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a0005

Alzheimer's Disease: MRI Imaging of Progressive Brain Change

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s0005

Introduction

p0005 Alzheimer's disease (AD) is the leading cause of senile dementia, affecting 10% of those over age 65. The disease causes irreversible memory loss, behavioral and cognitive decline, personality changes, and a decreasing ability to cope with everyday life. Ironically, up to 30 years elapse between the onset of the cellular pathology that causes AD (amyloid plaques and neurofibrillary tangles in the brain) and the clinical changes that lead to diagnosis. To help understand how the disease emerges and progresses, imaging technology can be applied that is safe, repeatable, and widely available. Magnetic resonance imaging (MRI) scans of AD patients reveal profound anatomic changes: severe cortical and hippocampal atrophy, sulcal and ventricular enlargement, and reduced gray matter and white matter volume. These changes occur in a distinct spatial and temporal sequence, and correlate with cognitive and metabolic decline. If patients are scanned repeatedly with MRI as their disease progresses, dynamic maps can be reconstructed that reveal a shifting pattern of cortical changes. This spreading cortical atrophy mirrors the spread of the underlying pathology (as defined by tangle and amyloid plaque deposition). Repeat MRI scanning can monitor disease progression in individual patients and can evaluate how drugs oppose these changes. It can also clarify how anatomical deficits link with cognitive and behavioral deficits as they emerge in individuals and populations.

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Impact

p0010 Alzheimer's disease is a severe and growing public health crisis. The incidence of AD doubles every 5 years after age 60. It afflicts 1% of those aged 60 to 64 and 30% to 40% of those over 85. Without a cure, the number of AD victims will rise from 2.0 to 3.5 million now to an estimated 10 to 14 million by 2030. A number of promising AD treatments are now being developed. These range from acetylcholinesterase inhibitors, which ballast neurotransmitter function, to experimental vaccines, which directly attack the amyloid plaques that are a key element of AD pathology. Most therapeutic trials of new drugs in AD rely primarily on cognitive tests to determine efficacy. Neuroimaging, however, can be extremely beneficial in this research. It supplies a variety of biological markers that measure disease progression. With novel brain mapping techniques, the disease can be tracked as it spreads in the living brain. In Alzheimer's patients, MRI scans show prominent hippocampal atrophy. Diffuse tissue loss is also found in the medial temporal lobes. These deficits are progressive, and their magnitude correlates with cognitive decline. Because it is vital to detect the disease early, there is great interest in developing MRI measures that predict imminent transition to dementia, in healthy elderly subjects. For example, significant hippocampal volume deficits are found in subjects with mild memory impairments, who do not yet have dementia. These deficits shown on MRI can also help to predict how soon an elderly individual will develop AD. Reliable MRI predictors are especially valuable, as cholinergic drugs are most effective in the mildest phases, when widespread neuronal loss has not yet occurred.

p0015 Several neuroimaging measures can be used to characterize dementia. For instance, MRI scans can assess the integrity of medial temporal lobe structures involved in memory, such as the entorhinal cortex and hippocampus. The region and rate of atrophic brain changes can be measured as the disease progresses, as can the profile of cortical thinning and gray matter loss. The required three-dimensional MRI scans can be performed in approximately 10 min, on a conventional 1.5-Tesla scanner. Although MRI is not routinely used to diagnose AD, new techniques in brain image analysis can be applied to MRI scans to reveal how the disease emerges, and track how medications affect the disease process. MRI scans are often used in dementia research to (1) screen at-risk populations to find anatomical measures that might help predict each individual's likelihood of developing AD, (2) discriminate AD from normal aging and other dementias (such as frontotemporal and Lewy body dementias, which have distinct anatomic patterns), and (3) monitor disease progress and therapeutic response, gauging the effectiveness of drug treatments.

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Brain Tissue Loss and Cognitive Decline

p0020 In the 1990s, MRI research in dementia focused on measuring medial temporal lobe structures. This was because AD pathology typically starts in the temporal cortex adjacent to the entorhinal cortex and quickly spreads to the entorhinal cortex before involving the

hippocampus. This temporal lobe pathology persists for several years before spreading cortically to engulf the rest of the temporal, frontal, and parietal lobes. A more recent trend in dementia research has been to move from cross-sectional studies to dynamic measures. Serial MRI scans (acquired from the same patients repeatedly over time) can provide much greater power to detect pathological atrophy, because they provide a baseline reference point to calculate change. Fox et al. found that AD patients lose brain tissue at a faster *rate* than age-matched controls. Evaluated with MRI for 5 to 8 years, AD patients lost brain tissue at a median rate of 2.20% per year (range, 0.82 to 4.19) versus 0.24% per year in controls (range, −0.35 to 0.64). These rates correlated with the rate of cognitive decline, reflected by worsening performance on the Mini Mental Status Examination (MMSE). In a recent 52-week clinical trial of milameline (a muscarinic receptor agonist), Jack et al. noted that hippocampal volume, measured with MRI, also tracked cognitive decline. Perhaps the most prominent sign of AD seen on an MRI scan is that the lateral ventricles are often greatly enlarged. Bradley et al. measured the ratio of the ventricular volume to the total brain volume (the ventricle-to-brain ratio [VBR]) in 39 elderly subjects scanned with serial MRIs over 3 to 6 month intervals. The VBR rate of change was 15.6% ± 2.8% (mean ± SD) per year for AD patients compared with 4.3% ± 1.1% per year in controls ($P < 0.001$). VBR did not separate groups when measured at only a single time point, supporting the value of longitudinal assessments. Power calculations revealed that 135 subjects would be needed in each arm of a placebo-controlled clinical trial if this measure of AD progression were to detect a 20% reduction in the excess rate of atrophy over 6 months, with 90% power.

Gray Matter Deficits

s0020

Brain changes in AD can also be visualized using three-dimensional maps. **Figure 1** shows the spatial pattern of cortical gray matter loss in mild to moderate AD. This type of image is a composite map; it results from a sequence of image processing steps that compare scans of AD patients with matched healthy elderly subjects. With image analysis techniques, three-dimensional brain MRI scans can be split up into regions representing gray matter, white matter, and cerebrospinal fluid. A measure is then computed that is related to the thickness of the cortical gray matter at each cortical location. Computer analyses

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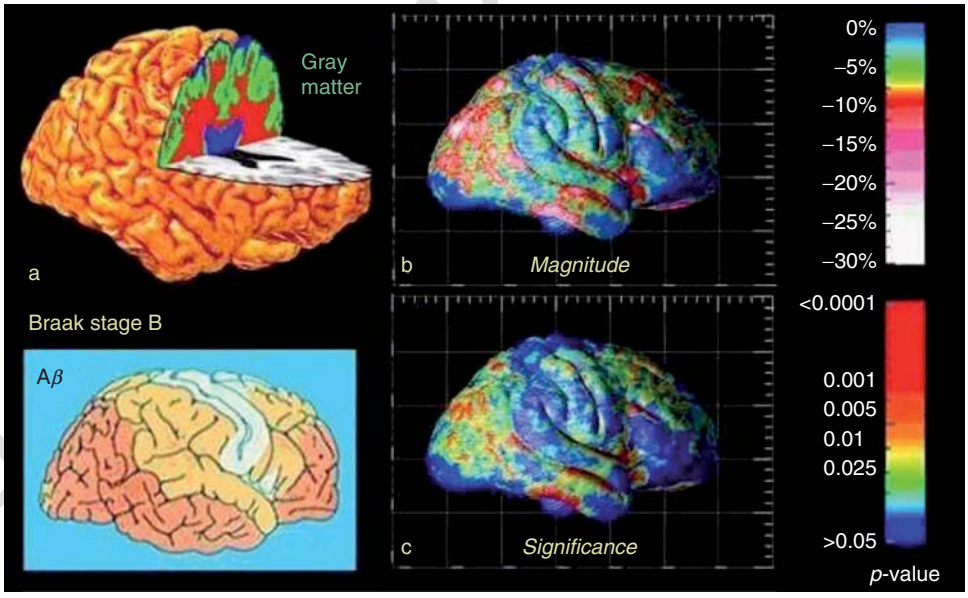

f0005 **Figure 1** Gray matter deficits in early AD. Here the local amount of cortical gray matter (green colors, [a]) is compared across 26 patients with mild to moderate AD (age, 75.8 ± 1.7 years; MMSE score, 20.0 ± 0.9) and 20 matched elderly controls (age, 72.4 ± 1.3 years). At this stage of AD, 30% of the cortical gray matter has been lost in the temporoparietal regions (b). (c) Statistical significance of these deficits. The pattern of temporal lobe gray matter loss, seen on MRI, spatially matches the pattern of (Aβ) deposition seen postmortem. The inset panel (Braak stage B) is adapted from data reported by Braak and Braak (1997). It shows regions with minimal (white), moderate (orange), and severe (red) Aβ deposition. Amyloid deposition and gray matter loss may not be synchronized, so these maps may represent different stages of AD; however, there is a clear spatial agreement in the severity of the deficits, between MRI and Aβ maps. Primary sensorimotor regions (white in the amyloid map), and the superior temporal gyri (blue colors in [c]) are spared relative to other temporal lobe gyri. These MRI patterns have been replicated in independent studies by Thompson et al. (2001), and Baron et al. (2001), and O'Brien et al. (2001).

then compare the amount of gray matter at each cortical location across subjects, while adjusting for potentially confounding factors, such as age and gender effects, and gyral patterning differences. Differences can be visualized locally in the form of color-coded statistical maps. These show how much gray matter volume is reduced in AD patients relative to healthy controls in each cortical region

Maps of Disease Progression

MRI scanning also reveals a dynamically spreading wave of gray matter loss in the brains of patients with AD. With novel brain mapping methods, the loss pattern can be visualized as it spreads over time from temporal and limbic cortices into frontal and occipital brain regions, sparing sensorimotor cortices. These shifting deficits are correlated with cognitive decline. As shown in **Figure 2**, cortical atrophy occurs in a well-defined sequence as the disease progresses, mirroring the temporal sequence of beta-amyloid and neurofibrillary tangle accumulation observed at autopsy. The trajectory of deficits also matches the sequence of metabolic decline typically observed with positron emission tomography.

To map AD progression, advancing deficits can be visualized as dynamic video maps that change over time, which distinguish different phases of AD and differentiate AD from normal aging. Frontal brain regions, spared early in the disease, show pervasive deficits later (>15% loss). Local gray matter loss rates ($5.3 \pm 2.3\%$ per year in AD versus $0.9 \pm 0.9\%$ per year in controls) are faster in the left hemisphere than the right, at least at this stage of AD. Transient barriers to disease progression also appear. A frontal band (0% to 5% loss) is sharply delimited from the limbic and temporoparietal regions that show severest deficits in AD (>15% loss). This pattern is consistent with the hypothesis that AD pathology spreads centrifugally from limbic/paralimbic to higher-order

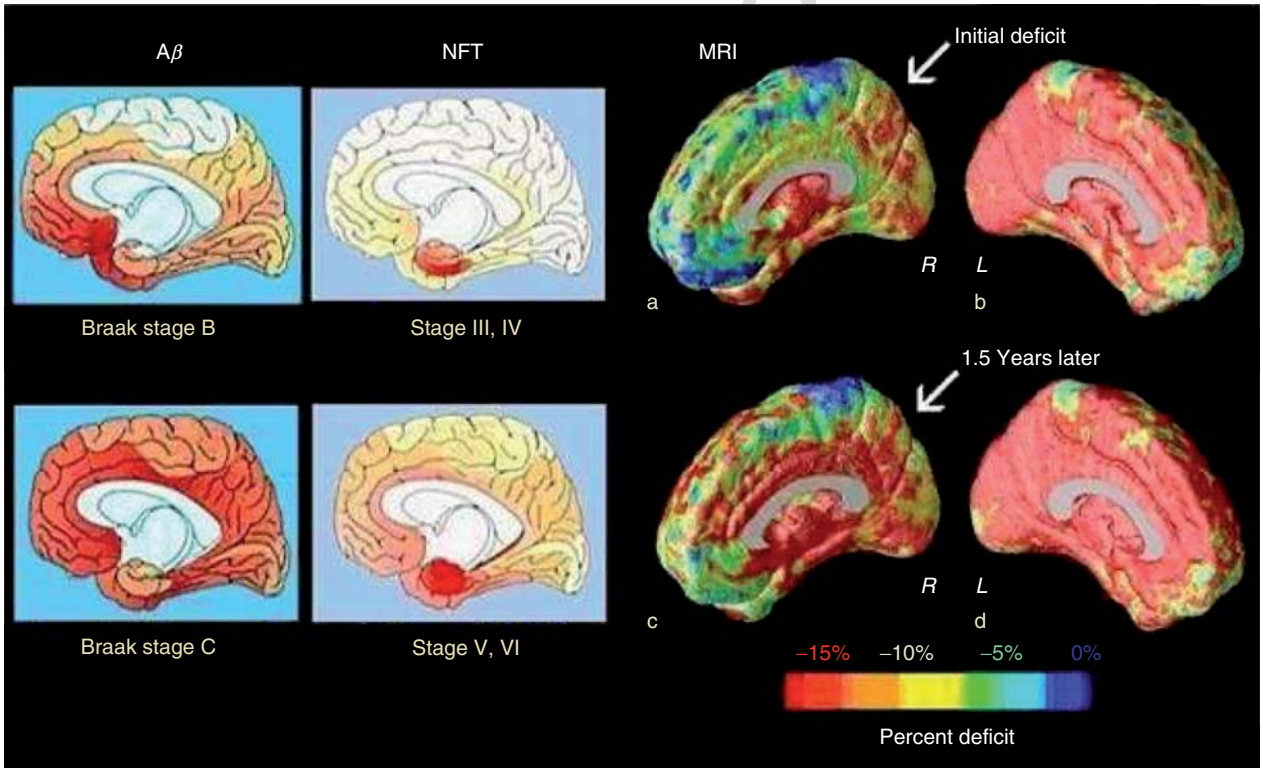

Figure 2 Gray matter deficits spread through the limbic system in moderate AD. Deficits during the progression of AD are detected by comparing average profiles of gray matter volumes between 12 AD patients (age, 68.4 ± 1.9 years) and 14 elderly matched controls (age, 71.4 ± 0.9 years). Colors show the average percent loss of gray matter relative to the control average. Profound loss engulfs the left medial wall (>15% [b], [d]). On the right, however, the deficits in temporoparietal and entorhinal territory (a) spread forward into the cingulate gyrus 1.5 years later (c), after a 5-point drop in average MMSE test scores. Limbic and frontal zones are prominently divided, with different degrees of impairment (c). MRI-based changes, observed in living patients, agree strongly with the spatial progression of Aβ and NFT pathology observed postmortem (Braak stages B and C and III to VI; left four panels adapted from Braak and Braak. 1997). NFT accumulation is minimal in sensory and motor cortices, but occurs preferentially in entorhinal pyramidal cells, the limbic periallocortex (layers II/IV), the hippocampus/amygdala and subiculum, the basal forebrain cholinergic systems and subsequently in temporoparietal and frontal association cortices (layers III/V).

association cortices. This degenerative sequence, observed as it develops in living patients, provides a quantitative, dynamic visualization of cortical atrophic rates in dementia, over a period of cognitive decline lasting 1.5 years.

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What is Gray Matter Atrophy?

p0040 Gray matter atrophy observed on MRI is linked with cognitive decline in AD and is attributable to several cellular processes. In healthy aging, age-related neuronal loss does not occur in most neocortical regions and appears specific to the frontal cortex and some hippocampal regions (e.g., CAI and the subiculum). In AD, however, there is substantial neuronal loss, with severe early losses in layer II of the entorhinal cortex.

s0035

Beta-Amyloid and Neurofibrillary Tangle Maps

p0045 MRI-based maps of cortical atrophy agree strongly with postmortem maps of beta-amyloid deposition (Aβ, **Figure 2**). Beta-amyloid is an insoluble protein that is a key feature of Alzheimer pathology. The spatial congruence of these two maps supports the hypothesis that Aβ deposition may participate in the cascade of events that leads to regional gray matter atrophy and neuronal cell loss. In both maps, primary sensorimotor cortices are relatively spared until late in the disease, and the superior temporal gyrus is less affected than other temporal lobe gyri. In early AD, intraneuronal filamentous deposits, or neurofibrillary tangles (NFTs), also accumulate within neurons. These deposits are composed of hyperphosphory lated tau-protein. This cellular pathology disrupts axonal transport and induces widespread metabolic decline; it eventually leads to neuronal loss, observed as gross atrophy on MRI. Braak and Braak noted on autopsy that NFT distribution was initially restricted to entorhinal cortices, spreading to higher-order temporoparietal association cortices, then frontal, and ultimately primary sensory and visual areas. MRI scans suggest that a similar wave of cortical atrophy can be mapped in patients while they are alive. This provides a biological marker of disease progression that can monitor the effects of therapy.

p0050 It remains a mystery why brain changes in AD occur in this sequence. Braak and Braak suggested that the atrophic trajectory in AD is somewhat the reverse of the sequence in which cortical areas are myelinated during development. For example, primary sensory regions myelinate first and degenerate last, and temporal regions mature last but degenerate first in AD. This palindromic sequence is largely supported by the pattern of cortical changes observed on MRI. The selective vulnerability of specific cortical systems in AD may relate to differences in cellular maturational rates and/or plasticity. The most plastic systems may also be most vulnerable to AD.

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Conclusion

p0055 MRI scans can measure brain change in AD, mapping the disease process in detail. MRI measures of disease progression, along with measures of genetic risk and abnormalities in specific neuropsychological tests, now provide key quantitative predictors to monitor brain degeneration and gauge how well it is decelerated or delayed in clinical trials.

See also: Aging of the brain and Alzheimer's Disease (00539); Molecular Genetics of (00545); Neuroimaging (00309); A magnetic resonance spectorscopy approach (01709); Magnetic resonance spectroscopy (00300); PET (00323); SPECT (01937).

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