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Review Article

Current understanding of magnetic resonance imaging biomarkers and memory in Alzheimer's disease

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Abstract Alzheimer's disease (AD) is caused by a cascade of changes to brain integrity. Neuroimaging biomarkers are important in diagnosis and monitoring the effects of interventions. As memory impairments are among the first symptoms of AD, the relationship between imaging findings and memory deficits is important in biomarker research. The most established magnetic resonance imaging (MRI) finding is hippocampal atrophy, which is related to memory decline and currently used as a diagnostic criterion for AD. While the medial temporal lobes are impacted early by the spread of neurofibrillary tangles, other networks and regional changes can be found quite early in the progression. Atrophy in several frontal and parietal regions, cortical thinning, and white matter alterations correlate with memory deficits in early AD. Changes in activation and connectivity have been detected by functional MRI (fMRI). Task-based fMRI studies have revealed medial temporal lobe hypoactivation, parietal hyperactivation, and frontal hyperactivation in AD during memory tasks, and activation patterns of these regions are also altered in preclinical and prodromal AD. Resting state fMRI has revealed alterations in default mode network activity related to memory in early AD. These studies are limited in part due to the historic inclusion of patients who had suspected AD but likely did not have the disorder. Modern biomarkers allow for more diagnostic certainty, allowing better understanding of neuroimaging markers in true AD, even in the preclinical stage. Larger patient cohorts, comparison of candidate imaging biomarkers to more established biomarkers, and inclusion of more detailed neuropsychological batteries to assess multiple aspects of memory are needed to better understand the memory deficit in AD and help develop new biomarkers. This article reviews MRI findings related to episodic memory impairments in AD and introduces a new study with multimodal imaging and comprehensive neuropsychiatric evaluation to overcome current limitations.

Keywords: Alzheimer's disease; Dementia; Magnetic resonance imaging; Memory; Biomarker

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting from pathological changes which typically spread through brain networks in a predictable pattern. AD pathology leads to early decline in memory, and some pathology can be detected years before measurable cognitive or functional change. At present, there are no disease-modifying treatments, and symptomatic treatment is limited in efficacy. Trials of novel therapeutics increasingly target the earliest brain changes, when a disease-modifying trajectory could potentially result in reduction or elimination of clinical impact. Memory measures remain an important way of assessing such clinical impact and are required in clinical trials in the United States [1].

Accurate diagnosis of AD was, until recently, confirmed only at autopsy. Today, there are several imaging biomarkers measuring neurodegeneration and amyloid β (Aβ) deposition in the brain to support the diagnosis [2]. Atrophy on

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structural magnetic resonance imaging (MRI), hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), and increased levels of craniospinal fluid (CSF) total and phosphorylated tau are used to assess neurodegeneration. CSF Aβ42 and Aβ PET, on the other hand, are used to assess Aβ pathology. Preclinical studies focus on groups at risk for AD, as defined by the apolipoprotein E e4 (APOEe4) status or examine cognitively normal control (CNC) performance in the context of other AD biomarkers, such as CSF Aβ. Large, shared, multisite, longitudinal multimodal data sets such as the AD Neuroimaging Initiative and similar studies initiated in Asia, Europe, and Australia allow for widespread exploration of structural and functional magnetic resonance imaging (fMRI) and PET data in addition to clinical, cognitive, and fluid biomarker data across the spectrum of disease. While there are several limitations, these data sets are an important resource in understanding imaging biomarkers in AD.

Memory is a complex construct. AD has an early and specific impact on episodic memory (i.e., the ability to learn and remember new information) [3], which can broadly be subdivided into encoding (or learning), recall, and recognition. Different types of stimuli (e.g., words, faces, and shapes) and memory tests (e.g., single trial and multi-trial presentations, free and prompted recall) can be used to detect deficits in these aspects of memory, and typically used measures often differ between clinical and research settings. Nonetheless, many studies of AD MRI biomarkers and biomarker candidates have included memory measures as correlates or validating factors.

At present, despite exploration of imaging biomarkers for AD, few have become widely accepted and approved for clinical use, and most remain experimental. In this targeted review, we focused on MRI studies. Following the conceptualization of AD as a biological and clinical continuum by Aisen et al [4], we assessed the MRI findings within preclinical (clinically normal individuals with evidence of AD pathology), and clinical (mild cognitive impairment [MCI] or prodromal AD, and AD dementia [ADD]) phases of AD. The transition between these phases is subtle, and individuals may report cognitive decline even when neuropsychological testing does not suggest any impairment. As episodic memory is the first cognitive domain to be affected along the course of AD, we aimed to investigate the association between MRI findings and episodic memory performance specifically. Current diagnostic criteria of MCI (prodromal AD) and ADD are based on clinical history, neuropsychological testing, and neurologic and psychiatric examinations [5,6]. Imaging methods, CSF, and blood tests are used only to support the diagnosis and to exclude other dementia causes. Nevertheless, subtle findings on MRI have been reported years before the onset of clinical symptoms. Thus, imaging findings correlating with the clinical profile may help identify underlying mechanisms and therapeutic targets for the debilitating memory deficit in AD.

2. Structural MRI

Aging is associated with a slow decline in both white matter (WM) and gray matter (GM) volumes, and this atrophy rate is increased in AD [7]. Although GM atrophy has been more frequently assessed in AD, structural MRI approaches also allow for the assessment of cortical thickness, as well as shape and WM alterations. This section will focus on studies investigating the relationship between episodic memory performance and structural changes in GM and WM using different imaging analysis approaches (Table 1). Structural differences between CNC and participants within AD spectrum without any episodic memory associations are beyond the scope of this review and will not be discussed.

2.1. GM changes

Hippocampal atrophy is included in the 2011 NIA criteria for ADD and MCI due to AD [3,5]. Before the advent of Aβ PET imaging, hippocampal volumetric changes that can be determined noninvasively and relatively cheaply using MRI were one of the earliest detectable imaging changes in AD. These changes can be quantified using NeuroQuant, an FDA-approved imaging processing tool [42]. Decline in hippocampal volume and thickness has been consistently associated with memory deficits in AD continuum. In preclinical AD, hippocampal and entorhinal cortex volume, and hippocampal and parahippocampal thickness have been associated with verbal memory [9,12,30]. There have also been reported associations between reduced medial temporal lobe (MTL) volume in CNC with AD risk factors and future memory decline [8]. Further along the course of the disease, in MCI and ADD, decline in hippocampal volume and MTL thickness was associated with worsening in verbal memory [13,16,19,21,23–27,29,33–35,39,40]. Although less extensively studied, visual memory has been associated with hippocampal volume in amnestic MCI (aMCI) [39]. Studies of hippocampal subregions revealed that CA1 volume declines within hippocampus were particularly related with recall performance in aMCI and ADD [26,29,37].

With time, GM changes in AD spread outside the MTL. Extratemporal regions implicated in episodic memory decline include the posterior cingulate gyrus (PCG)/precuneus [28,30,31] and middle frontal gyrus [27,28]. Both atrophy and thinning of these regions were associated with memory decline. In MCI patients, who converted to ADD over time, decreased inferior frontal gyrus volume was associated with the verbal memory decline [38], suggesting extratemporal involvement may be predictive of disease progression.

2.2. WM changes

While AD is a disease primarily associated with GM loss, concomitant WM change has a role in cognitive expression.