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Mapping Progressive Brain Structural Changes in Early Alzheimer's Disease and Mild Cognitive Impairment

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Abstract

Alzheimer's disease (AD), the most common neurodegenerative disorder of the elderly, ranks third in health care cost after heart disease and cancer. Given the disproportionate aging of the population in all developed countries, the socio-economic impact of AD will continue to rise. Mild cognitive impairment (MCI), a transitional state between normal aging and dementia, carries a 4–6-fold increased risk of future diagnosis of dementia. As complete drug-induced reversal of AD symptoms seems unlikely, researchers are now focusing on the earliest stages of AD where a therapeutic intervention is likely to realize the greatest impact. Recently neuroimaging has received significant scientific consideration as a promising *in vivo* disease-tracking modality that can also provide potential surrogate biomarkers for therapeutic trials. While several volumetric techniques laid the foundation of the neuroimaging research in AD and MCI, more precise computational anatomy techniques have recently become available. This new technology detects and visualizes discrete changes in cortical and hippocampal integrity and tracks the spread of AD pathology throughout the living brain. Related methods can visualize regionally specific correlations between brain atrophy and important proxy measures of disease such as neuropsychological tests, age of onset or factors that may influence disease progression. We describe extensively validated cortical and hippocampal mapping techniques that are sensitive to clinically relevant changes even in the single individual, and can identify group differences in epidemiological studies or clinical treatment trials. We give an overview of some recent neuroimaging advances in AD and MCI and discuss strengths and weaknesses of the various analytic approaches.

Introduction

Alzheimer's disease (AD), the most common cause of degenerative dementia, causes progressive brain atrophy. These atrophic changes are readily observed with structural neuroimaging. In the past three decades, several important technological leaps have allowed us to study the brain, as degeneration progresses. Magnetic resonance imaging (MRI), currently the structural neuroimaging method of choice for diagnostic and research efforts, revolutionized the field several decades ago. More recently, advanced analytic techniques have become available further empowering our ability to discover disease associated pathologic changes and clinical correlations *in vivo*. In this review we will provide a comprehensive

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overview of recent advances in MRI research on AD and related diseases, while critically appraising the methodology.

Alzheimer's Disease

AD is the commonest form of dementia worldwide - it currently affects 4.9 million elderly over the age of 65 and as many as 500,000 people under the age of 65 in the United States alone.(1) It manifests with relentlessly progressive cognitive decline presenting initially as memory loss and then spreads to affect all other cognitive faculties and the patients' ability to conduct an independent lifestyle. Pre-mortem, AD-associated brain changes can be clinically evaluated with the help of neuroimaging. They consist of global atrophy with an early predilection for the hippocampal region and the temporo-parietal cortical areas. Post-mortem examination reveals abundant cortical and hippocampal neuritic plaques (NP) and neurofibrillary tangles (NFT) as well as cerebellar atrophy upon gross inspection of the brain.

Several risk factors influence the prevalence of AD. Age is by far the greatest risk factor: at the age of 65, one in eight elderly individuals carries the diagnosis, but after the age of 85, the ratio is close to one in every two persons. Genetic predisposition for late-onset sporadic AD seems to be primarily conveyed by the presence of the apolipoprotein E4 (ApoE4) allele in a dose-dependent fashion – subjects with one ApoE4 copy have increased risk (odds ratio, OR=2.6–3.2), and those with two copies have greatly increased risk (OR=14.9) for developing AD, while the ApoE2 allele appears to be protective (OR=0.6) (2,3). Rare genetic variants of fully penetrant autosomal dominant forms of AD also exist and have been attributed to presenilin 1 and presenilin 2 gene mutations on chromosomes 14 and 1 and to an amyloid protein precursor gene mutation on chromosome 21. Even so, these autosomal dominant forms account for only 2% of all AD cases. (4)

The societal cost of AD is immense. AD is the 5th leading cause of death among the elderly. The total number of deaths caused by AD has increased by 33% between 2000 and 2004, but those from other major etiologies, such as heart disease, breast cancer, prostate cancer and stroke, have decreased by 3–10% each.(1) More than \$148 billion are spent on AD related healthcare costs annually. (1)

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a relatively recent concept introduced to recognize the intermediate cognitive state where patients are neither cognitively intact nor demented (5). The current prevalence rate for MCI among those 65 years and older is 12–18% (6) and 10–15% of these patients progress to develop dementia annually. (7) Many subjects with MCI have cortical and hippocampal atrophy. Most show unequivocal signs of AD pathology, including plaque and tangle accumulation, postmortem. (8–10) Nevertheless, some MCI patients harbor an alternative pathological diagnosis such as dementia with Lewy bodies, vascular dementia, hippocampal sclerosis, frontotemporal dementia, progressive supranuclear palsy, argyrophilic brain disease or a nonspecific tauopathy. (6) Some MCI cases can also be attributed to nondegenerative pathology. (6)

In recent years, MCI has attracted increasing research interest. It is now widely accepted that MCI is the single most important at-risk state for AD. Two major research questions have captured most attention – how can we predict which MCI patients will develop AD and which treatment would offer neuroprotection from future progression to dementia.

Neuroimaging approaches in AD and MCI

Neuroimaging is a powerful tool for creative exploration of the epidemiology, diagnostic sensitivity, progression and therapeutic efficacy in AD and MCI. Reliable biomarkers of the underlying pathology and such that can also predict disease progression in MCI are needed and several candidate brain measures have been examined in a wealth of cross-sectional and longitudinal neuroimaging studies. Neuroimaging has captured the interest of clinical trialists and may help establish disease-modifying effects in clinical trials by documenting slowing of brain atrophy rates or of amyloid accumulation. Structural measures such as total brain volume, hippocampal and entorhinal cortical volumes have been thoroughly evaluated and used as surrogate markers for clinical trials.(11–16) New powerful techniques for more precise 3D disease and treatment effect localization are likewise being explored (17–20), as are novel positron emission tomography tracers to label the hallmarks of AD in the living brain. (21–23)

The extent of brain degeneration in dementia can be quantified by purely structural techniques such as MRI and diffusion tensor imaging (which can examine white fiber integrity), and tomographic approaches, such as PET and SPECT (24,25), which can quantify cerebral blood flow and metabolism. The structural/functional distinction has been blurred to include PET studies with new ligands that label structural pathology (such as tracer compounds that bind to amyloid) (22,26–28), and MRI variants such as fMRI imaging of blood-oxygenation level dependent (BOLD) contrast (29), arterial spin labeling(30), relaxometry (31), spectroscopy (32), and magnetization transfer imaging(33). For structural MRI scans in particular, the oldest image analysis approach currently used in dementia research is the region of interest (ROI) technique. This measures the overall volume of specific brain substructures. It relies on manual delineation of the structures of interest on each successive image slice, followed by calculating the total volume of the structure, which is then used for statistical analyses. Manual volumetry is a powerful technique and has yielded a wealth of findings, but has several disadvantages. It requires proficient and knowledgeable tracers who can delineate the ROIs with high reliability and consistency. As an operator-dependent technique, the ROI method is most susceptible to subjective bias, although this can be reduced by blinding of analysts to disease status, and periodic assessments to avoid drift in tracing reliability over time. Additionally, it is time consuming and requires an accurate *a priori* hypothesis, so analyses often tend to be limited to one or two structures of interest. The ROI technique also requires a detailed and well-established tracing protocol that unambiguously defines segmentation criteria for each respective brain region. Several automated ROI segmentation techniques for the hippocampus, lateral ventricles, caudate nucleus and corpus callosum have been recently developed but have not yet been widely used. (17,34–38)

Voxel-based morphometry is a more recent methodology that can simultaneously visualize group differences or statistical effects on gray and white matter, throughout the whole brain. It is implemented in the widely used Statistical Parametric Mapping software package. (39) The ‘classical’ VBM approach segments the brain into three tissue classes – gray and white matter and cerebro-spinal fluid, then aligns the gray matter individual maps to a common 3D space and averages the data of all subjects while retaining information on the variability of each study group. Gray matter images are smoothed with a 8–12 mm kernel to reduce the confounding effects of individual morphological differences while retaining the global disease associated changes. The averaged gray matter maps are then compared at the voxel level via general linear modeling techniques. The resulting 3D maps show areas where the variable of interest (diagnosis, clinical score, clinical outcome, etc.) shows significant correlation with focal gray matter density.

The traditional VBM technique has been criticized for being nonspecific and possibly even biased as false-positive between-group disease effects could arise due to systematic image registration errors or systematic shifts in unaffected regions in close proximity to truly affected areas. (40) The newer generation VBM approaches addresses this problem by modulating the voxel intensity of the spatially normalized gray matter maps by the local expansion factor of a 3D deformation field that aligns each brain to a standard brain template. As a result, the final modulated voxel contains the same amount of gray matter as in the native pre-registered gray matter map. (41–43) This improved methodology accounts for voxel expansion/contraction effects and removes potential sources of bias in estimating group differences in brain structure, provided that corresponding cortical areas are successfully matched, and not systematically misaligned from one group to another.

Even with the improved methodology there is another limitation posed by the VBM methods. Spatial smoothing is a step necessary to counterbalance the inter-individual differences contained in the data. Digital filtering of gray matter maps is applied to remove high-spatial frequency differences in anatomy that remain because anatomy cannot be aligned exactly across subjects, and it is also applied so that the residuals of the statistical model at each voxel are better approximations to a Gaussian random field, allowing standard parametric statistics to be applied (such as t tests or analysis of variance). Although this approach makes it easier to detect systematic, global disease-induced effects as opposed to individual variability, it occurs at the expense of blurring of focal changes. Newer computational anatomy techniques that control inter-subject variability by setting focal constraints (such as for instance sulcal lines) for the local warping forces have achieved much improved co-registration of cortical anatomy. (18) In addition, surface modeling techniques have been used to create explicit 3D models of the cortex and hippocampus in the form of computational meshes, and these meshes can be aligned precisely point-by-point across subjects, even allowing higher-order matching of important landmarks that lie within surfaces (e.g., CA fields of the hippocampus, gyral/sulcal boundaries) when making group comparisons. (44–48)

Computational anatomy techniques are the newest generation of image analysis software. They view the brain or any ROI as a 3D shape or a complex geometrical pattern that can be modeled as a continuous 3D deformable mesh structure. These mesh models contain information on the focal geometry and the warping deformation vectors applied. They can be thus easily averaged across groups and subjected to statistical comparisons (see Gee and Thompson, 2007, for a recent review of the field). (49) Many are generally built upon the pre-existing ROI and VBM techniques. Most computational anatomy hippocampal analytic techniques rely on initial manual tracing of the hippocampus followed by complex mathematical approaches for 3D hippocampal modeling. (19,50) One such method, the *radial atrophy mapping* approach, computes the 3D distance from the hippocampal centroid in each coronal section (also called a medial curve or core) to each hippocampal surface point. This provides an intuitive 3D measure of hippocampal thickness, and provides metric estimates of hippocampal atrophy that can be compared point-by-point across individuals and groups. (19) The related *large-deformation high-dimensional brain mapping* approach is also used to study the changes in hippocampal morphology in AD. (50) This approach is so-called because, rather than relying on manual tracings of the hippocampus, a template hippocampus is traced on a single subject and fluidly warped to match the anatomy of new subjects. The transformation involved is high-dimensional, i.e. involves millions of degrees of freedom to produce a deformation that captures shape differences in detail. It is also a ‘large-deformation’ approach, meaning that the deformation model follows a continuum-mechanical law that prevents folding or tearing of the deforming template (known mathematically as a *diffeomorphism*).

The radial atrophy mapping approach was originally developed for the hippocampus, and grew out of work on medial representations (‘M-reps’) or ‘skeletonization’, in the computer vision

literature. Even so, the same approach is readily applicable to any structure that shrinks or expands over time, such as the lateral ventricles, for instance. One newly developed method for ventricular surface extraction and comparison (17,37) consists of manual tracing of the ventricles in a few randomly selected subjects from any given study cohort, followed by fluid propagation of the resulting parametric mesh models over the ventricles of the rest of the subjects in the study. This approach results in several automated ventricular models for each subject where the number is equal to the number of the individual ventricular “primers” used. These models are not identical due to registration variability. However, these models can be averaged to a single automated optimized individual ventricular model. This automated approach saves time and manual effort, reduces the possibility of subjective bias and reduces segmentation errors that invariably result from fluid propagation of only one ventricular model to the ventricles of all subjects in the study. These steps are then followed by the radial distance measurement technique.(19) The outputs are group-specific 3D ventricular expansion maps that can be statistically compared between the groups.

Similar to VBM many cortical computational anatomy techniques use the segmented gray matter maps and the gray matter density approach (18,51) or a more advanced gray matter thickness approach. (52–54)Some cortical mapping techniques are conceptually related to the VBM approach, in that they do not use intrinsic cortical surface features to guide the matching of cortical anatomy across subjects. (52,53) Other approaches such as the *cortical pattern matching* technique (18) specifically use primary and some secondary cortical sulci for optimized warping of the cortical gyral anatomy.(55) The latter technique allows for 3D mapping and visualization of cortical gray matter density or thickness, PET, fMRI, amyloid-imaging data. Its goal is to combine data across subjects from homologous cortical regions as far as possible (by matching gross anatomic landmarks). This greatly improved cortical registration can increase the signal-to-noise ratio and therefore the statistical power to detect disease-associated changes. In a sense, approaches that do not explicitly match cortical surfaces across subjects incur a substantial loss of power as similar features are misaligned when data from different individuals is integrated.

Another technique known as tensor-based morphometry (TBM) accomplishes time-efficient spatial registration. It first uses a linear registration for spatial alignment of the scans followed by a fully automated fluid warping algorithm of cortical and subcortical structures to maximize the mutual information (e.g., anatomical correspondence) between the images (for detailed description of the technique please see Chiang et al, 2007 (56,57)). The final product is the first image transformed into the shape of the second one, and, in addition, the Jacobian transformation necessary to deform one voxel to its counterpart in the other scan is saved and visually displayed in the color-coded “voxel compression” or “tensor map” on the follow-up scan. TBM allows efficient mapping and analysis of very large datasets and works quite well for subcortical analyses. For cortical analysis, most current implementations of TBM are comparable to VBM in that the automated whole-brain registration does not provide an explicit fine-scale cortical pattern registration as the sulcal-based warping technique does. Clearly, future studies will exploit the benefits of cortical surface-based and fully volumetric registration to capture changes cortically and subcortically with optimal power. (58–60) Given its great sensitivity and time efficiency TBM could present a promising surrogate marker tool for clinical trials. (Figure 1)

Region of interest studies in AD and MCI

The ROI technique has been heavily used in many AD and more recently MCI neuroimaging studies. Subtle hippocampal atrophy, on brain MRI, is also associated with normal aging. It affects 15% of 60–75-year-old population and 48% of 76–90-year-old population. (61) Hippocampal volume loss is strikingly more prevalent in both MCI and AD where 78 % and

96 % of patients are affected respectively.(61) Cross-sectional ROI studies have shown that the hippocampal (62–66) and entorhinal volumes (62,64–67) can reliably differentiate AD subjects from normal elderly. The absolute volumetric difference in entorhinal volume between amnesic MCI and normal elderly is approximately 13–17% and between mild to moderate AD and MCI from 30–38%, while for the hippocampus the differences are 7–11 % and 19–39 %, respectively.(68,69) The sensitivity of hippocampal volume measures for differentiating AD from controls ranges from 77–92% and the specificity is approximately 80–92%. (64,66, 70–72) The precision of differentiating MCI from normal controls and MCI from AD is substantially less accurate when using hippocampal volume (MCI vs. controls sensitivity 52–80 % and specificity 79–80% and MCI vs. AD sensitivity 45–60 % and specificity 80%). (66,68,70) The diagnostic accuracy of the entorhinal volume in the comparison of AD vs. normal controls has been reported as high as 92% (sensitivity 76–80% and specificity 80–90%). (64,66,73) Which structure is the more powerful discriminator when distinguishing MCI patients from normal controls is currently debated, with some studies siding with the hippocampus(62) and others with the entorhinal cortex.(69)

Longitudinal ROI studies have allowed researchers to estimate the rates of structural atrophy in normal aging, MCI and AD and to research the risk, protective and predictive factors for clinical conversion between these cognitive states. The annual atrophy of the hippocampus in healthy elderly subjects is about 1.6 to 1.7 % per year (74,75) while that of the entorhinal cortex is about 1.4 % per year.(73) Much higher hippocampal rates are observed in longitudinal epidemiologic studies in MCI and AD. Elevated atrophic rates have been reported in MCI subjects who decline to AD relative to those who remain stable (annual hippocampal atrophy rate for MCI patients who remain stable = 2.8%, for MCI converters =3.7% and for AD =3.5–4%). (74,75) The yearly volume loss for the entorhinal cortex in AD is about 7%.(73) Mutation carriers with the autosomal dominant genetic variants of AD with 100% penetrance were reported to have 6.7-fold greater annual atrophy rates 5.5 years before the clinical manifestation of dementia. (76) The odds ratio for conversion to sporadic AD over 1.2 – 4.8 years was reported to be 1.75 in MCI subjects with smaller relative to those with larger hippocampal volumes. (13)

The recently published results of a 3 year-long donepezil/vitamin E/placebo study in MCI reported somewhat higher atrophy rates for the hippocampus and entorhinal cortex in the placebo group (5.44% and 11.58, respectively) than the ones reported above.(11) The most likely contributing factor is that most of the studies above used less stringent criteria for MCI than the clinical trial did. For instance, a delayed recall score of 1.5 SD below the age- and education-adjusted mean was an enrollment criterion for the clinical trial while most of the studies above did not use a neuropsychological score as a cut-off and based their MCI diagnosis on clinical grounds alone.

Comparing the power of various ROIs for predicting conversion from MCI to AD, two research groups have independently reported additional predictive value for measures from some structures outside of the mesial temporal lobe. Convit et al. reported that a logistic regression model including volumes of the fusiform, inferior and middle temporal gyri achieved the best predictive value, while Jack et al. reported that whole brain and ventricular volume are good predictors for future cognitive decline across the spectrum from normal aging to AD.(13) Direct comparisons of hippocampus and entorhinal cortex have revealed that the entorhinal cortex volume may be a better predictor of future conversion from MCI to AD during follow-up of 12–77 months. (77,78) Other researchers have implicated the entorhinal cortex as predictive of impending cognitive deterioration from normal aging and both the hippocampus and entorhinal cortex from the MCI/early AD stage. (79)

Voxel-based morphometry studies in AD and MCI

VBM has been increasingly used to study AD progression and has also been used as a clinical trial surrogate measure (see section Neuroimaging techniques as promising surrogate markers for clinical trials). Relative to normal controls, the gray matter volume of even mild AD subjects is greatly reduced in multiple brain regions that are known to be heavily affected by AD pathology. Using the classical VBM technique to compare mild AD and normal elderly subjects, greater atrophy was evident in the mesial temporal lobe structures and precuneus followed by the perisylvian and temporopolar cortices. (80) Comparing mild to moderate AD and normal controls, another research group reported additional changes in the inferior and lateral temporal, posterior cingulate and insular cortices. (81) Cortical structural differences between MCI and normal controls localize to the mesial temporal, middle temporal and anterior subcallosal cingulate, while those between MCI and mild AD also spread to left precuneus, left parietal lobe, left superior and middle temporal gyri and the right middle temporal gyrus. (82)

Using the so-called 'optimized' VBM approach (which multiplies the spatially normalized gray matter volumes by the local warping factors required to match them to a common template brain), a comparative cross-sectional study of AD and normal elderly controls revealed differential atrophy of the bilateral parahippocampal, the fusiform and the left inferior temporal gyri. (83) Another optimized VBM study reported 6.5% less total gray matter volume in MCI relative to normal controls and 6.2% more total gray matter volume relative to AD patients from the full range of disease spectrum (MMSE range 4–28). (84) AD subjects showed greater parietal, anterior and posterior cingulate atrophy relative to MCI, while MCI subjects demonstrated greater superior temporal, left insular and posterior hippocampal atrophy relative to normal controls.

Several recent longitudinal VBM studies have increased our understanding of the AD-related cortical atrophy progression *in vivo*. Scahill et al. (85) used the classical VBM approach in a longitudinal study of 4 presymptomatic autosomal dominant AD, 10 mild and 12 moderate AD subjects. The presymptomatic and the mild AD subjects showed mesial, inferior and lateral temporal and posterior cingulate atrophy. Two studies used the optimized VBM approach: Bozzali et al. (86) clinically followed 26 MCI subjects, who all underwent a baseline structural MRI scan every six months for an average of 28.7 months. They compared the MCI to a normal control and an AD group. At baseline, MCI patients who converted to AD showed significantly more atrophy of the bilateral anterior cingulate, bilateral lateral temporal, left inferior temporal, left parietal and bilateral frontal association cortices relative to normal controls ($p_{\text{corr}} < 0.05$). The atrophy pattern seen in the stable MCI group relative to controls was restricted to the bilateral rectus and middle frontal gyri, and the left fusiform and inferior temporal gyri. AD subjects showed more atrophy than MCI converters in the right superior temporal, left paracentral and precuneal and the bilateral fusiform cortex. Chetelat et al. (87) enrolled 18 MCI subjects of whom 7 converted to AD during an 18-month follow-up interval. The annualized regional gray matter loss in MCI converters ranged from 0–4.5% and in MCI nonconverters from 0–4%. Fastest atrophy rates were identified in the temporal pole, entorhinal and lateral temporal cortices (2.5–4.5%). The prefrontal cortex appeared to be more affected in nonconverters. At baseline, greater cortical involvement was seen in the parahippocampal, fusiform, lingual and posterior cingulate cortices in MCI subjects who later converted to AD relative to those who did not. (Figure 2)

One very recent optimized VBM study (88) prospectively followed 136 cognitively normal elderly and 5 MCI subjects for an average of 5.4 years. 23 of them converted to MCI and 9 of the 23 further deteriorated to meet criteria for AD. At baseline, the group consisting of the 23

pre-MCI/pre-AD and the 5 MCI subjects demonstrated significant gray matter atrophy in the anteromedial temporal and left angular gyri, and the left lateral temporal lobe.

Computational anatomy studies in AD and MCI

Among the most recent advances in neuroimaging is the development of computational anatomy techniques for brain morphometry. These methods include newer metrics to create maps of structural differences throughout the brain without manual interaction with images. More subtle descriptors such as complexity or shape measures have also been employed. In the case of the hippocampus, the new proxy measures for focal hippocampal atrophy include radial atrophy measurements and surface deformation analyses. For cortex, the more elegant cortical thickness mapping techniques have recently been employed.(18,52,89–92)

NFT neuropathology does not affect the hippocampus uniformly. Tangles affect the entorhinal cortex first, and then the subiculum and CA1 subfield of the hippocampus, followed by a spread to the CA2/3 and finally CA4 region before invading the neocortex.(93) 3D computational modeling techniques have offered a novel insight into these regional and sequential changes in the hippocampus. (19,94–96) Using the *hippocampal radial atrophy mapping* approach, Thompson et al. showed profound hippocampal differences between normal controls and AD patients, that were also linked with MMSE scores.(19) Atrophy of the CA1 area was 15–20% greater (97) in AD versus cognitively normal elderly subjects. In one longitudinal(95) and one cross-sectional(94) study, Apostolova et al. sequenced the progressive spread of atrophy through the hippocampal subfields. MCI subjects who later converted to AD had significantly more atrophy of the subiculum and CA1 areas of the hippocampus relative to MCI subjects who either remained stable or improved (95) (Figure 3 and Figure 4 middle row). Furthermore, the cross-sectional comparison of MCI and AD patients showed that in subjects who meet criteria for AD hippocampal atrophy has spread to the CA2/3 areas as well (Figure 4 bottom row).(94) An additional cross-sectional hippocampal radial atrophy study also demonstrated subicular atrophy in single domain amnesic MCI and AD relative to normal controls. (98)

Two cross-sectional *large-deformation high-dimensional brain mapping* hippocampal studies have implicated the CA1 subfield to discriminate between normal aging and questionable AD (Clinical Dementia Rating Scale (CDR) = 0.5). (50,99) Longitudinal studies have demonstrated that the CA1 area predicts conversion from cognitively normal status to questionable AD (an AD subcategory inclusive of MCI and mild AD subjects) over a follow-up interval ranging from 0.9–7.1 years (100). Both CA1 and subicular atrophy were detected in questionable AD over a follow-up of 2 years.(99)

Computational anatomy has contributed significantly to our understanding of cortical changes that accompany AD. The first AD cortical pattern matching study, by Thompson et al., compared the baseline and 1.5-year follow-up cortical atrophy patterns between a mild to moderate AD and a normal group.(18) At baseline AD subjects had >15% greater atrophy in the lateral temporal and parietal as well as the mesial left frontal, parietal and occipital cortices. At follow-up differences relative to the control group were also seen in the frontal association fields and the mesial right hemisphereic surface. The researchers also developed an animated movie depicting the disease-associated pathology spread through the brain; this can be viewed at http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html. Recently, the same group compared the cortical atrophy pattern between amnesic MCI (mean MMSE=28.2± 1.6) and mild AD (mean MMSE=23.8±3.2). Despite the small absolute cognitive difference (MMSE difference=4.4) there was a highly significant difference in global right and left hemispheric cortical atrophy ($p<0.001$ for the whole hemisphere comparison bilaterally, corrected for multiple comparisons). Greatest absolute differences (15%) were seen in the entorhinal, right more than left lateral temporal, right parietal and bilateral precuneus followed by 10–15%

atrophy throughout the rest of the cortex. The observed changes closely resemble Braak and Braak amyloid stages A and B (Figure 5).

In another study, Ringman et al.(101) created 3D maps of cortical gray matter thickness in MRI brain scans of 12 (10 female, 2 male) subjects at increased genetic risk for familial AD (4 with the L235V, and 4 with the A431E PS1 mutation, and 2 with the V717I substitution in APP). In mutation carriers, mean cortical thickness was 15% lower in the right medial parietal lobe, left medial frontal lobe, and in the lateral occipital cortex adjacent to the parietal lobe on the left. This demonstrated that quantitative comparisons of cortical thickness using our cortical pattern matching techniques (18) are sensitive to early atrophy during the preclinical phase of familial AD.

Using a related cortical mapping approach, Lerch et al. reported that mild to moderate AD subjects (MMSE range 10–29) have on average 18% thinner cortices relative to healthy controls ($AD=3.1\pm0.28$ mm, $controls=3.74\pm0.32$ mm).(52) The thickness computation differed slightly, in that it was based on computing the distance between explicitly computed inner and outer cortical surface meshes. By contrast, other studies, including those by Thompson et al., 2003(18), Apostolova et al. (51), and Ringman et al.(101) use a method where gray matter thickness is computed with a voxel-coding technique from the gray/white matter segmentation, progressively coding cortical voxels with increasing 3D distance from the inner cortical mantle. The regional pattern in the Lerch et al. study agreed closely with the one reported by Apostolova et al. in their mild AD to amnesic MCI cortical pattern matching study. (51) A larger follow-up study also included an MCI group and reported as expected that MCI subjects fall between normal aging and AD by their average cortical thickness – MCI cortex was 0.18 mm thinner than normal controls and 0.26 mm thicker than AD subjects.(53) The entorhinal and lateral occipito-temporal cortices were driving the effects in the MCI to normal control comparisons.

Using a novel automated ventricular extraction approach, our group recently mapped the ventricular differences between AD and cognitively normal subjects and between healthy normal ApoE4 carriers and non-carriers. (37) AD subjects showed significant expansions of the posterior and superior horns of the lateral ventricle relative to controls. ApoE4 carriers demonstrated mainly superior horn dilations relative to ApoE4 non-carriers; this is generally consistent with the progressing trajectory of lobar atrophy in AD. (Figure 6) Using a related technique, but using a single surface template and an optical flow registration approach for ventricular segmentation, Carmichael et al. (102) compared the ventricular shape differences between MCI, AD and cognitively normal subjects. As expected progressive ventricular expansion was evident where MCI subjects had intermediate and AD subjects largest ventricles. (Figure 7)

Neuroimaging of early vs. late onset sporadic AD

Sporadic AD typically starts after age 65 (and is otherwise known as late-onset AD, or LOAD). Occasionally though, it presents earlier in life and in such cases the term early onset AD (EOAD) is generally used. The literature supports a more aggressive course and higher pathological burden in EOAD vs. LOAD subjects. *Post mortem*, EOAD subjects have greater NP and NFT burden relative to LOAD subjects throughout the brain. (103) Such phenomena can also be captured pre-mortem with neuroimaging. Using the classical VBM technique, Ishii et al. reported greater cortical atrophy in the parietal, posterior cingulate and precuneal regions in EOAD vs. LOAD subjects. (104) In agreement with pathologic observations, one recent cortical pattern matching study demonstrated widespread pancerebral gray matter atrophy with relative sparing of the primary sensorimotor and visual cortices in EOAD subjects when compared to age-matched controls. (105) The LOAD subjects in the same study showed a much more restricted atrophy pattern mainly centered on the lateral and mesial temporal and

mesial parietal and occipital lobes relative to an age-matched control group. This study implies that at the same level of cognitive impairment, younger subjects typically exhibit much heavier pathologic burden, relative to older subjects - perhaps as a result of higher cognitive reserve.

Correlations between cognitive performance and cortical and hippocampal atrophy in AD and MCI

AD is a neurodegenerative disorder presenting with progressive decline in all cognitive domains. Researchers have repeatedly looked into the cognitive correlates of the structural brain changes observed in AD. The hippocampus is the primary brain region where memory encoding, consolidation and retrieval occurs. Several neuroimaging studies have implicated the hippocampus in memory retention. (106,107) Verbal memory is thought to lateralize to the left and spatial memory to the right hippocampus. (108,109) Both memory and executive functions showed an association with hippocampal atrophy at baseline in a cohort comprised of normal, mildly impaired and demented subjects. (110) Verbal memory performance has also been associated with gray matter density in the parahippocampal gyrus in one VBM study (86) and in the bilateral precuneus, entorhinal/parahippocampal, inferior temporal and the left temporo-occipital cortices in a computational anatomy study. (95) Some recent advances in the structure-function memory correlations have been reviewed in detail elsewhere in this issue. (29)

Using the cortical pattern matching technique, one longitudinal (18) and one cross-sectional (111) study showed strong correlation between poorer MMSE performance and cortical atrophy in the entorhinal, parahippocampal, posterior cingulate, precuneal, lateral temporal, lateral parietal and subgenual cingulate association cortices with strong left-sided predilection. The longitudinal study demonstrated strong associations in the frontal association areas after 1.5-year follow-up period. (18) Associations between worsening MMSE score and hippocampal atrophy have likewise been reported in several ROI studies. (13,112)

Performance on a measure of semantic fluency (animal fluency) and a picture-naming test (Boston Naming Test) was strongly correlated with the structural integrity of posterior lateral temporal and temporo- and parieto-occipital cortices on the left. (113) Declining performance on both measures associated with left more than right frontal atrophy, but the effect size for the semantic fluency instrument was stronger. The opposite observation was noted for the visual association cortices where the visually driven Boston Naming Test elicited stronger interactions (Figure 8). Two other studies reported language-related brain associations. The study by Pantel et al. (114) found an association between the Aachen aphasia battery and the left temporal lobe volume, while the magnetization transfer study by van der Flier et al. reported a link between the Boston Naming and animal fluency tests and the temporal and frontal lobe volumes (33).

One recent study (115) included 14 controls, 32 MCI, and 14 AD subjects and investigated the structural correlates of one verbal memory (California Verbal Learning test) and several executive function tests (Wechsler Adult Intelligence Scale – III Trail Making test and Digit span). The authors reported correlations between verbal memory and lateral frontal and medial temporal gray matter volume. Executive function correlated with the frontal lobe gray matter volume.

The results of the imaging arm of the largest MCI therapeutic trial, to date, were recently published. (11) Aside of the main analyses concerned with the therapeutic effects of donepezil and vitamin E on hippocampal, entorhinal and global brain atrophy and ventricular expansion, the researchers scrutinized the associations between the cognitive measures used in the trial (MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and CDR

and the observed brain atrophy rates. The methods utilized were the brain boundary shift integral(12) for whole brain and lateral ventricles and the ROI method for the hippocampus and entorhinal cortex. The hippocampus and entorhinal cortex showed uniformly strong correlations with all cognitive measures. Global brain atrophy showed strongest correlations with the ADAS-Cog 11 and ADAS-Cog 13 measures and ventricular expansion with CDR and ADAS-Cog 13.

Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (ADNI; see Mueller et al., 2005 (116) <http://www.loni.ucla.edu/ADNI> and ADNI-info.org) is a large multi-site longitudinal MRI and FDG-PET study of 200 elderly controls, 400 mildly cognitively impaired subjects, and 200 Alzheimer's disease subjects. One goal of this project is to develop improved imaging methods to measure longitudinal changes of the brain in normal aging, during the transition to early Alzheimer's disease, and in Alzheimer's disease patients. ADNI studies published to date have focused on determining the optimal scanning approaches for such a longitudinal study, and have examined which factors affect the longitudinal stability of image-derived measures, and the repeatability, reproducibility, and variability of changes detected in different scan types. In the image analysis community, there are also considerable efforts to improve scanner calibration, corrections for image distortion and inhomogeneity, identification of small artifactual differences in overall image scaling over time (with phantom-based or scalp-based image registration), as these are among the major sources of experimental error in examining the spatial profile of degenerative brain changes over short intervals. (117–120)

Neuroimaging techniques as promising surrogate markers for clinical trials

Until recently, all AD clinical trials incorporated outcome measures of only two kinds – cognitive and functional scales. Unquestionably, any successful therapeutic intervention must unequivocally demonstrate clinical improvement (or, as it is more commonly observed, slowing of cognitive decline) in the active treatment relative to the placebo group. Even so, limiting ourselves to clinical outcomes alone as a measure of treatment effects has significant drawbacks. The cognitive instruments used in clinical trials are well established and have proven validity and reliability. Nevertheless, as with all other neuropsychologic measures, they suffer from test-retest fluctuations, learning/practice effects, and depend heavily on the patient's attention, motivation, drug-induced side effects, psychological and physical states (e.g., anxiety, lack of sleep, etc.). Diagnostically, changes detected by cognitive tests also lag behind structural and pathologic changes in the brain. It has been hypothesized that disease-induced pathologic changes start accumulating many years and perhaps even a decade before disease detection and accurate diagnosis by clinical examination and neuropsychological measures is possible. In clinical trial settings, several months are needed for cognitive changes to become apparent between treatment and placebo groups. Measures of events earlier in the disease pathway, such as brain atrophy measures, may thus better capture early therapeutic effects and document disease modification. Now that the pre-dementia state of MCI has been described with its most common underlying pathology being AD, we are even more invested in detecting powerful surrogate markers of disease progression. Neuroimaging with its multitude of techniques is a promising alley for development of successful and sensitive biomarkers for clinical trials.

Thus far, four therapeutic studies with neuroimaging biomarkers have been published. A milameline AD trial (121) - which was terminated early because of lack of therapeutic efficacy - was the first one to include structural MRI imaging and hippocampal ROI analyses as a surrogate marker. The treatment assignment was discontinued, but the imaging portion of the study was fully conducted and the feasibility of hippocampal volumetry as a proxy clinical

trial outcome measure was established. An A-beta immunotherapy trial also included structural MRI and VBM analyses of whole brain and ventricular changes in patients with AD.(14) Following several reports of meningoencephalitis, the trial was terminated. Post-hoc imaging analyses revealed that subjects who responded favorably to the therapy by antibody production actually had greater ventricular enlargement and greater total brain volume loss relative to non-responders. These surprising findings did not correlate with cognitive decline. One explanation for this paradox was that any amyloid clearance from the brain may in theory result in a reduction of brain neuropil volume, but this was not anticipated in advance and requires further study. A third small study investigated the effect of donepezil on hippocampal atrophy rate and showed slowing down of atrophy in the treatment relative to the placebo group. (16) A three-year ADCS Donepezil/Vitamin E/placebo MCI trial included a baseline and a follow-up MRI. The study's main objective was to establish if treatment with either donepezil or vitamin E would slow down the conversion of MCI to AD. (122) The MRI substudy of the trial (11) had several objectives: to ascertain whether or not there was a therapeutic effect of Donepezil and Vitamin E on structural MRI disease progression measures such as hippocampal, entorhinal, whole brain atrophy and ventricular expansion; to examine the correlations between clinical, cognitive and imaging measures and to evaluate and compare the annual atrophy rates in predefined study subgroups (e.g., converters vs. nonconverters and ApoE4 carriers vs. noncarriers). The imaging study reported no significant differences between subjects on donepezil, vitamin E or placebo. In the ApoE4 subanalyses a trend-level significant slowing down of hippocampal atrophy was observed in ApoE4 carriers vs. noncarriers in the donepezil treatment group. The latter finding relates well to the results of the main study where ApoE4 carriers randomized to donepezil were found to have the lowest conversion rates to AD. (122) As expected, the MRI substudy also reported higher atrophy rates in converters relative to nonconverters and in ApoE4 carriers relative to noncarriers. The cognitive correlations were all significant in the predicted direction (e.g., better performance in those with lower atrophy rates and *vice versa*). (11)

One natural history study from Japan (123) compared AD subjects who were taking up to 5 mg of donepezil (the maximal approved dose in Japan) from a research treatment cohort (N=54) and a historical control group (N=93) from before the drug was approved for clinical use in Japan. The authors reported that the patients treated with donepezil had significantly slower annual hippocampal atrophy rate relative to the historical control group ($3.82 \pm 2.84\%$ vs. $5.04 \pm 2.54\%$). The effect of donepezil remained significant after controlling for age, sex, disease duration, MRI interval, education, ApoE4 genotype and baseline cognition.

Taken together, this evidence suggests that hippocampal and brain atrophy may be advantageous surrogate markers for clinical trials, especially in cases where more sensitive techniques are required. Thus far, the only hippocampal analysis approach studied has been the ROI method. Newer, state-of-the-art methodologies allow for 3D visualization of the hippocampal and ventricular structures and for more powerful statistical comparisons of regional hippocampal and ventricular changes. These may well be the clinical trial biomarkers of the future. Computational anatomy techniques such as cortical pattern matching, automated ventricular segmentation, Freesurfer (89,124) and TBM, could likewise provide improved sensitivity and the much-needed evidence for therapeutic effects of anti-AD therapy on the living brain.

Conclusions

AD is now one of the most important health concerns of the 21st century, due to several factors – the progressive aging of the population, the impending graying of the baby boomer generation and its corresponding social and economic impact. The AD research agenda is progressively moving back in time to the pre-dementia state of MCI and even further back in an attempt to

identify cognitively normal elderly who already harbor the earliest AD-associated pathologic changes. These subjects would be the ideal therapeutic target for any disease modifying drug that may potentially abort or delay the onset of cognitive decline. In the past two decades, neuroimaging researchers have capitalized upon revolutionary technical advances. The rapid development of new techniques capable of reliable, sensitive and powerful detection of focal disease induced changes instills optimism that disease course and therapeutic response can be carefully monitored and appraised. With several promising disease-modifying agents in the pharmaceutical pipeline, most AD researchers anticipate imminent progress towards curing and preventing this devastating neurodegenerative disorder.

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Figure 1. Tensor based morphometry analysis showing the progression of brain atrophy in posterior cortical atrophy patient scanned at 6-month intervals. The images show progressive tissue loss (purple) in the right temporal and parietal and left frontal lobes and ventricular expansion red, yellow, green).

Figure 2.

Optimized voxel-based morphometry analysis of gray matter atrophy progression in MCI who converted to AD (converters) and MCI who remained stable (non-converters). The color-coded maps represent the percent annual volume loss projected on the 3D hemispheric brain customized average template (top) and on coronal sections of the template (bottom). (Reproduced with permission from Chetelat et al., 2005(87))

Figure 3.

The hippocampal radial atrophy technique was applied to identify regions of hippocampal atrophy that predict future decline from amnesic MCI to AD.⁽⁹⁵⁾ Illustrated are the statistical and percent difference surface map comparisons between the three MCI groups – converters vs. nonconverters (left panel), converters vs. MCI patients who improved cognitively (middle panel) and non-converters vs. MCI patients who improved (right panel). In each case, red and white colors (in the top row) denote regions where those with poorer outcomes showed greater atrophy at their baseline scan. In some regions, the baseline level of atrophy is locally 10–20% greater in MCI subjects who later convert to AD.

Figure 4.

Using the hippocampal radial atrophy mapping technique Apostolova et al. revealed the stage wise spread of hippocampal atrophy through the hippocampus in amnesic MCI and AD. MCI converters show significantly more atrophy in the subiculum and CA1 areas of the hippocampus relative to MCI subjects who either remained stable or improved (middle row). (95) AD subjects show in addition significantly more atrophy in the CA2/3 area on the left relative to amnesic MCI. (94)

Figure 5.

Cortical atrophy differences between amnesic MCI and mild AD subjects can be visualized using the cortical pattern matching technique. (51) The 3D maps on the left demonstrate significantly greater atrophy in mild AD relative to MCI in most cortical areas (red colors) with relative preservation of the primary sensory and motor regions (blue colors). The anatomical pattern resembles stages A and B from the Braak and Braak amyloid staging maps (right panels). Clearly, amyloid accumulation and cortical atrophy may not occur at exact the same times in all patients, but the anatomical sequence of cortical thinning closely matches the typical trajectory of plaque and tangle accumulation (from medial temporal, to frontal, sparing primary cortices until later).

Figure 6.

The ventricular mapping technique was used to study the effects of AD and of ApoE4 genotype on ventricular expansion. AD subjects when compared to age-matched controls demonstrated posterior and anterior ventricular horn expansion (left panel). When the analysis is restricted to healthy control subjects only, ApoE4 carriers demonstrated predominantly anterior ventricular horn expansion relative to ApoE4 non-carriers (right panel).

Figure 7.

Using a single surface template and an optical flow registration approach for ventricular segmentation, Carmichael et al. (102) compared the ventricular shape differences between MCI, AD and cognitively normal subjects. The figure shows the average thickness, percent deficit and significance maps of the three comparisons – cognitively normal subjects vs. MCI (top row), cognitively normal subjects vs. AD (bottom row) and MCI vs. AD (middle row). As expected, progressive ventricular expansion was evident - MCI subjects had intermediate and AD subjects largest ventricles.

Figure 8.

Using the cortical pattern matching technique Apostolova et al. (113) studied the association between the performance on Boston Naming Test (BNT) and the Animal Fluency test and cortical atrophy in 19 subjects with AD and 5 MCI who later converted to AD. Declining performance on both measures associated with left more than right perisylvian and frontal atrophy.