ALZHEIMER'S DISEASE: MRI IMAGING

OF PROGRESSIVE BRAIN CHANGE

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1. Introduction

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 thirty 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 (Thal et al., 2002). To help understand how the disease emerges and progresses, imaging technology can be applied that is safe, repeatable, and widely available. MRI scans of AD patients reveal profound anatomical 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 be used to 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.

Impact of Alzheimer's Disease. 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 30-40% of those over 85. Without a cure, the number of AD victims will rise from 2 to 3.5 million now to an estimated 10-14 million by the year 2030 (Malmgren, 2000). 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 early detection of the disease is vital, there is great interest in developing MRI measures that can predict imminent transition to dementia, in healthy elderly subjects (Kaye et al., 1997; Convit et al., 2000). For example, significant hippocampal volume deficits are found in subjects with mild memory impairments, who do not yet have dementia. These MRI deficits can also help to predict how soon an elderly individual will develop AD (Jack et al., 2003). Reliable MRI predictors are especially valuable, as cholinergic drugs are most effective in the mildest phases, when widespread neuronal loss has not yet occurred.

Several neuroimaging measures can be used to characterize dementia (Chetelat and Baron, 2003). 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 3D MRI scans can be performed in approximately 10 minutes, on a conventional 1.5 Tesla scanner. While 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 anatomical patterns); and (3) monitor disease progress and therapeutic response, gauging the effectiveness of drug treatments.

Brain Tissue Loss and Cognitive Decline.   In the 1990s, MRI research in dementia focused on measuring medial temporal lobe structures (Jobst et al., 1994). This was because Alzheimer pathology typically starts in the temporal cortex adjacent to the entorhinal cortex and quickly spreads to the entorhinal cortex before involving the hippocampus (Braak and Braak, 1997; Frisoni et al., 1999; Laakso et al., 2000). This temporal lobe pathology persists for several years before spreading cortically to engulf the rest of the temporal, frontal, and parietal lobes (Thal et al, 2002). A more recent trend in dementia research has been to move from cross-sectional studies to dynamic measures. Serial MRI scans (i.e., acquired from the same patients repeatedly over time) can provide much greater power to detect pathological atrophy, as they provide a baseline reference point to calculate change. Fox and colleagues (2001) 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] (Scahill et al., 2002). These rates correlated with the rate of cognitive decline, reflected by worsening performance on the MMSE (Fox et al., 2001). In a recent 52-week clinical trial of milameline (a muscarinic receptor agonist), Jack et al. (2003) noted that hippocampal volume, measured with MRI, also tracked cognitive decline. Perhaps the most prominent sign of Alzheimer's disease seen in an MRI scan is that the lateral ventricles are often greatly enlarged. Bradley et al. (2002) measured the ratio of the ventricular volume to the total brain volume (i.e., the ventricle-to-brain ratio; VBR), in 39 elderly subjects scanned with serial MRI over 3-6 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. 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 Alzheimer's disease progression were to detect a 20% reduction in the excess rate of atrophy over 6 months, with 90% power.

Gray Matter Deficits in Alzheimer's Disease.   Brain changes in Alzheimer's disease can also be visualized using 3-dimensional *maps*. Figure 1 shows the *spatial pattern* of cortical gray matter loss in mild to moderate AD (Thompson et al., 2001). This type of image is a composite map; it results from a sequence of image processing steps that compare scans of AD patients and matched healthy elderly subjects (Thompson et al., 2003). With image analysis techniques, 3D brain MRI scans can be split up into regions representing gray matter, white matter, and cerebrospinal fluid (CSF). A measure is then computed that is related to the thickness of the cortical gray matter, at each cortical location. Computer analyses 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 the extent to which the gray matter volume is reduced, in AD relative to healthy controls, in each cortical region.

Maps of Disease Progression in AD.   MRI scanning also reveals a *dynamically spreading* wave of gray matter loss in the brains of patients with AD (Thompson et al., 2003). 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 Fig. 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 (PET).

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 (Thompson et al., 2003). Frontal brain regions, spared early in the disease, show pervasive deficits later (>15% loss). Local gray matter loss rates (5.3±2.3% per year in AD *versus* 0.9±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 (0-5% loss) is sharply delimited from the limbic and temporo-parietal 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 association cortices (Mesulam, 2002). 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 (see

URL, http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html for several of these time-lapse movies).
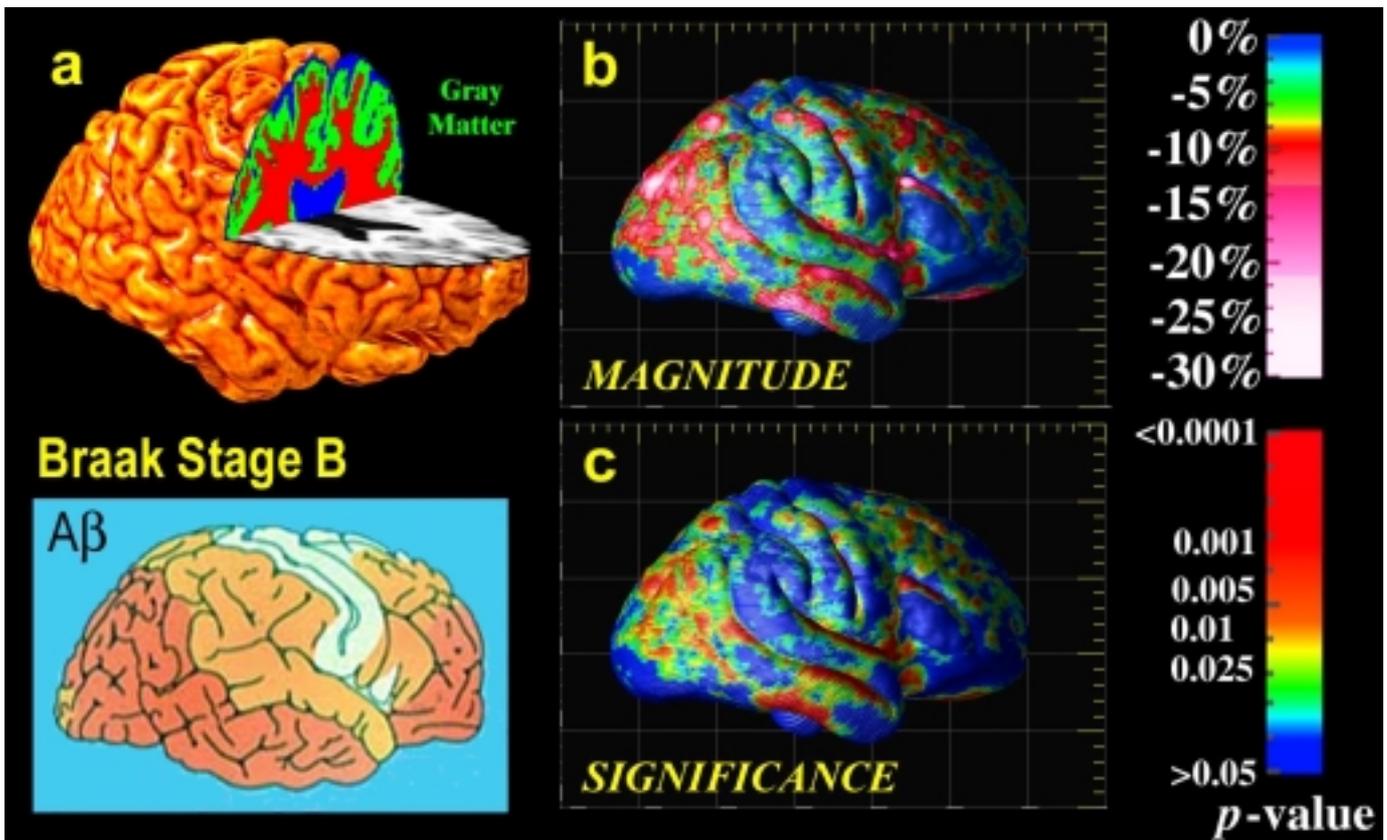

Figure 1. Gray Matter Deficits in Early AD. Here the local amount of cortical gray matter (*green colors*, (a)) is compared across 26 patients with mild to moderate AD (age: 75.8±1.7 yrs.; MMSE score: 20.0±0.9) and 20 matched elderly controls (72.4±1.3 yrs.). At this stage of AD, 30% of the cortical gray matter has been lost in the temporoparietal regions (b). (c) shows the statistical significance of these deficits. The pattern of temporal lobe gray matter loss, seen with MRI, spatially matches the pattern of beta-amyloid (Aβ) deposition seen *post mortem*. 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*) beta amyloid 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 beta amyloid 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), Baron et al. (2001), and O'Brien et al. (2001).

What is Gray Matter Atrophy? Gray matter atrophy observed with MRI is linked with cognitive decline in Alzheimer's disease, and is attributable to several cellular processes. In healthy aging, age-related neuronal loss does not occur in most neocortical regions (Morrison and Hof, 1997), and appears specific to the frontal cortex and some hippocampal regions (e.g., CA1 and the subiculum; Peters et al., 1998). In AD however, there is substantial neuronal loss, with severe early losses in layer II of the entorhinal cortex (Gomez-Isla et al., 1997).

Beta-Amyloid and Neurofibrillary Tangle Maps. MRI-based maps of cortical atrophy agree strongly with *postmortem* maps of beta-amyloid deposition (Aβ; Fig. 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 hyperphosphorylated 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 (1997) noted at autopsy that NFT distribution was initially restricted to entorhinal cortices, spreading to higher order temporo-parietal 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 be used to monitor effects of therapy.
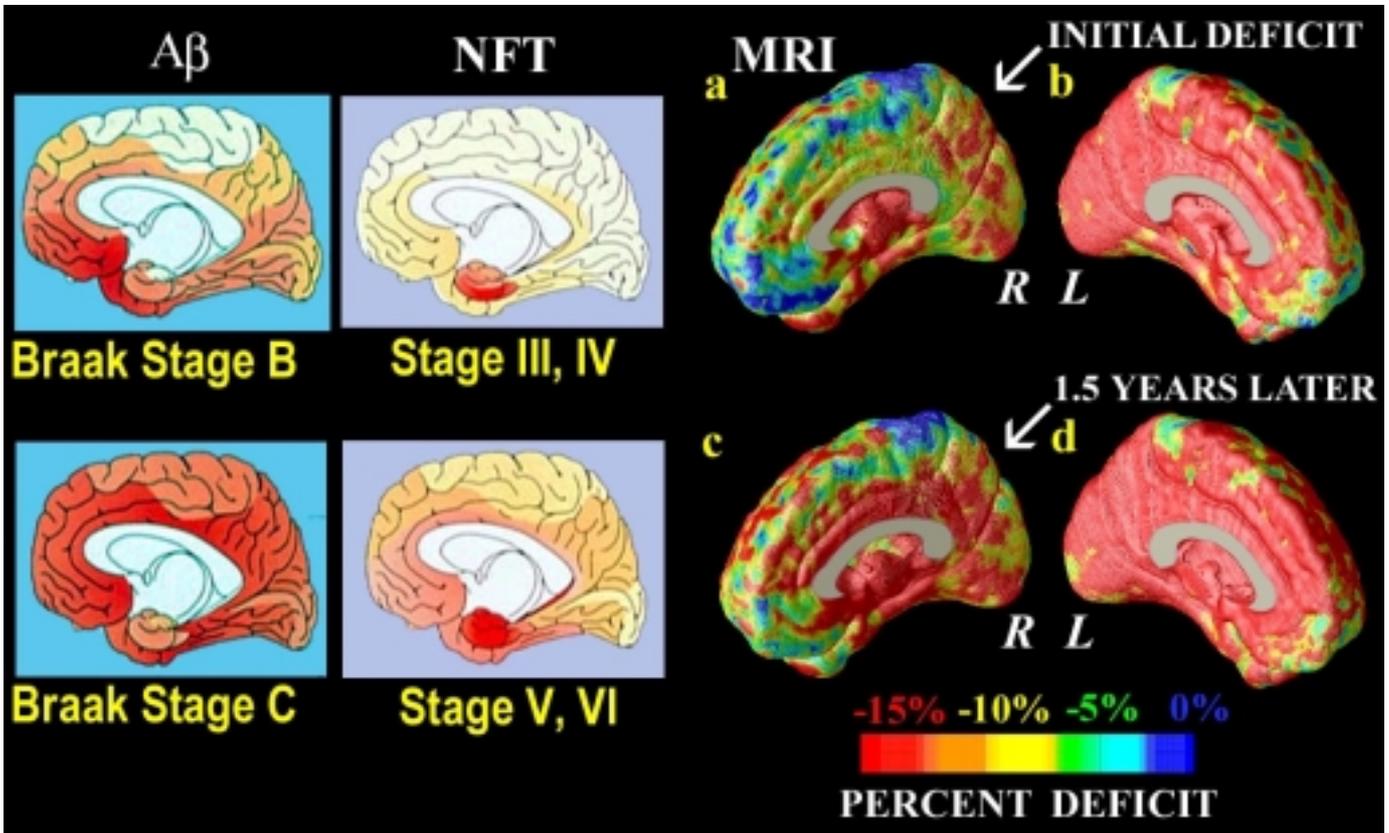
Figure 2. Gray Matter Deficits Spread through the Limbic System in Moderate AD. Deficits during the progression of AD are detected by comparing average profiles of gray matter volumes between 12 AD patients (age: 68.4±1.9 yrs.) and 14 elderly matched controls (age: 71.4±0.9 yrs.). Colors show the average 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 temporo-parietal and entorhinal territory (a) spread forwards into the cingulate gyrus 1.5 years later (c), after a 5 point drop in average MMSE cognitive test scores. Note the prominent division between limbic and frontal zones, with different degrees of impairment (c). MRI-based changes, observed in living patients, agree strongly with the spatial progression of beta-amyloid (Aβ) and neurofibrillary tangle (NFT) pathology observed *post mortem* (*Braak Stages B,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 temporo-parietal and frontal association cortices (layers III/V; Arnold et al., 1991).

It remains a mystery why brain changes in AD occur in this sequence. Braak and Braak (1997) 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, while temporal regions mature last but degenerate first in AD. This palindromic sequence is largely supported by the pattern of cortical changes observed with 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 (Mesulam, 2002).

Conclusion

MRI scans can measure brain change in Alzheimer's disease, 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:

Time Lapse Videos of Brain Change in Alzheimer's Disease

http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html

Time Lapse Videos of Brain Change in Schizophrenia

http://www.loni.ucla.edu/~thompson/MOVIES/SZ/sz.html

Further Reading

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