes nerve cell degeneration in the frontal and temporal lobes[18]. They implemented STAND-Maps and machine learning techniques including support vector machine (SVM) classifiers on T1-weighted MRI images to reach a high differentiation accuracy with AUROC (Area Under Receiver Operating Characteristic curve) values of 0.78 to 0.90, suggesting good to excellent performance of classification. Once again, Vemuri and colleagues in 2010 took it one step further by developing a more sensitive MRI-based differential diagnosis system, Differential-STAND, which made the differential process between AD and DLB more precise and efficient[19]. By analyzing gray matter density from 91 brain regions, the model distinguished between AD, DLB, and FTLD with high accuracies ranging from 78.6% to 90.7%, and high specificities ranging from 84% to 98.8%. Patterns across sMRI images revealed that AD was characterized by atrophy in memory-related regions like the hippocampus and temporal lobe, while DLB was characterized by atrophy and thinning in areas related to visuospatial and attentional functions. Although the STAND and Differential STAND systems show strong classification metrics, the reliance on a fixed set of 91 brain regions may suggest potentially missing novel atrophy sites. Therefore, a wider range of brain regions should be examined in the future to examine all possible atrophy pattern sites to ensure that there is no reduced sensitivity for atrophy that falls outside of the fixed regions.

Furthermore, Barber and colleagues in 1999 gathered 104 DLB and AD patients' average ages between 75 and 78 years to examine medial temporal lobe (MTL) atrophy using Coronal T1-weighted sMRI images[20]. The study found that AD patients had the greatest MTL atrophy which was located in the center region of the brain. Additionally, DLB patients had significantly greater atrophy compared to control subjects but significantly less than those with AD, while MTL atrophy increased with age and correlated with memory impairment. It is important to note, however, that the narrow age range limits the applicability of the study to a broader expanse of ages, especially younger age groups, which is crucial for the application of findings for early-stage atrophy patterns in the hippocampus and MTL for AD. Similarly, in a sMRI study by Watson and O'Brien in 2012 examining MRI images of 101 DLB patients, 69 AD patients, and 38 controls, DLB was found to have less cortical atrophy compared to AD, containing structures like the hippocampus and MTL[21]. The MTL is an important structure of the limbic lobe, connected to the hippocampus and amygdala which control learning, memory, and emotion. This suggests that DLB is more characterized by a pattern of atrophy that affects subcortical and occipital regions more than memory or emotional processing areas. We can also see this connect to the common clinical symptoms of AD and DLB; While AD affects the MTL resulting in symptoms connected to memory and emotional regulation, DLB more so affects subcortical and occipital regions, resulting in more visuospatial and motor symptoms.

The use of Voxel-Based Morphometry (VBM), a technique of sMRI also holds great potential in differential diagnosis. VBM process segments brain images of gray and white matter and cerebrospinal fluid into a template space, smooths out the images, and performs statistical analysis on a voxel-by-voxel basis to identify differences in brain volume between groups of subjects. Burton and colleagues in 2004 used this VBM framework in a cross-sectional study using T1-weighted MRI scans to compare cerebral atrophy in patients with PD, PDD, AD, DLB patients, and controls[22]. For AD and DLB specifically, the study concluded there was greater temporal lobe atrophy pattern for AD than DLB. Similarly, Whitwell and colleagues in 2007 used VBM to compare characteristic patterns of gray matter cerebral

atrophy between 72 patients with DLB, 72 patients with AD, and 72 controls[23]. Results showed that DLB showed most of its gray matter atrophy localized in the dorsal midbrain, substantia innominata, and hypothalamus. In contrast, AD showed a widespread gray matter atrophy pattern in the MTL. Direct comparisons revealed that AD had greater MTL but less temporal atrophy than DLB. Furthermore, DLB showed more severe atrophy in the substantia innominate and midbrain than AD. This suggests that AD follows a more widespread atrophy pattern affecting the hippocampus and temporoparietal cortex, while DLB follows a more focused, localized pattern affecting the midbrain, hypothalamus, and substantia innominata. These atrophy patterns appropriately match with the clinical pathological evidence of Lewy body progression from the brain's brainstem to basal regions. It is important to note that while Burton et al. (2004) and Whitewell et al. (2007) used 1.5T protocols for their VBM procedure, Vemuri et al. (2009, 2011) and the protocol for STAND and Differential-STAND draw from scanners with varying field strengths and acquisition parameters. Thus, it must be recognized that the differences in MRI application frameworks can affect volumetric and thickness measures, leading to variation in outcomes.

2.3 Differentiating PDD and DLB

Differentiating between DLB and PDD is particularly challenging compared to differentiating between AD and PDD or AD and DLB, because both diseases share overlapping symptoms relating to Parkinsonian features and neuroanatomical patterns. The two diseases also fall under the Umbrella term "Lewy Body Dementia," both containing abnormal deposits of Lewy Bodies with no noticeably distinguishable hallmark features. It is also a commonly accepted way to distinguish in order of symptom onset, because for PDD, dementia begins at least 1 year after onset of Parkinson disease (PD), whereas in DLB, dementia coincides with or precedes parkinsonism. But instead of having to rely on an arbitrary one-year rule, using sMRI is a decisive method to reach clear distinction between the two diseases by comparing patterns of atrophy or cortical thinning structure.

A reason why PDD and DLB are difficult to differentiate from each other neuropathologically is due to the indistinguishable changes in atrophy. An sMRI study by De Schipper and colleagues in 2019 compared volume of the hippocampus in T1-weighted MRI images between 14 patients with DLB patients and 62 patients with PD without dementia[24]. It is important to note the discrepancy between DLB and PD groups, which may introduce a bias towards the group for PD. DLB patients showed more atrophy than PD in the hippocampus and parahippocampal gyrus, a curved band of brain tissue located in the medial temporal lobe next to the hippocampus. This finding is important as this specific area is responsible for the forming of spatial memory, related to the recognition of places and navigating through environments. However, both diseases also display some extremely similar characteristics. A review by Watson and colleagues found that both PD and DLB exhibit similar sMRI patterns, including volume shrinkage of the brain, subcortical atrophy, and minimal preservation of the MTL compared to AD[25]. In addition, a review by Yousaf and colleagues found that DLB and PDD show less atrophy in the hippocampus compared to AD, but DLB tends to have slightly more hippocampal and parahippocampal atrophy than PDD[26]. Simply put, while PDD patients exhibit atrophy in the brainstem and subcortical regions, reflecting motor-dominant pathology, the hippocampal and parahippocampal atrophy patterns in DLB appropriately reflect its visuospatial symptoms.

Despite the complication created through mixed results, studies employing more rigorous MRI methods and analyses reveal greater distinguishing atrophy patterns, finding that patients with DLB have greater temporal, parietal, and occipital gray matter cortical atrophy than patients with PDD. Borroni and colleagues in 2015 used VBM to distinguish atrophy patterns between PDD and DLB[27]. The analysis confirmed that, despite some clinical overlap, PDD had significant bilateral frontal atrophy, while DLB showed more parietal and occipital atrophy. Relating back to the clinical symptoms, the findings match appropriately. Bilateral frontal atrophy in PDD, affecting an area crucial for motor control, leads to executive dysfunction, slowed cognitive processing, and worsening movement symptoms more commonly recognized for PDD. On the other hand, Parietal and Occipital atrophy in DLB, affecting areas crucial for visual processing and spatial awareness causes early visuospatial problems as well as hallucinations and lacking spatial awareness as the disease progresses. The key takeaway is that both PDD and DLB share widespread subcortical atrophy, particularly in basal ganglia and brainstem regions making global volume loss a poor discriminator. In the MTL, De Schipper et al. (2019) and Yousaf et al. (2021) report that DLB patients show subtly greater hippocampal and parahippocampal shrinkage than PDD, but Watson et al. (2012) find that both groups exhibit similarly reduced MTL volumes when compared against AD, muddling a clear atrophy pattern. The most robust and clinically intuitive marker comes from Borroni et al. (2015)'s extensive voxel-based morphometry analysis: PDD is characterized by pronounced bilateral frontal atrophy, responsible for its motor-control and executive-function deficits, whereas DLB shows relatively preserved frontal lobes but significantly greater thinning in parietal and occipital cortices, responsible for its early visuospatial impairments and hallucinations. Thus, the frontal versus parieto-occipital atrophy pattern offers the clearest sMRI indicator for distinguishing PDD from DLB. While hippocampal differences may provide support for differentiation, Borroni's study offers the clearest sMRI distinction, highlighting that greater frontal atrophy in PDD and greater parietal and occipital atrophy in DLB represent the most consistent sMRI markers for differentiation. With the

utilization of sMRI, we are able to understand some critical differences among the neuroanatomical patterns of AD, PDD, and DLB. The findings show that AD typically shows widespread cortical thinning and gray matter loss in the brain's temporal region, located near the middle of the brain's bottom, and parietal regions, located at the top rear of the head, while PD and DLB may exhibit more concentrated, localized characteristics of thinning. Furthermore, sMRI is efficient in differentiating based on gray and white matter volume. The studies shown reinforce the pattern that AD is correlated with significant gray matter loss, particularly in memory-related areas, while PD and DLB show smaller changes, with DLB often showing less hippocampal atrophy compared to AD.

3 Discussion

This review discussed the role and potential of sMRI as a promising neuroimaging modality used to diagnose and differentiate AD, PDD, and DLB – common dementia types with one of the highest misdiagnosis rates in the world. Misdiagnosis rates for these conditions remain dangerously high due to the countless overlapping clinical symptoms and shared neuropathological features. As a noninvasive diagnostic tool that can show detailed images of brain structure and gray and white matter regions, sMRI is an important tool for dementia diagnosis because it allows doctors to identify characteristic patterns of atrophy, shrinkage, and thinning in the brain. Not just that, repeated MRI scans can track changes in brain volume over time, allowing clinicians and doctors to monitor the progression of the disease. Furthermore, the emerging potential of machine learning in differential diagnosis must be recognized. Machine learning models, such as the Differential STAND framework, have demonstrated significant accuracy and specificity in distinguishing dementias[18,19]. However, an MRI alone cannot provide a definitive diagnosis of dementia. To fully address the issue of accurate differential diagnosis for patients with dementia, there must be a solid framework for combining clinical and neuroimaging data to achieve accurate diagnosis. Additionally, several limitations emerged, including the use of single-timepoint MRI scans, which reduce insight into long-term atrophy progression, and inconsistencies in MRI protocols and settings that raise a question to the broad application of these patterns in findings across studies with different methodologies. Minor concerns primarily involve the data of reviewed studies include imbalanced datasets, age-limited patient groups, and average diagnostic accuracies in machine learning models. Therefore, to be successful in a clinical setting, studies should be interpreted through broader, larger datasets and multivariable approaches, including the combination with clinical symptoms, cognitive assessments, and other specific biomarkers, to check off all possible boxes to reach the most accurate diagnosis.

3.1 Meta Analysis

Across 23 quantitative studies differentiating among AD, PDD, and DLB, the average sensitivity, specificity, and accuracy of sMRI-based models were found to be 76.8%, 82.2%, and 80.0%, respectively (Figure 3). These values suggest that sMRI performs reasonably well, especially in specificity, or correctly identifying non-disease cases. Average accuracy levels suggest MRI's reliability in classifying patients into correct diagnostic categories. However, the comparatively lower sensitivity indicates some difficulty in catching all true positive cases, potentially reflecting the clinical complexity and symptom overlap of these dementias.

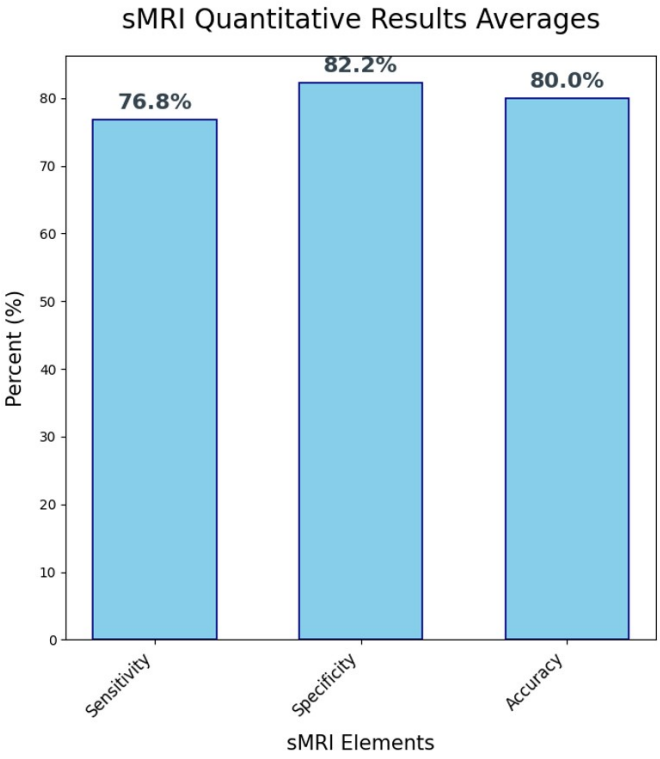

Fig. 3 Average Sensitivity, Specificity, and Accuracy of sMRI-Based Diagnostic Models

It is important to note that the average sensitivity, speificity, and accuracy does not reflect the variation in low to high accuracies across different studies. When evaluating models based on the average of their combined sensitivity, specificity, and accuracy scores, the majority fell into the Medium (65–80%) and High (80–90%) performance ranges (Figures 4 and 5). Specifically, 34.8% of models were medium-performing, 30.4% were high-performing, and 21.7% achieved very high performance (90%+), while only 13.0% were categorized as low-performing (below 65%). These distributions suggest a promising overall effectiveness of sMRI in clinical settings, though only a sub-

set of models reaches the level of performance desirable for widespread adoption in differential diagnosis protocols. Thus, it is important to refine models with careful precision, countless trials of testing, and carefully picked datasets to ensure higher evaluations.

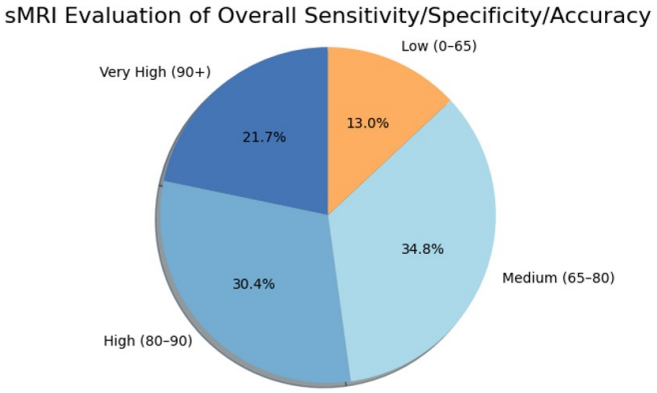

Fig. 4 Proportional Distribution of sMRI Models by Diagnostic Performance Category

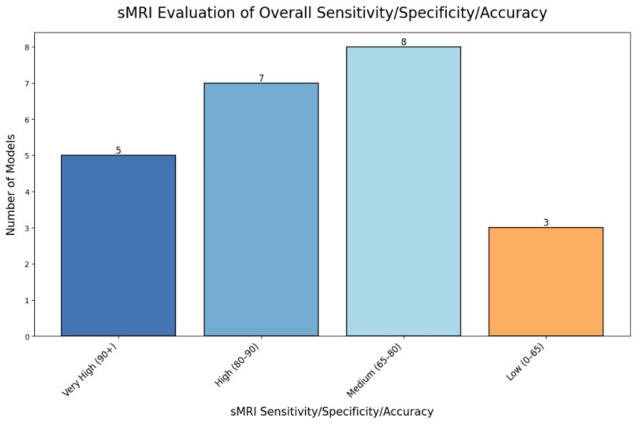

Fig. 5 Number of sMRI Models by Overall Diagnostic Performance Category

sMRI accuracy varied substantially depending on the specific diagnostic group being compared (Figure 6). The highest number of studies focused on AD + DLB comparisons (14 models), followed by AD + PDD + DLB (8 models), with only 1 study focusing solely on PDD + DLB and none on AD + PDD. Despite this disparity, the majority of studies either involved the comparison between AD and DLB or AD and Lewy Body Dementia (LBD), the umbrella term which encompasses both PDD and DLB, so there was still ample differentiation of sMRI models among these diseases. The models were further categorized by diagnostic performance. Most of the AD + DLB models achieved medium to very high accuracy, and the mixed group (AD + PDD + DLB) also displayed most of the models achieving medium to high accuracy despite a slightly more variability. These findings reflect the greater availability and diversity of data for comparisons involving AD and LBD. PDD-specific comparisons are underdeveloped, however, representing a gap in the field. Future research should aim to include larger, more diverse datasets and focus on challenging differential diagnoses involving PDD.

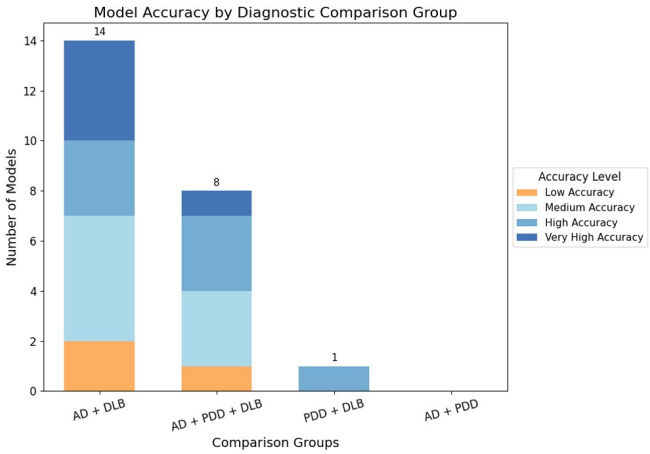

Fig. 6 Distribution of Model Accuracy Levels by Diagnostic Comparison Group

3.2 Future Directions

Studies investigating the differential diagnosis among AD, PDD, and DLB still remain relatively minimal, which is often the reason why misdiagnosis rates are so high – due to the lack of clear biomarkers and distinguishing factors that set these diseases apart. Although it has been around since the 1970s, sMRI is an effective, noninvasive biomarker for differentiating AD, PDD, and DLB. By identifying specific atrophy patternssuch as hippocampal shrinkage in AD, subcortical involvement in PDD, and occipital thinning in DLB,sMRI enhances diagnostic accuracy beyond traditional clinical evaluations. In the eyes of a patient, an accurate diagnosis is a matter of life or death, a deciding factor between worse or better treatment, proper or improper medication use, and progression or mitigation of the harmful effects from the progressive disease. Simply put, studies using sMRI for a differential diagnosis framework has shown significant potential in accuracy and differentiation of these diseases, confirming the utilization of sMRI as a gold standard of accurate clinical diagnosis. But there is much more to be done.

The integration of AI and machine learning into diagnostic frameworks in the field has great potential but lacks much clinical use. The Computational STAND framework by Vemuri and

colleagues in 2009 and 2011 was a notable framework using sMRI to distinguish dementia[18,19]. By implementing machine learning SVM classifiers, the classification model analyzing gray matter density across 91 brain regions distinguished AD, DLB, and FTLD with high accuracy (78.6% to 90.7%) and specificity (84% to 98.8%). Integrating machine learning models into clinical practice has the potential to reduce misdiagnoses, optimize treatment plans, and contribute to earlier and more reliable detection and distinction of neurodegenerative disorders. In fact, further studies utilizing SVMs show incredible promise and success for disease diagnosis and differentiation, transition prediction, and treatment prognosis using neuroimaging data[28,29]. However, current research endeavors should rely less on limited datasets that reduce the generalizability of results at a larger scale. Larger, more diverse datasets must be used to validate and generalize future findings.

Furthermore, the differential studies covered in this review lack the use of multimodal or multivariable analysis. Combining multiple sMRI features, like volumetric, morphometric, and vascular characteristics, enhances differential diagnosis accuracy among various dementia types[30–32]. Recent diagnostic frameworks increasingly incorporate imaging biomarkers to improve accuracy and consistency in diagnosing neurodegenerative diseases. For Alzheimer's disease, for example, the ATN framework, which stands for Amyloid, Tau, and Neurodegeneration, categorizes biomarkers into three groups. SMRI's detail on hippocampal and cortical atrophy patterns are used as markers of Neurodegeneration. However, while sMRI can support or suggest an AD diagnosis, it is not as specific as amyloid PET or CSF tau biomarkers. For DLB, the McKeith criteria incorporates biomarkers such as preserved MTL volume, which helps distinguish DLB from AD. In contrast to Alzheimer's disease and DLB, PDD does not currently have a formalized imaging-based diagnostic framework like the ATN system or McKeith criteria, and lacks a widely accepted sMRI biomarker for PDD, studies suggest greater atrophy in bilateral frontal structures compared to the parietal and occipital lobe atrophy in DLB, but relatively less MTL atrophy than in AD. While this review specifically focuses on sMRI, combining it with other neuroimaging tools could significantly enhance diagnostic accuracy. Structural MRI is great for detecting atrophy patterns, but not so much in detecting the brain's metabolic and functional changes that often precede structural degeneration. PET and fMRI imaging fills in this exact gap; PET can identify abnormal protein deposits like amyloid and tau in AD, while fMRI can visualize the connectivity of neural networks. Therefore, while sMRI contributes meaningfully to differential diagnosis, it should be understood as one potential piece of the puzzle when differentially diagnosing, rather than a standalone marker. In a clinical setting, neuroanatomical patterns from sMRI images directly correspond with clinical symptoms. AD's characteristic hippocampal atrophy correlates to severe memory impairment symptoms seen in patients. DLB's early thinning in the insula and occipital regions also matches symptoms like impairments in visual memory, hallucinations, and attentional deficits, while PDD's cortical thinning in motor areas reflects its loss in motor control. Moreover, thinning in regions like the frontal cortex in PDD and posterior cortex in DLB similarly reveal the connection cognitive decline and visuospatial difficulties seen in these diseases. Therefore, real clinical data like the patient's medical history or related tests should be applied in more studies to portray a more realistic diagnosis. To add on, a review in 2018 by Filippi and Agosta analyzed the use of morphometric MRI in distinguishing non-Alzheimer's dementias like DLB[33]. They concluded that MRI could predict AD pathology in DLB and even differentiate and classify for other dementia types, but longitudinal studies are necessary to reinforce the framework of MRI as an effective tool for monitoring progression, particularly in early, presymptomatic stages. Additionally, a 2020 review by Ferreria emphasizes the need of multivariate data analysis in structural imaging for DLB[34]. Multivariate analysis considers many variables of the image – like intensity values across different time points instead of just looking at individual pixels. This framework allows machine learning models to detect the structural pattern uniqueness that differentiates AD, PDD, and DLB from each other in earlier stages. Therefore, future studies should try incorporating these effective methods – assessing imaging data with data of patients' clinical symptoms or other related tests for a realistic diagnosis, implementing longitudinal studies, or methods like multivariate, multivariable, or multimodal imaging. The connection between neuroanatomy and clinical symptoms is crucial especially if biomarkers are relevant at an early stage, because early diagnosis impacts the lifelong, therapeutic management of these patients as the disease progresses. Finally, Clinical implementation of sMRI differential diagnosis faces some obstacles. Variability in sMRI protocols and scanner strength can affect the applicability and reliability of studies' findings and the potential for the tool to be used clinically. Moreover, these tools must be cost-effective, easily integrated with existing diagnostic frameworks, like the McKeith criteria for DLB and ATN framework for AD, and undergo thorough testing and high accuracy in large, diverse patient groups before they can be adopted widely in clinical practice.

4 Methods

The methodology of this paper is designed to explore the current methods and framework evaluating the potential for structural MRI as an effective neuroimaging tool to aid in differential diagnosis among dementia types – specifically AD, PDD, and DLB. The primary method to conduct this research is a literature review, exploring and analyzing current differential diagnosis criteria and framework covered throughout various studies. It

does not include other functional or structural imaging modalities such as Functional MRI (fMRI), CT, PET, EEG, or SPECT. Some possible limitations include potential biases in studies due to many different imaging approaches used by studies, constraints in their sample sizes, and the generalization of findings from a limited study to an entire population.

4.1 Search Strategy

The literature review was conducted through one reputable database: PubMed. Articles that were peer-reviewed or officially published by government entities after 2005 were prioritized, with only 3 articles being included before that date. The search consisted of phrases or key words such as "Structural MRI," "Alzheimer's Disease," "Parkinson's Disease," "Dementia with Lewy Bodies," and "Differential Diagnosis."

We began by searching PubMed (n = 1,783) using the comprehensive set of search terms, then included "Volume," "VBM," and "Cortical Thickness" to specifically capture studies focusing on structural MRI (sMRI) relevant to the differential diagnosis of AD, PD, and DLB (Figure 7). No records were excluded by automation tools or other reasons prior to screening. After removing irrelevant records based on title and abstract screening (n = 1,325 excluded), 458 articles were selected for full-text retrieval and eligibility assessment. No records were unretrievable. During full-text review, studies were excluded if they did not meet two criterias. First, the use of non-structural MRI specific methodologies studies employing fMRI (n = 385), Diffusion Tensor Imaging (DTI, n = 16), or Susceptibility Weighted Imaging (SWI, n = 0) were excluded, as these techniques are not strictly structural in focus. Seondly, studies using animal models (n = 28) were excluded to maintain clinical applicability to human dementia diagnosis. Following these steps, 29 studies met the inclusion criteria and were included in the final systematic review. No new studies were identified through other sources.

4.2 Inclusion Criteria

Studies were selected based on the following criteria.

- Peer-reviewed articles published in English
- Studies and articles focused on sMRI as a diagnostic tool for differentiating AD, PDD, and DLB.
- Studies employing quantitative imaging methods such as volumetry or cortical thickness analysis.
- Comparative studies analyzing atrophy patterns across at least two of the three dementia subtypes.
- Studies involving techniques using sMRI, such as VBM or Differential STAND Machine Learning
- Studies with clear and detailed methodologies, results, and discussion of implications for clinical diagnosis.

4.3 Data Analysis and Extraction

For data analysis and extraction, a systematic framework was used to identify common themes, trends, and relationships of the studies' methods and findings. Information from the selected studies were extracted, capturing the articles' authors, publication year, design and methodology, objective, participant characteristics, and imaging framework. The information was recorded in a table in a separate document, so relevant themes and findings could be connected and applied particularly in the results section of the review. For the Meta-analysis, additional quantitative studies' sMRI sensitivities, specificities, or accuracies were noted. Finally, a total of 29 articles or studies were selected and included based on the inclusion criteria (Figure 7).

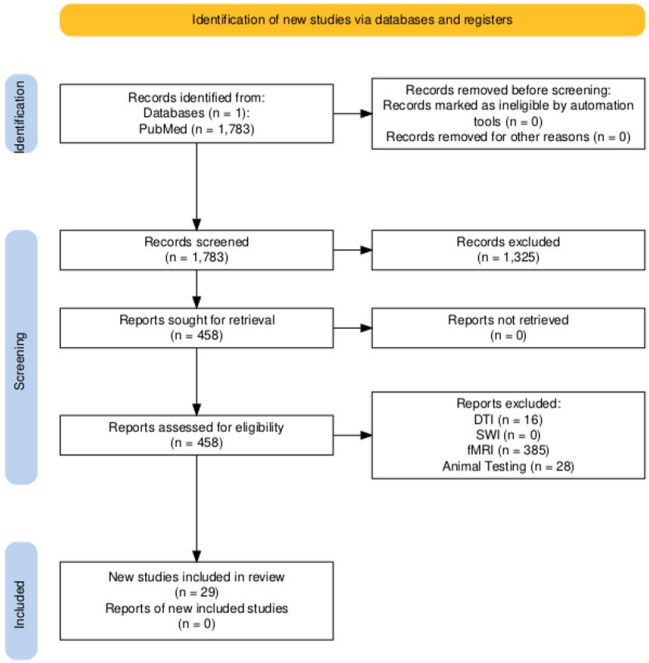

Fig. 7 PRISMA style flow diagram for MRI Differential Diagnosis among AD, PDD, and DLB

5 Conclusion

AD, PDD, and DLB are becoming major global threats especially for our aging population. The lack of accurate diagnosis and differentiation methods remains problematic due to clinical and neuropathological commonalities among these diseases. The primary objectives of the study were to assess the current state of biomarkers, the role of sMRI, and the impact of machine learning in differentiating AD, PDD, and DLB. Through a comprehensive review of current literature and methodologies, the objectives were met.

It is unequivocally clear that sMRI analyses provide crucial information about brain structure and function. When misdiagnosis rates of dementia are so high, advancing this field requires research and studies that systematically examine neuroanatomical changes across disease stages through a longitudinal framework, integrates multimodal or multivariable imaging techniques to enhance structural and functional correlations, or utilizes machine learning models for accurate and efficient diagnosis through the recognition of MRI image patterns. Once future studies start pursuing these areas, we can deepen our understanding of the intricate connection between atrophy patterns and actual clinical symptoms. But the real significance of expanding our knowledge of imaging and dementia comes into play in the clinic – where a faulty or accurate diagnosis becomes the difference between early intervention or irreversible decline – Life or death. With millions suffering from dementia, misdiagnosis can mean years of uncertainty, ineffective treatment, or lost time they could've spent with loved ones. We can revolutionize diagnostic strategies, bring patients out of the dark, and give them something they desperately need – hope and health.

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