

Multimodal magnetic resonance imaging of brain asymmetries in Alzheimer's disease: a systematic review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by widespread cognitive decline, typically affecting functions that are intrinsically lateralized in the human brain, such as language and visuospatial processing. Identifying alterations in brain asymmetry therefore offers a principled framework for understanding selective vulnerability and network-level disruption in AD. In this review, we systematically synthesize evidence from multimodal magnetic resonance imaging studies examining hemispheric asymmetries across the clinical AD continuum, including subjective cognitive decline, mild cognitive impairment (MCI), and dementia. Three convergent patterns were indicated in the literature. Firstly, structural investigations suggest increased hippocampal asymmetries in AD, evident in both volumetric and shape measures. In parallel, connectivity-based analyses indicate a pronounced left-hemispheric vulnerability, characterized by decreased leftward or increased rightward asymmetry driven predominantly by degeneration of the left hemisphere. Importantly, distinct amygdala shape asymmetry profiles observed in MCI relative to healthy aging suggest sensitivity to early pathological changes and potential utility as a state-specific biomarker. Collectively, these findings position disrupted brain asymmetry as a systems-level hallmark of AD rather than a secondary epiphenomenon. This suggests that integrating asymmetry-informed metrics across imaging modalities may enhance early detection, refine disease staging, and improve sensitivity to longitudinal progression in AD.

Introduction

Alzheimer's disease (AD), one of the most prevalent neurodegenerative disorders, represents a major global public health challenge¹. Neuropsychological deterioration and pathological changes begin many years before clinical diagnosis, highlighting the importance of identifying early markers of disease vulnerability and progression^{2,3}. Among the cognitive domains affected early in AD, visuospatial and language functions, both strongly lateralized, have drawn increasing attention⁴, raising the possibility that alterations in hemispheric asymmetry may constitute a fundamental feature of the disease process. Indeed, lateralized cognitive decline and interhemispheric imbalances have been reported in preclinical and prodromal stages of AD, suggesting that disrupted brain asymmetry may provide insight into early disease mechanisms^{5,6}.

Consistent with this view, asymmetry-related cognitive changes can emerge up to seven years before AD onset^{2,7,8}, and nearly two decades before mild cognitive impairment (MCI) diagnosis⁹. Within-participant asymmetries in verbal versus visuospatial performance have been observed during the preclinical phase and proposed as potential predictors of subsequent cognitive decline^{10,11}. In addition, handedness, a behavioral phenotype closely linked to hemispheric specialization, has shown a trend to differentiate AD subtypes, further underscoring the relevance of brain asymmetry to disease heterogeneity^{12,13}. Together, these findings motivate a systematic examination of hemispheric asymmetries as a potentially informative dimension of AD-related neurodegeneration.

Magnetic resonance imaging (MRI) offers a non-invasive and scalable means of quantifying brain asymmetry in vivo and has been widely applied to investigate structural and functional alterations in AD¹⁴. Unlike cerebrospinal fluid^{15,16} biomarkers or positron emission tomography (PET)^{17–20}, which provide molecular-level information but are invasive or costly, MRI enables the assessment of interhemispheric differences across multiple domains. Brain asymmetry can manifest as a global “torque” pattern as well as region-specific differences between homologous areas of the two hemispheres²¹. Most MRI studies quantify these differences using laterality indices to capture both directional and non-directional asymmetry^{22,23}.

Using such approaches, a growing body of MRI research has investigated how hemispheric asymmetry varies across normal aging and along the AD continuum. Some studies have reported age-related reductions in structural asymmetry, although the direction and regional specificity of these effects remain inconsistent^{24–26}, while others have observed opposite trends²⁷. Findings in AD are similarly heterogeneous^{25,28–30}. For instance, Thompson et al. (2003) conducted a longitudinal study showing that gray matter loss occurs more rapidly in the left hemisphere than the right in AD patients, and that total gray matter volume, including cortex and deep nuclei, showed increased asymmetry over time in the AD group, but not in the matched healthy control (HC) group. Subsequent studies have linked brain asymmetry to AD progression, including stages such as MCI and subjective cognitive decline (SCD)^{31–34}. However, other investigations reported no AD-related asymmetry differences^{28,35}, pointing to substantial inter-individual variability. This inconsistency highlights the need for a systematic synthesis to identify convergent patterns of brain asymmetry in AD and to evaluate their potential as neuroimaging biomarkers.

To clarify how hemispheric asymmetries evolve across the AD continuum, we conducted a systematic review of neuroimaging studies examining inter-hemispheric differences in healthy aging and AD-related conditions, such as AD, MCI and SCD. We systematically identified studies that quantified brain asymmetry in individuals with AD, MCI, and SCD, and synthesized evidence across disease stages using a multimodal framework. Specifically, we integrated findings derived from complementary MRI-based measures, including gray matter volume, cortical thickness and surface area, shape-based indices, as well as structural and functional connectivity. By jointly considering these dimensions, this review provides a comprehensive synthesis of how hemispheric asymmetries are altered and reorganized during AD progression. Such evidence could help establish hemispheric asymmetry as a unifying lens for understanding disease-related neurodegeneration and its potential diagnostic relevance.

Results

A total of 46 eligible studies were identified (Fig. 1), and most of them exhibited a low risk of bias (see Table S3).

Among the identified studies, various types of neuroimaging measures, including the gray matter volume, cortical thickness, surface area, shape, and brain connectivity, have been employed for mapping

alterations of brain asymmetry in AD, MCI, and SCD. These analyses were based on 10 to 1,065 individuals with AD or related cognitively impairments (i.e., MCI, SCD; median sample size = 119), with most studies (32 out of 46) focusing on volumetric asymmetry (Fig. 2). For more details of them please refer to Table S1. Below, we summarize relevant findings for AD, MCI, and SCD, separately.

Brain asymmetries in AD

Hippocampus asymmetries A number of studies have reported the lack of AD-related effects in hippocampal directional volume asymmetry. For instance, early studies have analyzed the left-right asymmetry of hippocampal volume and found no marked changes in patients with AD compared to matched healthy elderly controls^{35,38,39}. In line with this, a later meta-analysis including 700 individuals with AD and 915 healthy participants also observed no significant AD-related differences in hippocampal asymmetry²⁸. This absence of AD-related effect has also been supported by more recent studies focusing either on the whole hippocampus^{30,40–42} or the hippocampal subfields⁴³.

In terms of non-directional asymmetry (i.e., the absolute hemispheric differences), increased hemispheric differences in the hippocampal volume were found in people with AD compared to the HC^{32,42–51}. Similar results, that is increased hemispheric volume differences in AD, have also been reported when examining the hippocampal subfields such as the molecular layer, granule cells in the molecular layer of the dentate gyrus (GC-ML-DG), and cornu ammonis 4 (CA4)^{43,48,50}. Moreover, a recent study indicated that asymmetry progression of hippocampal subfields may follow a central-to-peripheral pattern in AD⁵⁰. These results suggest that the non-directional asymmetry, rather than the directional asymmetry, of hippocampal volume may play an important role in the pathogenesis of AD.

In addition, with more sophisticated approaches (see details in Table S1), shape analysis studies have reported increased hippocampal shape asymmetry in AD compared with healthy control participants^{32,42,52–54}, suggesting a potential new neuroimaging biomarker for AD. Notably, the finding reported by Shi et al. (2007) was considered to be at high risk of bias due to unclear participant selection criteria (see Table S3).

We also reviewed studies reporting associations between brain asymmetries and neuropsychological performance. Notably, the non-directional volume asymmetry of the hippocampal parasubiculum region was found to negatively correlate with verbal learning performance, whereas no associations were observed in other subfields and the whole hippocampus^{48,53}. Additionally, increased hippocampal shape asymmetries were associated with poorer global cognitive performance, with this relationship being particularly pronounced in patients with AD^{32,52,53}.

Asymmetries of subcortical structures Regarding directional asymmetries of other subcortical structures, existing studies in AD have predominantly focused on the amygdala and thalamus. Evidence was mixed in both cases. For the amygdala, some studies have reported a stronger rightward volume asymmetry in AD compared to HC^{30,38,41}, but others did not find significant between-group

differences^{40,55,56}. Similarly, a stronger leftward volume asymmetry pattern has been reported in the thalamus in AD patients³⁰, but this was not supported by other studies^{41,57,58}. At the subfield level, Low and her colleagues observed greater rightward asymmetry in the ventral thalamus⁵⁷, however, a recent study reported significant alterations in ventral thalamic asymmetry in early MCI rather than AD⁵⁸, underscoring the potential influence of MRI segmentation method and the need for standardization across studies. Additionally, volume asymmetries in other subcortical structures, including the putamen, nucleus accumbens, and pallidum, have also been investigated and showed no differences between people with AD and healthy controls⁴¹.

Some researchers have employed the “BrainPrint” method^{32,53} to investigate the non-directional asymmetries in volume and shape across various subcortical structures. Consistent findings have revealed increased shape asymmetry of the nucleus accumbens in AD patients, while results for other measures were mixed^{32,53}. For example, Wachinger et al. (2016) reported strong evidence for larger volumetric asymmetry in the caudate, but no significant changes in the amygdala or nucleus accumbens. In contrast, Fu et al. (2021) identified increased non-directional volume asymmetries in the amygdala and nucleus accumbens, but not in the caudate. Similar inconsistencies have been observed in studies examining shape asymmetries of the amygdala, caudate, and putamen. These discrepancies may stem from differences in study design and image acquisition protocols.

Nevertheless, potential clinical correlates have been identified for alterations in subcortical asymmetry. Specifically, greater volumetric and shape asymmetry of the amygdala and caudate has been positively associated with AD severity and cognitive decline^{30,32}. Moreover, reduced leftward asymmetry of the ventral thalamic nucleus, rather than global thalamic asymmetry, was linked to diminished verbal fluency and increased disease severity in AD and MCI patients⁵⁷. Fu et al. (2021) further reported that greater asymmetries in both volume and shape of the nucleus accumbens were associated with lower cognitive performance and impaired verbal memory in AD.

This growing body of evidence underscores the relevance of subcortical asymmetries, particularly the shape asymmetry of nucleus accumbens, in understanding the progression and clinical manifestations of AD.

Cortical asymmetries At the cortical level, the global cerebral cortex did not show marked differences in directional volume asymmetry between patients with AD and healthy individuals^{40,41,59}. However, stronger non-directional asymmetry patterns have been reported in AD patients, both in cortical volume⁵⁹ and thickness^{60,61}.

Zooming in on specific regions, researchers have found considerable AD-related effects in asymmetries of various regions, including the dorsolateral prefrontal cortex, gyrus rectus, superior frontal gyrus and the inferior temporal gyrus^{40,62,63}, while these results need further validation for their potential bias related to asymmetry index definition or group matching (see Table S3). Cortical thickness analyses

reported a weaker leftward asymmetry in the angular gyrus and parahippocampal gyrus⁶⁴, and a steeper decline in leftward asymmetry in the anterior temporal cortex and various frontal regions in AD²⁵. Interestingly, the loss of leftward lateralization in the planum temporale has been linked to word list memory recall performance⁵⁹.

In terms of regional non-directional volume asymmetries, studies have yielded increased asymmetries in various cortical regions including the temporal, parietal, and occipital lobes in patients with AD^{45,59}. Additionally, Thompson et al. (1998) analyzed several major deep sulcal fissures and discovered a stronger shape asymmetry in the sylvian fissure in the AD group.

Asymmetries in brain connectivity Brain connectivity measures with diffusion-weighted imaging (DWI) and functional magnetic resonance imaging (fMRI) have been considered as potential biomarkers for AD^{65–67}. Based on DWI data, Yang et al. (2017) used graph theory methods to analyze the hemispheric topological properties including the efficiency of brain nodes and networks, defined by the average of the inverse shortest path length among given nodes. They compared the asymmetries of these properties and discovered increased rightward asymmetries in global and local network efficiencies in AD, as well as in asymmetries of nodal efficiencies of various regions, including the cuneus, lingual gyrus, and anterior parahippocampal gyrus⁶⁸. Evidence from fMRI showed that the leftward asymmetry pattern observed in healthy older adults was not present in AD patients⁶⁹. Consistent reductions of leftward functional connectivity have also been observed between the amygdala and precuneus³⁰, as well as within the posterior default mode network (DMN)⁷⁰ in AD. Furthermore, a recent study examining functional gradients (i.e., the similarity of functional connections across a continuous cortex) has revealed a significant reduction of the normal left-lateralized pattern in the hemisphere, particularly within the DMN and control network (CN), among patients with AD⁷¹. These findings suggest that AD-related changes in brain connectivity asymmetries may be linked to the decreased connectivity in the left hemisphere.

Additionally, several studies have used the Rey Auditory Verbal Learning Test (RAVLT) to assess patients' verbal learning and memory functions, reporting that poorer RAVLT performance is associated with weaker leftward asymmetry in DMN⁷⁰, as well as more pronounced rightward asymmetry in both local and global network efficiency and the nodal efficiency of regions such as the anterior fusiform gyrus and the cuneus⁶⁸. Beyond specific cognitive domains, disease severity of AD has also been positively correlated with reduced left-hemisphere functional connectivity, including connectivity between the amygdala and precuneus³⁰, and with alterations in left-lateralized patterns of DMN and CN gradients⁷¹. These results highlight the critical role of network asymmetries in disease progression in AD.

Brain asymmetries in MCI

Hippocampus asymmetries Similar to AD, most studies have reported no significant alterations in hippocampal directional volume asymmetry in MCI, at both the whole hippocampus level^{28,41,43,72–74} and the subfield level^{43,73,74}. In contrast, only one study observed a reduced rightward asymmetry of the hippocampus in individuals with MCI compared with HC³⁴. Regarding non-directional hippocampal volume asymmetry in MCI, unlike the AD stage, findings have been mixed across the whole hippocampus^{32,43,44,48–51,53} and several subfields such as the subiculum and the molecular layer^{43,48,50,75}, which may partly reflect variability in diagnostic criteria for MCI. In addition, hippocampal shape asymmetry in MCI notably differs from that in the AD group (larger in AD), but its comparison with the HC group remains unclear^{32,52,53}.

Asymmetries of subcortical structures Inconsistent results have been reported regarding the volume asymmetry of the amygdala. Yue et al. (2018) reported weaker leftward asymmetry, whereas Mabrouk et al. (2023) demonstrated a stronger rightward pattern in individuals with MCI, while Cherbuin et al. (2010) did not identify differences. Moreover, for asymmetry of the thalamus, the majority of studies reported no significant alterations in MCI^{41,57,72,74}, whereas a recent study has shown altered volumetric asymmetry in the whole thalamus and in specific subfields (e.g., the ventral lateral posterior and medial geniculate nuclei) among participants with early MCI, but not in late MCI or AD⁵⁸. When directly comparing MCI and AD, an opposite pattern of asymmetry in the ventral thalamus was observed, with MCI showing a leftward asymmetry and AD showing a rightward asymmetry⁵⁷, however, this finding requires confirmation in larger samples. Asymmetries in the caudate, putamen, and nucleus accumbens have also been investigated, but no noticeable changes were observed^{41,72}.

Regarding the shape asymmetries, MCI individuals exhibited a stronger pattern in the amygdala, but not in other structures such as the thalamus, caudate and putamen^{32,53}. Longitudinal analyses have suggested that increasing shape asymmetry in several subcortical structures (e.g., hippocampus, amygdala) might increase the risk of MCI developing into AD³².

Cortical asymmetries At the hemispheric level, several studies have indicated that cortical volume asymmetry remains unaltered in individuals with MCI^{41,59,72}. When each hemisphere was divided into 34 regions based on the Desikan-Killiany parcellation method⁷⁶, Yang et al. (2023) found a stronger rightward asymmetry of surface area in the pars orbitalis in MCI compared with HC. Increased rightward asymmetry has also been reported in the surface area asymmetry of the precuneus in MCI compared with SCD individuals, as well as larger leftward asymmetry in the superior temporal gyrus and weaker rightward asymmetry in the insula of cortical thickness asymmetries⁷⁴. In addition, other morphological asymmetries have been analyzed using various indices, such as composite microstructural measure⁷⁷ and the local gyrification index⁷⁴, but no notable differences were found between the MCI and HC groups. However, a longitudinal study comparing individuals with MCI who later developed AD with those who did not, revealed differences in morphological asymmetries (i.e., measured by a combination of surface area, curvature index, and cortical thickness) across the entorhinal cortex, frontal pole, and

rostral anterior cingulate gyrus⁷⁸, underscoring the importance of longitudinal follow-up. In terms of non-directional cortical asymmetries, Derflinger et al. (2011) have reported larger non-directional volume asymmetry of the occipital lobe in MCI than HC. When compared with individuals with AD, those with MCI exhibited smaller asymmetries in the temporal lobe and parietal lobe⁵⁹.

Asymmetries in brain connectivity No marked changes in the asymmetries of white matter volume⁷² or white matter hyperintensity (WMH) volume⁷⁹ were observed across most cortical lobes in individuals with MCI. When comparing MCI with AD, opposite directions in WMH volume asymmetry in the occipital lobe have been observed⁷⁹. In addition, by using graph theory approach, Yang et al. (2017) have discovered increased rightward asymmetries in nodal efficiency of the cuneus and anterior parahippocampal gyrus in MCI, whereas no differences were observed at the network level⁶⁸. Moreover, evidence from fMRI has indicated that people with MCI exhibited a reduced leftward asymmetry in the posterior DMN compared with the amyloid- β negative HC, while no notable changes were observed in amyloid- β positive HC individuals or in people with AD⁷⁰, suggesting a potential relation between asymmetry with amyloid load. In addition, recent research has shown a gradual decrease in left-lateralized hemispheric functional gradients from HC through MCI to AD, along with significant differences in DMN and CN between the MCI and AD groups⁷¹, indicating that diminished left-hemisphere connectivity may emerge early in the AD progression. Nevertheless, longitudinal studies with larger samples are required to further clarify this trajectory.

Brain asymmetries in SCD

Relevant research on SCD is limited, and both directional and non-directional volume asymmetries in the hippocampus and amygdala have shown no significant changes in individuals with SCD^{34,53,74}. Similarly, shape asymmetries in many subcortical structures (e.g., hippocampus, amygdala, thalamus) remain unaltered in SCD⁵³. However, smaller shape asymmetries in the global brain⁷⁷ and hippocampus⁵³ have been found in individuals with SCD compared to both those with MCI and AD. However, due to the limited number of studies, a consistent pattern has yet to be established.

Discussion

This systematic review reveals convergent, stage-dependent alterations in hemispheric brain asymmetry across the AD continuum, highlighting asymmetry as a meaningful systems-level feature of AD-related neurodegeneration (Fig. 3). Across modalities, AD is consistently associated with increased non-directional asymmetry in subcortical structures, most prominently involving hippocampal volume and shape as well as nucleus accumbens morphology. At the cortical level, directional asymmetries are selectively reduced, with attenuated leftward asymmetry in temporal and frontal regions, including the parahippocampal gyrus. Connectivity-based studies further reveal a disproportionate vulnerability of bilateral hemispheres, evidenced by greater connectivity reductions in the left hemisphere relative to the right. In prodromal stages, MCI shows distinct asymmetry profiles, with altered hippocampal and

amygdalar shape: hippocampal asymmetry is more pronounced in AD than in MCI, whereas amygdalar asymmetry is greater in MCI than in HC. By contrast, current evidence does not demonstrate robust asymmetry alterations in SCD. Importantly, greater disease severity and poorer cognitive performance are associated with reduced leftward or increased rightward asymmetry, indicating progressive left-hemispheric vulnerability. Collectively, these findings delineate a coherent trajectory of asymmetry reorganization across AD progression and underscore the relevance of hemispheric asymmetry for linking AD neurodegeneration to clinical decline.

The hippocampus, together with several subfields (e.g., the molecular layer, GC-ML-DG, and CA4), exhibited greater non-directional volume and shape asymmetries in people with AD in some studies^{43,48,50}, with evidence suggesting that non-directional asymmetry increased gradually as AD progresses^{44,48,53}. However, no differences were reported regarding directional asymmetry measures. Taken together, these findings indicate that the direction of the hippocampal asymmetry changes varied across individuals with AD, potentially reflecting the heterogeneity of AD subtypes. For instance, language and visuospatial abilities are two hallmark cognitive functions in AD that show opposite patterns in hemispheric lateralization, typically left-lateralized for language and right-lateralized for visuospatial function⁴. Therefore, we speculate that subtype-specific profiles (e.g., language-predominant AD subtype, visuospatial-predominant AD subtype) may be associated with distinct, and potentially opposing, directions of hippocampal asymmetry alteration relative to HC, reflecting potential compensation or dedifferentiation mechanisms. This interpretation is aligned with previous work demonstrating divergent patterns across AD subtypes in pathological trajectories, biological alterations, atrophy patterns, and cognitive impairments^{80–84}, as well as subtype-related brain asymmetry patterns^{84,85}. Moreover, given that hippocampal subfields may exhibit asymmetric vulnerability in AD and are linked to distinct cognitive functions⁸⁶, further research employing subfield-level analyses, together with pathology biomarkers and cognitive profiles will be crucial for clarifying how subtype-specific AD contribute to hippocampal asymmetry alterations.

Regarding cortical asymmetry in AD, our review identified an overall pattern suggesting greater vulnerability of the left hemisphere compared with the right. Across studies, patients with AD exhibited either an increased rightward asymmetry or decreased leftward asymmetry pattern when compared to HC, particularly in connectivity-based measures, and these AD-related alterations might be impacted by the stronger deteriorations in the left hemisphere^{30,68–71}. These neuroimaging findings align with evidence from PET imaging and postmortem studies, which have observed that amyloid- β and tau pathology are asymmetrically distributed across hemispheres in many AD individuals, and more cases are showing leftward pattern with more severe neurodegeneration^{84,87–90}. Moreover, recent work has identified strong associations between lateralized patterns of amyloid- β and tau deposition, supporting the hypothesis of hemisphere-specific vulnerability to AD pathology⁸⁷. Notably, although Anijarv et al. (2025) reported null finding regarding the relationship between tau asymmetry and interhemispheric connectivity, the potential links between lateralized connectivity alterations and asymmetric tau burden remain insufficiently explored, which may further support the hemisphere-specific vulnerability

hypothesis based on multimodal measurements. Despite these emerging observations, the mechanisms underlying the susceptibility of the left hemisphere remain unclear. While several explanations involving epigenetic regulation and neurochemical asymmetries have been proposed⁵, longitudinal multimodal studies are still required to elucidate how these factors contribute to asymmetric cortical degeneration in AD.

MCI and SCD represent critical intermediate stages along the AD continuum and are therefore essential targets for early detection. In our review, we identified significant alterations in hippocampal and amygdalar shape asymmetry across HC, MCI, and AD individuals^{32,53}. The hippocampus and amygdala are regarded as the earliest regions to show AD-related neurodegenerative changes⁹¹. Moreover, asymmetric alterations of them have been linked to cognitive and emotional impairments in individuals with MCI and preclinical AD^{17,48,92,93}, highlighting their potential utility for tracking AD progression. However, the current evidence regarding amygdala asymmetry differences between AD and healthy control participants remains mixed, and investigations on stage-dependent brain asymmetry alterations in SCD are scarce. Given the broader accessibility of MRI over PET in preclinical populations, more MRI-based longitudinal studies are needed to evaluate whether asymmetry measures can reliably predict progression to AD, with implications for early identification and intervention⁹⁴.

Notably, given the heterogeneous nature of AD, measure-specific changes have been observed in multiple brain regions (e.g., the nucleus accumbens), suggesting that no single neuroimaging metric can fully capture the complex, multifaceted brain changes associated with AD. Recent advances in machine learning and deep learning have enabled automated classification and prediction of AD progression by integrating multimodal neuroimaging features^{95,96}. Importantly, models incorporating brain asymmetry features have demonstrated improved performance compared to models without asymmetry data^{97,98}, indicating that brain asymmetry measures provide valuable complementary information beyond established biomarkers. Accordingly, multimodal frameworks that integrate diverse measures and global brain asymmetry perspective hold promise for distinguishing AD subtypes and tracking disease progression²¹, though further research is required to refine these methods.

Despite these advances, several limitations remain. An important limitation of the present review is that hemispheric asymmetries identified across the AD continuum cannot be assumed to be specific to AD. In particular, early clinical stages such as subjective cognitive decline and mild cognitive impairment are etiologically heterogeneous and may precede other dementia syndromes. As a result, some of the reported asymmetry patterns may reflect transdiagnostic neurodegenerative or vascular processes rather than AD-specific pathophysiology. Next, mixed findings across studies may reflect false positives and/or methodological differences, including imaging and segmentation techniques, asymmetry index definitions, and sample heterogeneity^{99–101}. Given the substantial interindividual variability in hemispheric asymmetries^{6,99}, future work should report comprehensive participant information, including biological confirmation of participants (e.g., amyloid- or tau-positive status) and detailed methodology, to better identify the sources of inconsistency. Moreover, limited data hindered

quantitative meta-analysis, as exemplified in recent work on handedness in AD and dementia^{12,102}. Collaborative efforts like ENIGMA consortium^{103,104} will facilitate exploration of complex asymmetry patterns over AD progression. Finally, it remains uncertain regarding the intricate relationship between aging and AD-related pathology¹⁰⁵. Notably, the pattern of greater left-hemisphere vulnerability synthesized here appears to diverge from the traditional “right hemi-aging” model, which posits that the right hemisphere shows greater age-related deterioration than the left hemisphere¹⁰⁶, yet it is broadly consistent with recent large-scale evidence indicating prominent aging-related changes linked to the left hemisphere¹⁰⁷. Longitudinal mechanism-oriented designs may help disentangle age-related and pathology-specific contributions to asymmetric brain degeneration.

In summary, this review identifies disrupted hemispheric brain asymmetry, most notably increased hippocampal asymmetry and progressive left-hemispheric vulnerability, as a consistent feature of AD across clinical stages. Associations with cognitive impairment and disease severity support hemispheric asymmetry as a complementary marker of neurodegeneration. Observed heterogeneity across studies likely reflects biologically and clinically distinct AD subtypes, underscoring the need for integrative approaches. Integrating asymmetry metrics with molecular pathology, cognitive phenotyping, and network-level analyses may enable subtype-specific stratification and more precise tracking of disease progression in AD.

Methods

Literature Search

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines³⁶, two authors (Y.A. and X.K.) searched for relevant studies via PubMed and Web of Science using the following keywords in the title/abstract: ((asymmetr*) OR (laterali*)) AND ((MRI) OR ("magnetic resonance imaging")) AND ((Alzheimer*) OR ("mild cognitive impairment") OR ("subjective cognitive decline")). The search process was initially conducted in April 2024 and updated in January 2026 to include the most recent studies. No formal protocol was prospectively registered.

Inclusion and Exclusion Criteria

Two authors (Y.A. and X.K.) selected eligible studies that met all of the following criteria: (1) the study data were based on human brain measurements obtained via MRI; (2) the study analyzed brain asymmetry index and reported its calculation method; (3) the brain asymmetry index was compared between AD-related participants (i.e., SCD, MCI, and AD) and matched HC individuals, or among AD-related groups, with the necessary statistical information provided; (4) the study was a peer-reviewed research article. References of above included articles were screened for additional studies. Notably, studies were excluded if they did not include explicit measures or statistical comparisons of brain asymmetry between HC and AD-related conditions, as well as case reports.

Data Extraction

For each eligible study, key information on participants and neuroimaging measurements were systematically extracted (see Table S1). Participant data included the source of the dataset, diagnostic criteria, sample size, mean age, and cognitive scores of each group. Neuroimaging details encompassed the asymmetry index formulae used, the regions of interest analyzed, and the methodological parameters of the applied techniques. Any discrepancies during the data extraction process were resolved through consensus discussion. Notably, the brain asymmetry indices presented in this review were directly obtained from the original articles, with no additional effect size calculations performed.

Quality Assessment

Risk of bias was assessed with the Newcastle-Ottawa Scale³⁷, and studies with a high risk of bias are highlighted but not excluded. The PRISMA checklist is completed in Table S2, and full risk-of-bias results are provided in Table S3.

Declarations

Authors' contributions

Y.A conducted the article screening, full-text review, data extraction, quality assessment, and manuscript writing. W.C reviewed the manuscript and provided comments. R.S reviewed the manuscript and provided comments. Z.Z obtained funding, reviewed the manuscript, and provided comments. X-Z.K conceptualized and led the study, obtained funding, conducted the article screening, full-text review, and manuscript writing.

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Competing interests

The authors report no financial interests or potential conflicts of interests.

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Figures

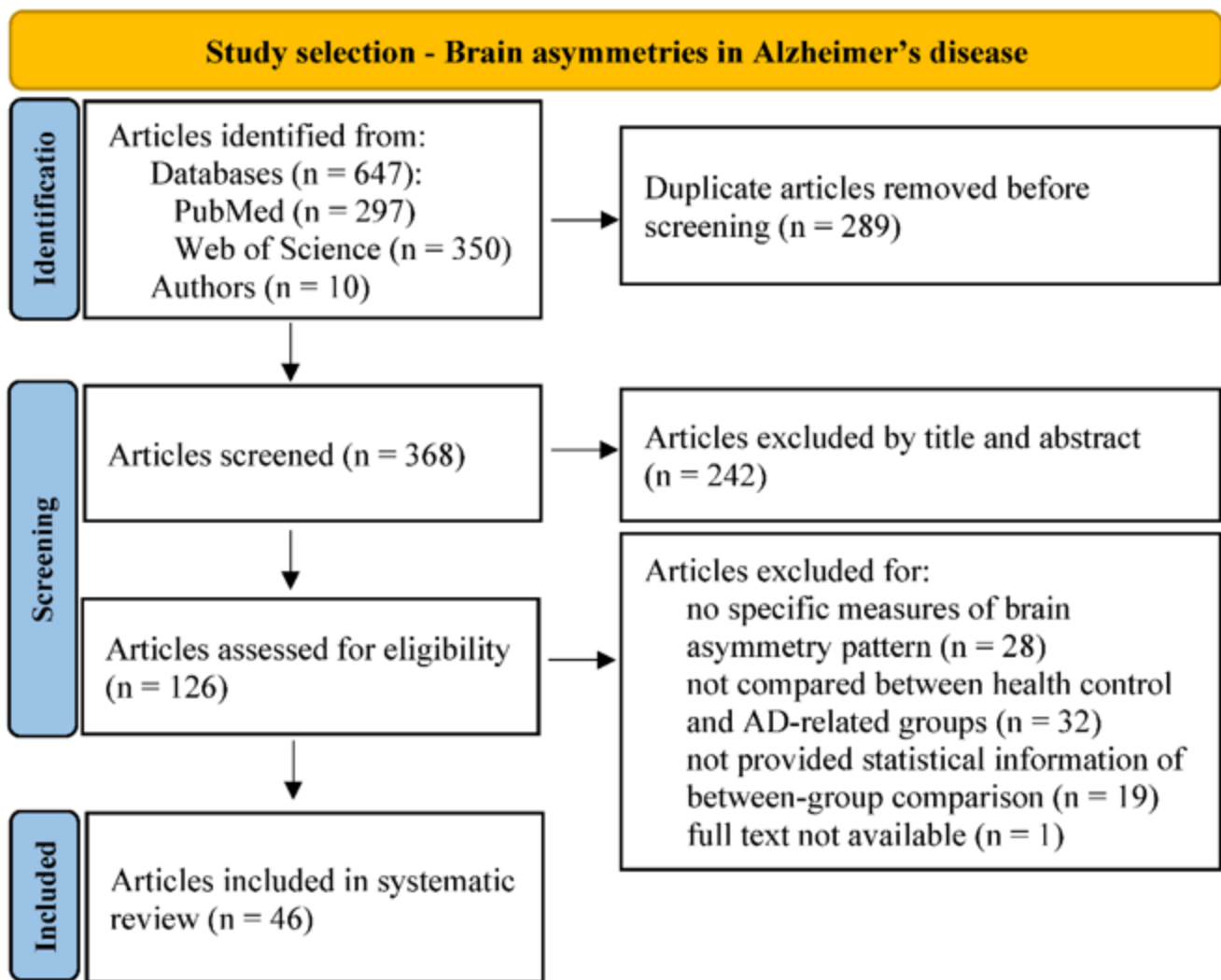


Figure 1

Flowcharts of study selection.

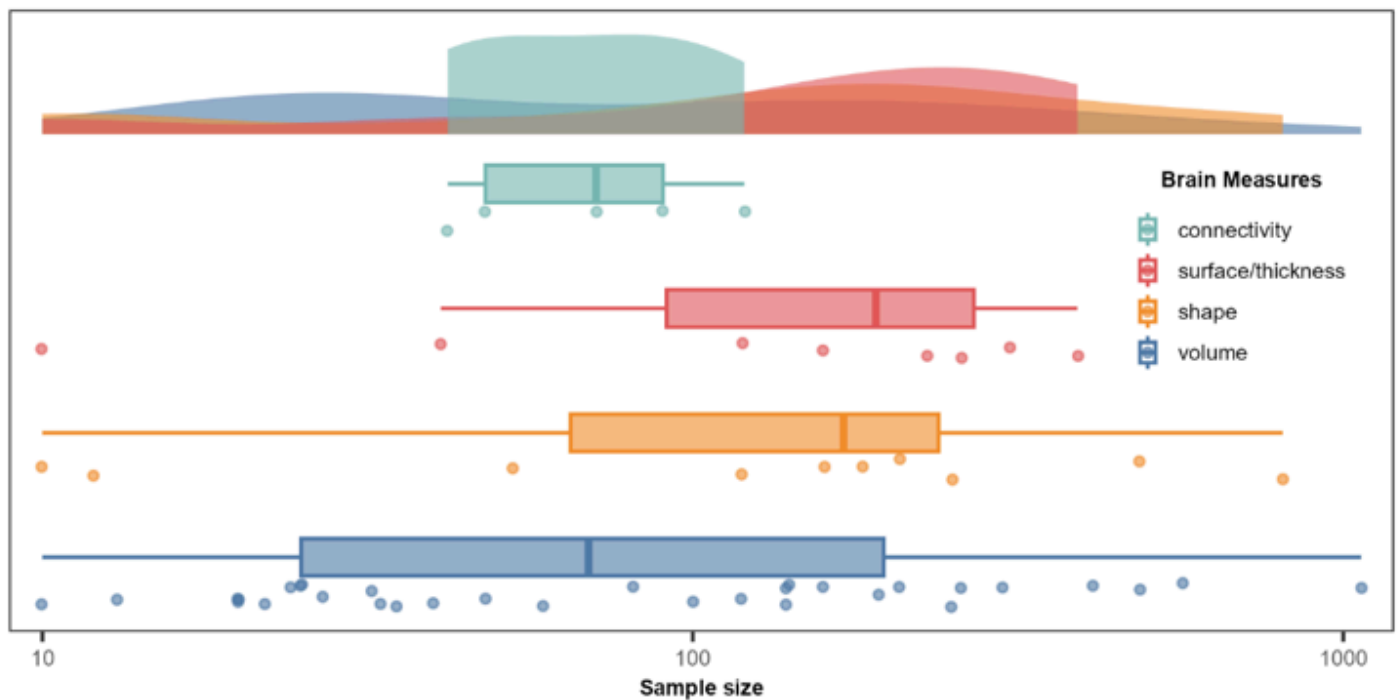


Figure 2

Sample size distributions of patients of the identified studies. Studies with different measures (i.e., volume, shape, surface area/thickness, and connectivity) were plotted separately. Each point indicates a study. Note that studies could report more than one measure, thus could be included multiple times in this plot.

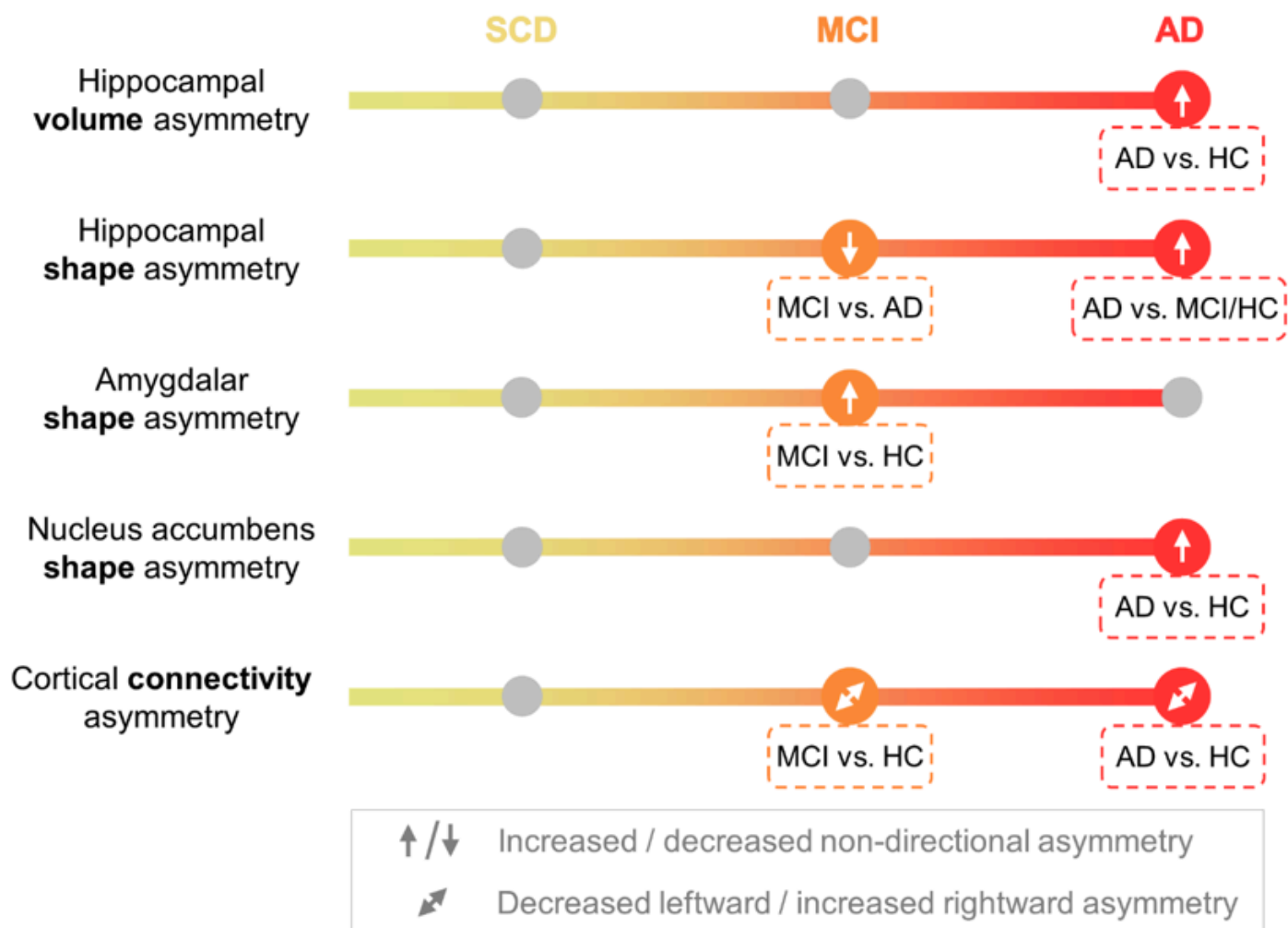


Figure 3

Stage-dependent alterations in hemispheric brain asymmetry across the AD continuum. Arrows represent convergent changes in directional or non-directional asymmetry. Findings supported by limited or inconsistent evidence across studies are denoted by gray dots. SCD: subjective cognitive decline; MCI: mild cognitive impairment; AD: Alzheimer's disease.

Supplementary Files

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- [TableS1Includedresearch.xlsx](#)
- [TableS2PRISMAchecklist.docx](#)
- [TableS3Riskofbiasresults.docx](#)
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