Gray Matter Atrophy and Cognitive Symptoms in Alzheimer's Disease: Concordance, Mismatch, and the Moderating Role of Cognitive Reserve

Pengcheng Shen

International Campus, Zhejiang University, Jiaxing, China
Pengcheng.22@intl.zju.edu.cn

Abstract Alzheimer's disease (AD) is characterized by progressive gray matter (GM) atrophy, which is typically detected using structural MRI. Although atrophy is often associated with cognitive impairment, the relationship is not absolute: individuals with similar levels of atrophy may exhibit considerable differences in cognitive performance. This review discusses the correlations and inconsistencies between GM atrophy and cognition in AD, as well as the factors that influence this relationship. Evidence supports this correlation, particularly between medial temporal lobe structures and memory function, and it can be observed even before clinical diagnosis. However, mismatches occur across whole-brain and regional measurements and at different disease stages, indicating that atrophy severity alone cannot fully account for the severity of cognitive impairment. Cognitive reserve (CR) is an important factor that may explain part of this mismatch. Individuals with higher CR may show more severe pathology at comparable levels of cognitive performance. However, the explanatory power of CR is limited and appears to depend on the brain region, reserve indicator, and disease stage. Other factors, including vascular burden, sex, and differences in imaging and cognitive assessment methods, may also contribute to these inconsistencies. Therefore, structural MRI should be interpreted together with CR, disease stage, and other pathological factors. Longitudinal imaging and multimodal approaches may help clarify individual differences in the relationship between atrophy and cognitive symptoms.

Keywords Alzheimer's disease; gray matter atrophy; cognitive impairment; cognitive reserve; structural MRI

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive decline in memory and other cognitive functions. Pathologically, it is marked by the accumulation of amyloid-β and tau proteins, along with the loss of neurons and synapses. Gray matter (GM) atrophy is one of the pathological features of AD. Since GM loss can be measured regionally or throughout the brain and can be tracked over time, it is widely used as a key biomarker for AD. Structural MRI has become a crucial tool for capturing this pathology[1].

It is generally assumed that if GM atrophy reflects the degradation of the nervous system that supports cognition, then the more severe the regional or whole-brain atrophy, the greater the cognitive impairment. Some studies have shown correlations consistent with this assumption, indicating that brain atrophy is an important structural factor contributing to cognitive disorders in AD, and the rate of cognitive decline is also driven by the rate of neurodegeneration[2]. However, this relationship is not deterministic. Atrophy is a related structural feature, but not a direct cause-and-effect relationship between clinical severity and atrophy. Individuals with similar levels of GM atrophy may exhibit significant differences in cognitive performance. Moreover, the rate of structural changes does not always parallel the rate of cognitive decline over time. Modeling GM atrophy as a function of time, aging, or cognitive decline yields different patterns, meaning that the GM atrophy and cognitive decline are not interchangeable concepts[3]. These findings raise the question that cannot be answered solely by the degree of atrophy: what causes the discrepancy between structural changes and cognitive decline?

Cognitive reserve (CR) provides an important answer. It

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is believed to reflect individual differences in tolerance to the pathological processes associated with AD[4]. Some research noted that in mild AD, education level is associated with more severe structural and functional damage under the same cognitive performance[5]. However, this does not mean that CR is the only explanation for this discrepancy. The relationship between atrophy severity and structural regulatory mechanisms needs further analysis.

Existing studies have discussed structural atrophy, cognitive performance, and CR separately, but there is a lack of integration regarding the relationships among these factors, as well as other biological, disease-stage, and methodological factors. Therefore, this review aims to provide a comprehensive overview of the consistency and inconsistency between atrophy patterns and CR, as well as the mechanisms that regulate this relationship. Based on this, the review raises the following questions: (1) What evidence supports the correlation between GM atrophy and cognitive impairment in AD? (2) Under what conditions can there be a mismatch between structural severity and cognitive severity? (3) How does CR regulate the atrophy-cognition relationship? What other biological, clinical, or methodological factors contribute to the inconsistencies?

2. Theoretical Background

2.1 GM Atrophy as a Structural Indicator of AD

In structural MRI, GM atrophy refers to a reduction in cortical thickness or GM volume, which reflects the loss of downstream neurons and synapses[1]. However, what this measurement indicates depends on how it is defined. Atrophy can be measured in specific regions, such as the hippocampus or medial temporal cortex. It can also be measured as a general index for the entire brain. There are fundamental differences between these two measurement methods. Regional measurements indicate how specific brain areas are affected and can be linked to the cognitive functions they support, whereas global atrophy reflect the overall degree of brain degeneration and are more closely related to general cognitive status. This distinction is important because different brain areas are responsible for various cognitive functions. Atrophy in one area does not necessarily cause the same clinical symptoms as atrophy in another area[6]. Different measurement scales may lead to different relationships between atrophy and cognition. Therefore, treating atrophy severity as a single metric may lead to confusion between structures and functions that are not directly related.

2.2 Why Is Atrophy Associated with Cognitive Symptoms?

The expectation that atrophy is associated with cognitive symptoms is based on a theoretical premise. Cognitive functions depend on the nervous systems distributed across different brain areas. The loss of GM weakens the connections within these systems and is associated with cognitive disorders. For example, the medial temporal lobe has been considered related to episodic memory. Its degradation explains why patients with early AD experience memory problems[7]. Jack et al. found that ventricular enlargement is associated with cognitive decline, while amyloid-β deposition is not[2]. This suggests that structural changes are more relevant than some molecular markers in predicting clinical progression. However, this relationship should be seen as a correlation rather than a direct causal link. Equal levels of structural loss may also involve different degrees of damage. Therefore, the expectation of a connection between atrophy and cognitive symptoms is merely a tendency, not a certainty. The association is region- and function-specific.

2.3 CR, Brain Reserve, and Compensation

CR explains why patients with similar pathological conditions exhibit significant differences in clinical performance[4]. CR differs from brain reserve. Brain reserve refers to structural conditions such as brain size or synaptic density. These factors set a threshold at which symptoms begin to appear[8]. In contrast, CR is typically measured indirectly through educational or cognitive stimulating activities[4]. Neural compensation, on the other hand, describes the process by which alternative neural networks are recruited or existing neural networks are activated to maintain function during pathological accumulation[4].

3. Literature Review

3.1 Evidence of the Consistency Between GM Atrophy and Cognitive Symptoms

The relationship between GM atrophy and cognitive impairment in AD has received great attention. In a study by Lerch et al. involving 36 participants, it was found that cortical thickness in various regions of the brain decreased significantly in AD patients. The most notable changes occurred in the medial temporal lobe[7]. The degree of thinning increased as the disease progressed. This indicates that the severity of structural loss indeed reflects the severity of overall cognitive impairment.

The association between regional brain atrophy and cognitive impairment in AD further underscores this consistency. Doré et al. discovered that in individuals with amyloid-β positive without cognitive impairment, thinning of the precuneus and hippocampus was associated with deficits in episodic memory. This result shows that structural damage and cognitive issues are present even before clinical diagnosis[9]. In the same study, longitudinal analysis showed that in those with amyloid-β positive, GM atrophy in the temporal lobe and hippocampus progressed more rapidly over 36 months, thereby supporting the link between regional GM atrophy and cognitive deficits in

AD[9].

Together, these two study support a stable association between GM atrophy and cognitive impairment in AD, with the most consistent evidence converging on the medial temporal lobe and hippocampus, and with episodic memory as the most frequently implicated cognitive domain[7,9].

Another study on brain atrophy considered both regional and overall regions. Researchers found that areas with reduced cortical thickness were concentrated in a specific brain network. The pattern of atrophy in this network resembled that seen in AD patients. Additionally, the stronger the connections between this network and other brain regions, the faster the cognitive and functional decline over the following five years[10]. These findings indicate that the relationship between structure and cognition is not just a correlation at a single point in time, but rather one that continues to reflect disease progression over time.

However, this relationship is not absolute. Indicators of brain atrophy, such as ventricular expansion, are associated with cognitive decline in AD, but the strength of this association varies depending on the specific brain regions evaluated.

3.2 Evidence of Mismatch Between Atrophy and Symptoms

Despite the overall consistency observed, studies on AD have reported cases where there is a significant mismatch between structural changes and the severity of clinical cognitive symptoms. This mismatch can be grouped into three main patterns: (1) significant GM atrophy with relatively preserved cognition, (2) relatively mild atrophy with severe cognitive impairment, and (3) a discrepancy between the rate of structural atrophy and the rate of cognitive decline.

The first pattern involves significant GM atrophy alongside relatively preserved cognitive function. Sato et al. observed this inconsistency in 135 patients with AD. Some patients showed severe brain atrophy as indicated by MRI, yet their cognitive impairment was only mild[11]. In this case, the severity of atrophy and the severity of symptoms are not correlated. Global atrophy measures may not capture the functional integrity of specific networks that support cognition.

The second pattern is the opposite. The atrophy detected is relatively mild, but the symptoms are severe. This phenomenon is less frequently reported in structural MRI studies, partly because patients with severe cognitive impairment almost always show significant atrophy. Such mismatches tend to emerge at the level of global atrophy that may underestimate some regional pathology in atypical AD.

The third pattern involves a discrepancy between the rate of structural atrophy and the rate of cognitive decline. Dicks et al. found that modeling GM atrophy based on time, age, or cognitive decline yields different anatomical patterns. This means that whether the structural and cognitive process appear consistent depends on the reference framework used. A patient might show rapid atrophy under one model but slower atrophy under another[3]. In another research, Chételat et al. reported that the correlation between amyloid-β load and atrophy is strong in cases of subjective cognitive impairment. But it disappears in cases of mild cognitive impairment (MCI) and AD[12]. This indicates that measurements of the same structural changes may have different clinical implications at various stages. This mismatch at different stages means that the relationship between atrophy and symptoms changes as the disease progresses.

It is worth noting that, a longitudinal analysis by Hosseininasabnajar et al. showed that global brain volume primarily affects the rate of cognitive decline, while indicators such as hippocampal volume affect the current level of cognition[13]. This suggests that the relationship between global brain atrophy and regional atrophy and cognition is not identical.

3.3 CR as a Key Regulatory Factor

CR acts as a regulatory factor in the relationship between atrophy and symptoms. And it is usually measured using alternative indicators. Education is one such common indicator[4]. The diversity of these indicators reflects different aspects of CR, which means that research results cannot be directly compared.

According to the framework based on CR, individuals with higher reserve should exhibit greater structural pathology at the same cognitive performance level. Staekenborg et al. found that individuals with higher education levels showed more severe atrophy in the medial temporal lobe at the same cognitive scores, which is consistent with this prediction[14]. Zhu et al. reported a similar pattern in mild AD, where education was associated with more severe structural and functional impairments at the same cognitive performance level[5]. However, Lövdén et al. found that education did not influence the relationship between hippocampal volume changes and memory changes, suggesting that the effect of CR may be specific to certain regions or may not exist under some certain conditions[15]. This result does not invalidate the CR framework, but it indicates that its explanatory scope is limited.

Therefore, CR should be considered as an important but not exclusive regulator of the relationship between atrophy and cognition. It can explain part of the mismatch between atrophy and symptoms, but its moderating effect relies on region, indicator, and disease stage. Other biological factors therefore also need to be taken into account.

There are usually two explanations for the performance of CR. The first is related to neural reserves. CR may be mediated by the neural networks in the body. When an in-

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dividual has a network with higher efficiency and greater capacity, they are better able to cope with changes such as those caused by age or diseases[4]. The second explanation involves a more efficient utilization of the remaining neural resources, which is neural compensation. In the study, when the efficiency of the key neural networks in older participants was limited, they tended to activate alternative neural networks, although the performance might be poorer[4].

3.4 Other Biological and Clinical Factors

In addition to CR, there are several biological and clinical factors that may influence the relationship between atrophy and symptoms. Vascular burden is indicated by white matter hyperintensity (WMH). Dadar et al. found that WMH is associated with GM atrophy in the insular and parieto-occipital regions in MCI and AD, and it leads to more severe cognitive deficits in AD compared to control groups[16]. This indicates that cerebrovascular pathology is not just a cumulative effect of neurodegenerative structural changes.

Sex has also emerged as a significant regulatory factor. Lee and colleagues found that in women with AD, the rate of thinning of the cortical layers in the prefrontal and temporal regions was faster over a period of five years compared to men[17], indicating that the relationship between brain atrophy and cognitive function varies depending on sex.

All these factors together suggest that the relationship between atrophy and symptoms is regulated by various elements. Such mismatches cannot be attributed solely to differences in CR.

3.5 Methodological Sources of Apparent Mismatches

Not all inconsistencies reflect biological factors. Methodological differences can produce apparent mismatches that are distinct from biological mismatch. Differences in MRI acquisition techniques, segmentation methods, and methods for quantifying atrophy have been well documented. Pini et al. pointed out that manual and automated methods for segmenting the hippocampus yield different volume estimates[1].

Cognitive assessments introduce further variations, as the different tools used are sensitive to changes in different ways. Studies that use the Mini-Mental State Examination (MMSE) may detect a stronger correlation between structural changes and cognitive functions than those that use comprehensive memory tests. This is because the former is less sensitive to subtle changes in specific cognitive areas[18].

The composition of the sample and the adjustment of covariates are also important. Whether a study adjusts for factors such as age, sex, education, and intracranial volume determines whether any associations are observed.

Therefore, methodological sources of mismatch deserve special attention and should be distinguished from biological mismatch. Apparent mismatches arising from MRI acquisition, segmentation, atrophy quantification, cognitive scales, or covariate differences should not be interpreted as evidence of biological regulatory mechanisms.

4. Discussion and Synthesis

4.1 Integration of the Relationship Between Atrophy and Cognition

GM atrophy is an important structural factor associated with cognitive impairment in AD. However, it is not the only determinant of the severity of symptoms. The association between GM atrophy and cognitive impairment in AD is most evident in the medial temporal lobe and episodic memory. This relationship can be observed even in preclinical stages[7][9]. Once analysis extends beyond memory and medial temporal lobe regions, this relationship becomes conditional.

Inconsistent literature shows these variations. Patients with severe atrophy does not necessarily translate into severe cognitive impairment. They may experience only mild impairments[11]. And mild atrophy can coexist with pronounced symptoms, especially in atypical AD. Longitudinally, the rate of structural change and the rate of cognitive decline are not always parallel. The connection between them can depend on the reference framework used[3]. Disease stage further modulates this relationship: the same structural measure may carry different clinical implications in subjective cognitive impairment compared with MCI and AD[12]. The relationship between atrophy and cognition depends on multiple factors. Just looking at the severity of atrophy may explain some aspects of cognitive status, but it cannot fully describe the actual brain-wide cognitive conditions. Atrophy sets a baseline for cognitive expression, but the gap between the baseline and the actual clinical severity is determined by CR, pathology, disease stage, and measurement conditions.

4.2 How CR Explains Inconsistencies

CR partly explains why atrophy and cognitive impairment are separate. Individuals with higher CR are thought to possess more efficient or higher-capacity neural resources and to recruit alternative networks when primary ones are compromised[4]. This explains why individuals with higher education tend to have more atrophy under the same cognitive performance[5,14].

However, education cannot regulate the relationship between hippocampal volume changes and memory changes[15], which means the effect of CR is not universal across all regions and its explanatory power has limits. The capacity of neural resources may varies across different brain regions. As for the indicator, since education captures only one aspect of CR, it may not reflect other contributors[4]. Moreover, as the stage of pathology ac-

cumulates, the compensation of CR may weakens. Thus, CR can explain part of the mismatch, but its explanatory power depends on region, indicator, and stage.

This also clarifies why CR should not be treated as the sole explanation. Compared to other biological and methodological factors, CR occupies a different position. Vascular burden and Sex changes the relationship between atrophy and symptoms through mechanisms that do not rely on CR[16,17]. Methodological differences may lead to inconsistencies without any biological basis[1][18]. CR serves as an important framework for understanding the discrepancy between atrophy and cognitive disorders. It works together with other factors, playing different roles in various situations. Overlooking other factors would lead to an incomplete understanding of the mismatch between atrophy and cognition.

4.3 Clinical and Research Significance

For clinical practice, when assessing the severity of cognitive disorders, structural MRI should not be interpreted in isolation. The severity of atrophy provides useful information, but its interpretation depends on the CR, disease stage, and other pathology of patients. The same degree of GM atrophy may have different meanings in a patient with high education and MCI stage compared to a patient with additional vascular burden and deeper AD stage.

For future research, it is necessary to combine longitudinal imaging studies. Standardization of cognitive assessments is also important to reduce biases caused by methodological factors. Additionally, clearer indicators of CR are needed, rather than relying only on educational factors. Other disease stages and pathological conditions should also be taken into account.

5. Conclusions

This review supports three main conclusions. First, there is a correlation between GM atrophy and cognitive deficits in AD. This relationship exists even before clinical diagnosis and persists over time[9]. Second, there are indeed discrepancies between structural atrophy and cognitive impairment. These discrepancies should not be interpreted as exceptions that can be explained by the severity of atrophy. Third, CR is a key factor that helps explain these discrepancies. Individuals with high CR often exhibit more pathological features under the same cognitive performance levels. but the role of CR in explaining these differences is limited. Overall, GM atrophy provides the structural basis for cognitive impairment in AD, but clinical cognitive performance is not determined by atrophy severity alone. Rather, it is jointly influenced by regional pathology, disease stage, CR, and measurement-related methodological factors.

Longitudinal imaging and multi-modal approaches are valuable for understanding individual differences in clinical manifestations. Longitudinal imaging allows us to distinguish between baseline and rate-related associations, while multi-modal approaches enable the integration of structural, functional, molecular pathological, and cognitive data. Only through these methods can we better understand why patients with similar levels of atrophy may exhibit different symptoms.

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