Tracking Alzheimer's Disease

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Abstract (250 words; 250 words max.)

Population-based brain mapping provides great insight into the trajectory of aging and dementia, as well as brain changes that normally occur over the human life-span. We describe three novel brain mapping techniques, *cortical thickness mapping*, *tensor-based morphometry*, and *hippocampal surface modeling*, that offer enormous power for measuring disease progression in drug trials, and shed light on the neuroscience of brain degeneration in Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). We report the first time-lapse maps of cortical atrophy spreading dynamically in the living brain, based on averaging data from populations of subjects with Alzheimer's disease and normal subjects imaged longitudinally with MRI. These dynamic sequences show a rapidly advancing wave of cortical atrophy sweeping from limbic and temporal cortices into higher-order association and ultimately primary sensorimotor areas, in a pattern that correlates with cognitive decline. A complementary technique, *tensor-based morphometry*, reveals the 3D profile of atrophic rates, at each point in the brain. A third technique, *hippocampal surface modeling*, plots the profile of shape alterations across the hippocampal surface. The three techniques provide moderate to highly automated analyses of images, have been validated on hundreds of scans, and are sensitive to clinically relevant changes in individual patients and groups undergoing different drug treatments. We compare time-lapse maps of AD, MCI, and other dementias, correlate these changes with cognition, and relate them to similar time-lapse maps of childhood development, schizophrenia, and HIV-associated brain degeneration. Strengths and weaknesses of these different imaging measures for basic neuroscience and drug trials are discussed.

Keywords: MRI, Alzheimer's Disease, aging, MCI, dementia, brain degeneration, PET

1. Introduction

Alzheimer's Disease (AD) is arguably the greatest threat to public health in the 21st century. Dementia doubles in frequency every five years after age 60, afflicting 1% of 60-64 year-olds but 30-40% percent of those aged 85 and older (Jorm et al., 1987). With the size of the elderly population rising dramatically and incidence of dementia also increasing, there are clear warning signs of an approaching socioeconomic disaster. As novel, disease-modifying agents emerge, brain imaging measures are vital to help demonstrate the effectiveness of pharmacologic treatments evidenced by any slowing of disease progression in the

brain. Brain imaging measures facilitate drug development in animal models and patient studies (Jack et al., 2003; Fox et al., 2005), and are also emerging as important tools for differential diagnosis of dementia (Silverman and Thompson, 2006).

MRI and PET studies allow visualization of brain structure and function in 3-dimensional detail. When performed repeatedly over time, they can be used to visualize disease progression in living patients. Based on data from many subjects, measures of regional brain volumes and rates of atrophy may eventually aid in predicting who will suffer cognitive decline among those at risk for dementia; these measures are already being used to gauge the effects of therapy in drug trials. Imaging can also be used to track how different degenerative diseases spread in the living brain, providing a better theoretical understanding of how the various types of dementia differ (such as Alzheimer's disease versus vascular or semantic dementia). Imaging can also be used to explore how the brain changes with normal aging (Sowell et al., 2003), pinpointing changes associated with specific behavioral alterations such as apathy or declining executive function (Apostolova et al., 2006).

Brain imaging is also revealing important new information on other degenerative dementias, such as that resulting from HIV infection. Forty million people are infected with HIV worldwide, and at least 40% of these patients suffer from cognitive impairments ranging from minor cognitive motor disorders (MCMD) to HIV-associated dementia, often with a progressive trajectory leading to death. The trajectory of brain degeneration in HIV is markedly different from that seen in Alzheimer's disease - the caudate, white matter, and cortex degenerate progressively in a sequence that was recently visualized for the first time (Thompson et al., 2005a,b; Chiang et al., 2006; Lepore et al., 2006). As in Alzheimer's disease, maps of degeneration based on MRI scans are increasingly needed to help gauge the success of neuroprotective therapies (e.g., memantine, CPI-1189, or NMDA-receptor antagonists in neuro-AIDS). As we describe later, MRI may also be combined with image analysis methods to track disease progression in individual patients.

Our understanding of degenerative disease has grown considerably due to rapid advances in brain imaging technologies. When combined with sophisticated analysis methods, structural MRI can now detect subtle, systematic brain volume changes of the order of 0.5% per year in individual subjects (Smith et al., 2002; Fox et al., 2005). If the same group of subjects is scanned repeatedly as their disease progresses, the dynamic trajectory of cortical atrophy can be reconstructed as it spreads over time in the living brain (Thompson et al., 2004). New PET tracer compounds are being developed to visualize the profile of accumulating pathology (Barrio et al., 1999; Shoghi-Jadid et al., 2002; Klunk et al., 2005; Kepe et al., 2006; Small et al., 2006). Hailed as a breakthrough in the AD research community, these PET tracers visualize amyloid plaques and neurofibrillary tangles (NFTs) in the living brain – hallmarks of AD previously only detectable at autopsy. These molecular probes are labeled with positron emitting isotopes - when they bind to the hallmark lesions of AD, their distribution in the brain can be determined using PET scanning. Both the UCLA and Pittsburgh compounds – respectively called [^{18}F]-FDDNP and [^{11}C]-PIB (Pittsburgh compound B) - show the expected pattern of accumulating pathology in initial studies of patients with AD and in small samples of MCI subjects (Klunk et al., 2005; Small et al., 2006). As PET and MRI measures track different aspects of the disease process, there is a race to determine which imaging measures are most sensitive to disease progression, which techniques are most accurate in predicting imminent degenerative changes, and which are best at discriminating pathological from healthy aging. Clearly, techniques with a relatively high *diagnostic* specificity (such as CSF measures of beta-amyloid levels) may not offer the greatest sensitivity to disease progression over time. The pace of analytic developments in computational anatomy is also high. Newer computational methods, such as tensor-based morphometry, can detect increasingly subtle brain changes in conventional MRI scans, and newer imaging techniques, such as diffusion tensor imaging, are providing new insight into the pattern of deteriorating fiber architecture.

1.1. Imaging of Alzheimer's Disease and Mild Cognitive Impairment (MCI). Imaging studies have become a priority in Alzheimer's disease research as they can be used to evaluate treatments that may

slow or delay the disease process (Jack et al., 2003; Fox et al., 2005). A major practical goal is shortening the minimum feasible follow-up interval in a drug trial, or reducing the sample size required to detect a given degree of slowing of brain degeneration. This would have immediate practical advantages as new drugs could be tested much more efficiently. Clinical testing is commonly combined with neuroimaging to determine how best to identify pre-symptomatic candidates for preventive treatments before the extensive neuronal damage of AD has set in. MCI, or mild cognitive impairment, for example, is a transitional state between normal aging and dementia. MCI subjects have a cognitive complaint and test 1.5 standard deviations below age- and education-adjusted norms on one or more neuropsychological tests, but they are still capable of independent living (Petersen et al., 1999, 2000). MCI is defined using neuropsychiatric criteria, but many brain imaging studies aim to develop measures that are sensitive enough to distinguish MCI from healthy aging with high specificity (Becker et al., 2006). Other studies attempt to differentiate between MCI subjects who will imminently convert to AD, over a specific follow-up interval, versus those who remain stable or even recover (Apostolova et al., 2006; Carmichael et al., 2006).

Scientific interest in MCI is rising as MCI subjects convert to full-blown AD at a rate 3-6 higher than normal subjects (Petersen et al. 1999, 2000). Alarmingly, post mortem studies have shown that most patients with MCI already have the pathological hallmarks of AD - neocortical senile plaques, neurofibrillary tangles, atrophy and neuronal loss in layer II of the entorhinal cortex (Price and Morris, 1999; Kordower et al., 2001). Many imaging studies target individuals with MCI as they are more likely than the general elderly population to obtain diagnoses of AD later in life. Research efforts may ultimately be of greater benefit to those with MCI given that early intervention may eventually prevent progression to global cognitive decline. As the risk of AD increases exponentially with age, delaying disease onset, even by a couple of years, would vastly reduce the overall number of cases of AD.

1.2. Statistical Power. Improved treatment is needed for patients at all stages of AD, but many drug trials focus on MCI subjects for pragmatic reasons. Cognitively normal elderly subjects convert to AD at a rate

of only 1-2%/year, so trials to resist conversion from normality to MCI or AD would need to follow 3,000-6,000 subjects for 5 to 7 years to achieve sufficient clinical endpoints (Jack et al., 2003). This is prohibitively expensive and too slow to be practical. On the other hand, MCI subjects convert to AD at a rate of 12%-15%/yr. Secondary prevention studies (to prevent conversion from MCI to AD) typically need to assess only several hundred subjects, as a large proportion will convert to AD in 1-4 years (the duration of a typical research study). Even so, long timeframes are necessary because of the high variability in clinical endpoints, and the relatively small degenerative changes that are barely detectable in brain images unless data from large numbers of subjects are combined (see Leow et al., 2006, for studies of the detection limits of sequential MRI).

If any imaging method could demonstrate slowing, in a quantitative measure of the disease process, the hurdle for treatments to pass would be greatly lowered - drug evaluation would be greatly accelerated. For example, a treatment would be regarded as promising if it were shown to slow whole brain atrophic rates, in MCI, by at little as 10% over a 6-month interval. Many more clinical trials would be attempted, as the time required, costs, and associated economic risks, would be greatly reduced. With this in mind, developers of computational techniques now aim to extract the maximum amount of information from images of disease progression, often by compiling population-based repositories of statistical data on expected rates of atrophy. Other efforts are mathematically distilling new sources of contrast from images (using new tracer kinetic models for PET, or combining scans acquired at different magnetic field strengths to detect new features such as iron (ferritin) accumulation in the brain; Bartzokis et al., 1994, 2006).

Here we review recent progress in the neuroimaging of dementia, focusing on structural brain mapping studies that track the disease as it spreads in the living brain. These imaging approaches are being used to map disease progression in individuals and populations, revealing group patterns of cortical thinning, gray and white matter atrophy, and shape changes in subcortical structures such as the hippocampus. Functional and structural imaging methods may also be combined, relating anatomical deficits to plaque and

tangle pathology observed *post mortem* or with new PET tracers. These brain mapping techniques show promise in identifying predictors of imminent decline and disease onset, which are valuable for identifying candidates for drug trials. An overarching goal of most brain mapping studies is to extract and analyze statistical data on the disease process and develop new mathematical methods to quantify how well treatments resist AD (see Thompson et al., 2004, for a review).

2. The Trajectory of Alzheimer's Disease

Recent imaging studies have successfully tracked the emergence and spread of Alzheimer's disease pathology in the living brain (see e.g., Thompson et al., 2003). AD pathology progresses in a known, stereotypical sequence (**Figure 1**), whether it is tracked with MRI, PET, SPECT, or in *post mortem* histologic studies of patients at different stages of the disease.

The time-course of disease progression varies substantially among individuals with AD, but neurofibrillary pathology typically starts in the transentorhinal cortex and quickly spreads to the entorhinal cortex before involving the hippocampus (Braak and Braak, 1991, 1997; Gomez-Isla et al., 1996). This temporal pathology persists for several years (Smith, 2002) before spreading cortically to engulf the rest of the temporal, frontal, and parietal lobes (Braak and Braak, 1997; Frisoni et al., 1999; Laakso et al., 1996, 1998; Dickerson et al., 2001; Thal et al., 2002; Thompson et al., 2003).

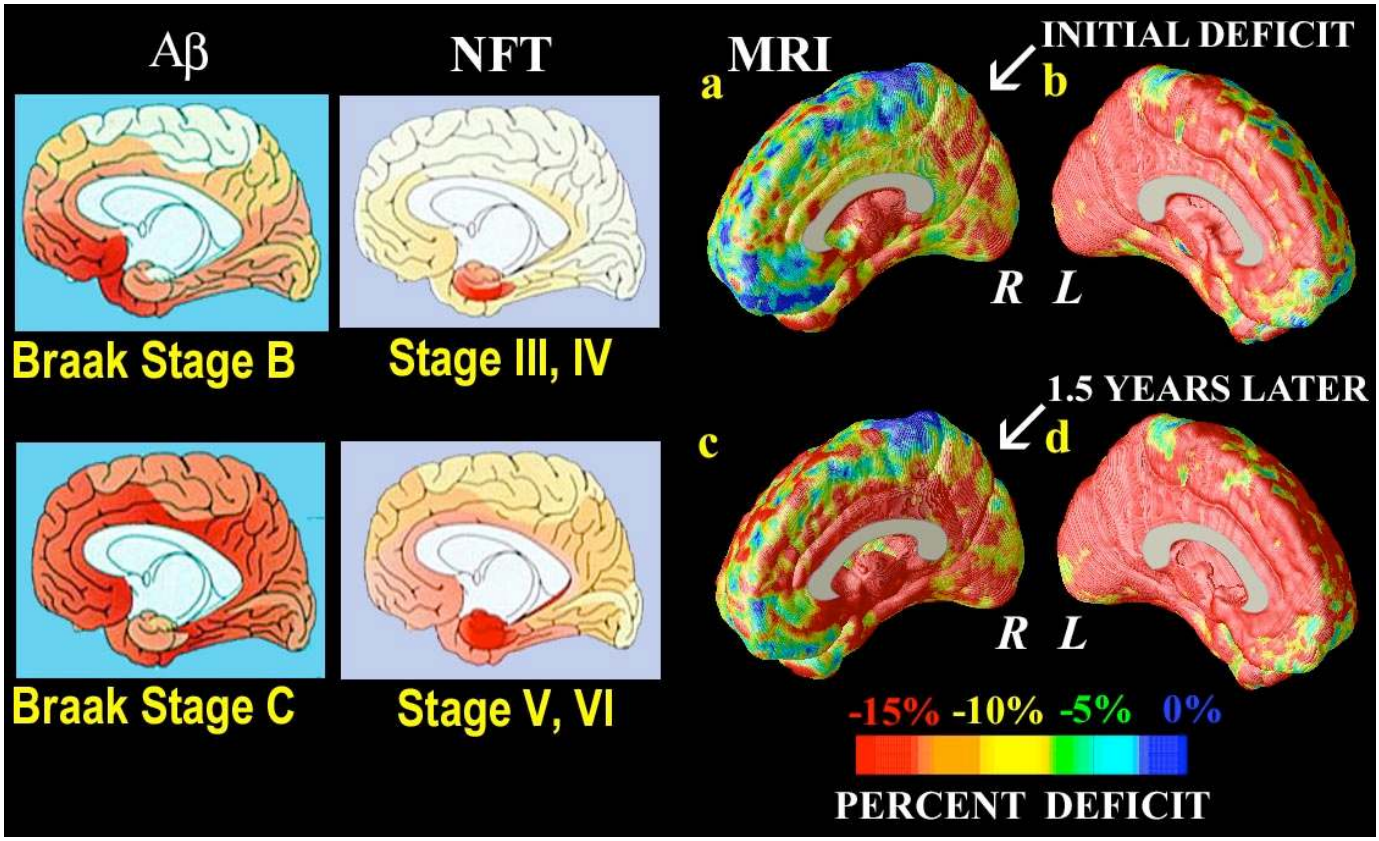

Figure 1. Gray Matter Deficits Spread through the Limbic System in Moderate AD. Cortical atrophy occurring during the progression of AD is detected by comparing average profiles of gray matter between 12 AD patients (age: 68.4±1.9 yrs.) and 14 elderly matched controls (age: 71.4±0.9 yrs.). Average maps of gray matter density in patients and controls are subtracted at their first scan (when mean Mini-Mental State Exam score was 18 for the patients; *(a) and (b)*) and at their follow-up scan 1.5 years later (mean MMSE=13; *(c) and (d)*). Colors show the average percent loss of gray matter relative to the control average. Profound loss engulfs the left medial wall (>15%; *(b) and (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. Limbic and frontal zones clearly show different degrees of impairment (c). The corpus callosum is indicated in white; maps of gray matter change are not defined here, as it is a white matter commissure. MRI-based changes, 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*). The deficit sequence also matches the trajectory of neurofibrillary tangle distribution observed *post mortem*, in patients with increasing dementia severity at death (Braak and Braak, 1997). Consistent with the deficit maps observed here, 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; Pearson et al., 1985; Arnold et al., 1991). Cortical layers III and V selectively lose large pyramidal neurons in association areas (Brun and Englund, 1981; cf. Hyman et al. 1990).

Longitudinal 3D MRI scanning of groups of subjects can be used to map this process in detail. Time-lapse maps have been constructed from sequential brain MRI scans to reveal the anatomical sequence of cortical atrophy (Thompson et al., 2003; see http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html for movies of disease progression, that can be viewed over the internet). Cortical regions that myelinate first – and most heavily – in development are typically least vulnerable to AD pathology (e.g., primary sensorimotor and visual cortices). By contrast, neurofibrillary tangles and neuropil threads in dendrites accumulate early in the late-myelinating heteromodal association cortices, the posterior cingulate, and phylogenetically older limbic areas that remain highly plastic throughout life (Mesulam, 2000).

2.2. Why Does AD progress in this Sequence? It is not known why AD engulfs the brain in this limbic-to-frontal sequence. The sequence is well-documented and is largely agreed upon by the AD research community. Essentially the same degenerative sequence was observed *post mortem,* and in FDG-PET data, many years before MRI scanning had sufficient resolution to gauge how cortical atrophy progresses. More recently, PET ligands that track the molecular hallmarks of AD show that pathology accumulates in a similar spreading pattern. Cross-sectional studies at UCLA and the University of Pittsburgh, using the molecular probes [^{18}F]-FDDNP and [^{11}C]-PIB, suggest that amyloid plaques do deposit sequentially in the brain, appearing first in cingulate cortex, progressing to temporal/parietal cortices and the caudate, and finally engulfing occipital and sensorimotor cortices (Klunk et al., 2005; Small et al., 2006). This sequence agrees very closely with the *post mortem* Braak maps (Braak and Braak, 1997), and with MRI-based maps of cortical degeneration (Thompson et al., 2003).

Why the changes occur in this sequence is the subject of debate. The term "retrogenesis" has been used to describe some of the regressive behavioral changes that occur in dementia, when behavior may regress to a form resembling childhood or infancy. The sequence of cortical atrophy in Alzheimer's disease is in some respects an 'unraveling', or recapitulation in reverse, of the anatomical sequence of childhood brain

maturation. Primary sensory areas myelinate first in early infancy, but offer greatest resistance to neurodegeneration, staying intact in late AD. We recently developed a time-lapse map of cortical maturation, based on serial brain MRI scans of 13 children aged 4 to 21, scanned every two years for eight years (Gogtay et al., 2004; see http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html for videos of these changes). In these images, a shifting pattern of gray matter loss appeared first (around ages 4-8) in dorsal parietal and primary sensorimotor regions near the interhemispheric margin, spreading laterally and caudally into temporal cortices and anteriorly into dorsolateral prefrontal areas. As expected from *post mortem* studies of cerebral myelination (Yakovlev and Lecours, 1967; Benes et al., 1994), the first areas to mature were those with the most basic functions, such as processing the senses and movement. Areas involved in spatial orientation and language (parietal lobes) followed, around the age of puberty (11-13 years). Areas with more advanced functions - integrating information from the senses, reasoning and other "executive" functions (prefrontal cortex) - matured last (in late adolescence). Phylogenetically older cortical areas matured earlier than the more recently evolving higher-order association cortices, which integrate information from earlier maturing cortex. Provocatively, the last brain regions to develop in childhood are among the first to degenerate in dementia; and the earliest developing brain regions - subserving vision and sensation - are spared until the very latest stages of AD. As such, the age-related degenerative process progresses from late- to earlier-myelinating regions (*cf.* Yakovlev and Lecours, 1967; Benes et al., 1994).

Bartzokis et al. (2004) examined this myelination sequence and suggested that late-myelinating regions are especially vulnerable in AD and other adult-onset disorders such as schizophrenia; in support of this, the frontal cortex in schizophrenia has been found to undergo derailed maturation in patients and in at-risk relatives who subsequently convert to full-blown psychosis (Thompson et al., 2001; Cannon et al., 2002; Pantelis et al., 2003; Sun et al., 2006). If this is true, the anatomical trajectory of white matter maturation and degeneration has been comparatively overlooked in neuroimaging research. Recent work, with diffusion tensor imaging, appears to support this view. In Kochunov et al. (2006), we found that the most prominent age-related drop in diffusion anisotropy occurred in late-myelinating white matter, such as the

genu of the corpus callosum which innervates the frontal lobes. The cognitive consequences of this drop need to be established, but this is consistent with prior reports that late-myelinating regions are most vulnerable to age-related degeneration (Bartzokis, 2003, 2004; Salat et al., 2004; for a review see Bartzokis, 2004).

2.3. Other Dementias. Cortical changes do not follow the same trajectory in Alzheimer's disease as in other neurodegenerative diseases, or even other forms of dementia. In a recent study of Lewy Body dementia, for example, we found that cortical gray matter in temporal and orbitofrontal cortices was comparatively preserved in 16 LBD patients (age: 76.4±6.7SD), compared with 29 AD patients matched for age and dementia severity. LBD patients showed severe anterior cingulate atrophy compared to 38 matched controls (Ballmaier et al., 2004). This was somewhat expected based on earlier neuropsychological studies of LBD, which suggested that temporal lobe degeneration and memory decline appear relatively late in LBD (Harvey et al., 1999; McKeith et al., 2005).

We also compared the 3D profiles of cortical atrophy in fronto-temporal dementia (FTD) and semantic dementia (SD; Apostolova et al., 2006). SD patients typically present with impoverished speech, but FTD patients show lack of empathy, disinhibition and poor judgment. Congruent with these findings, we found predominantly posterior, left-sided GM atrophy in SD (N=5) and more frontal, right-sided GM atrophy in FTD (N=10). These studies, and others like them, suggest that pathophysiological differences underlying different forms of dementia are evident in brain images. Differential diagnosis based on MRI and PET is an active field (Silverman and Thompson, 2006).

2.4. Neurodegeneration in HIV/AIDS. Perhaps the most startling finding in comparing degenerative patterns with MRI was the observation of selective cortical neurodegeneration in patients with HIV/AIDS, with greatest deficits in sensorimotor and supplementary motor cortices, and in the underlying white matter, basal ganglia, and hippocampus (Thompson et al., 2005; Chiang et al., 2006; **Figure 2**).

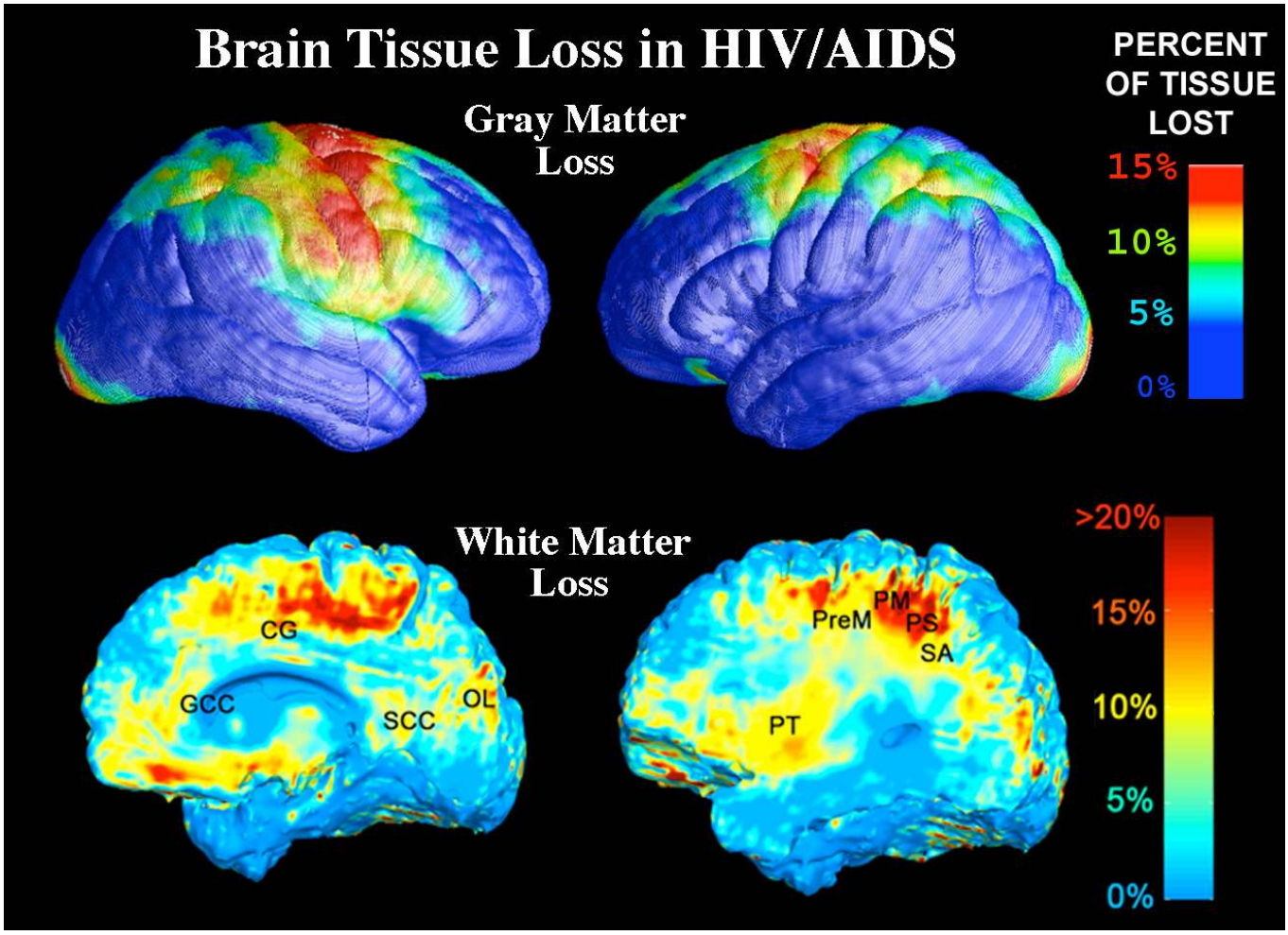

Figure 2. Visualizing Brain Tissue Loss in HIV/AIDS. *(top row):* In an MRI study of cortical thickness in 27 HIV/AIDS patients and 14 healthy controls, the primary sensory, motor and premotor cortices were 15% thinner, and prefrontal and parietal tissue loss correlated with cognitive and motor deficits. Thinner frontopolar and language cortex also correlated with immune system deterioration measured via blood levels of CD4+ T-lymphocytes. *(bottom row):* When the same subjects were studied using tensor-based morphometry (Chiang et al., 2006), the pattern of white matter loss was in remarkable agreement with the cortical maps. The white matter volume was reduced in premotor areas where the cortex was significantly thinner, suggesting that cortical degeneration may be accompanied by degeneration in the underlying white matter pathways. Taken together, these and other studies support the notion that brain degeneration is present even in apparently healthy HIV-positive people on powerful drug regimens (HAART; *highly active anti-retroviral therapy*). [Data in the top row are from Thompson et al., 2005; data in the bottom row are from Chiang et al., 2006].

The resulting maps provide a new approach to gauge the impact of HIV on the living brain (see also Chiang et al., 2006, Lepore et al., 2006, for related maps of white matter degeneration). This unusual degenerative

pattern is the opposite of that seen in common non-infectious dementias such as AD, where the medial temporal, limbic, and association cortices are affected first, and primary sensorimotor and visual cortices only later. Clearly, different degenerative disorders may have quite different stereotypical patterns of atrophy and progression. Some have suggested the HIV virus migrates from the ventricles through the white matter to the cortex (Masliah et al., 2000), where HIV virus-encoded proteins overactivate NMDA-type glutamate receptors and the excess extracellular glutamate causes excitotoxic injury and cell death. Why specific brain systems are especially vulnerable to the neurotoxic effects of HIV is not yet understood, but brain mapping is providing vital information on the trajectory of the disease.

2.4. Association with Specific Symptoms. If different forms of dementia progress in different ways, it is legitimate to ask whether different patterns of symptoms and functional decline are associated with different patterns of atrophy. In AD, we found that distinct cortical atrophy patterns were associated with apathy, versus language dysfunction, or versus global cognitive decline (Apostolova et al., 2006a,b; Cummings et al., 2006). In a language study, we computed an individual average language domain *Z* score from each subject's *Z* scores on the Boston Naming Test and Animal Fluency test. 3D statistical maps then revealed that language performance was associated most strongly with left-sided gray matter loss in 19 AD and 5 MCI patients. More of the left hemisphere showed atrophy that linked with language function, suggesting that language abilities in AD are strongly influenced by cortical integrity in left perisylvian areas. A related study of healthy developing children revealed that thickening of language-related cortices, but not motor cortices, was linked with improvements in language function, and thickening of motor cortices, but not language cortices, was linked with improvements in motor function (Lu et al., 2006). This type of double dissociation is remarkable, as a more simplistic model might predict that all functional domains would improve somewhat equally in concert with a generalized maturation of the cortex. In healthy adults, the quantity of gray matter overall and especially in the frontal lobes is associated with better performance on standardized IQ tests, and both of these measures are under strong genetic control (Thompson et al., 2001; Gray and Thompson, 2004). This suggests a moderately strong

linkage between regional brain volumes and intellectual ability. The association between brain volume and IQ has been replicated in numerous meta-analyses (e.g., McDaniel and Nguyen, 2002), and may contribute to any detected association between cognitive performance and brain volumes in degenerative disease as well.

MMSE scores offer a more general measure of overall cognitive decline in AD, and declining MMSE is associated with widely distributed atrophy in both hemispheres (Thompson et al., 2003; Apostolova et al., 2006). Anterior cingulate and supplementary motor cortices were more atrophied in 18 AD patients *with apathy* versus 18 without apathy but matched for dementia severity (Cummings et al., 2006). We also studied late-life depression in non-demented controls (Ballmaier et al., 2004). We found a regionally-specific 5%-20% gray matter deficit in the orbitofrontal cortex of 24 depressed patients compared to 19 age-matched non-depressed subjects. In a collaboration with the University of Brescia (Pievani et al., 2006), we compared cortical thinning in 10 late-onset and 10 early-onset AD patients of similar clinical severity (MMSE: 18.6$\pm$3.5 *vs* 19.2$\pm$3.5). Early-onset was defined as diagnosis before age 65. Early-onset AD primarily affected temporoparietal areas and late-onset AD affected the medial temporal gray matter. These results may explain why early-onset AD features primarily neocortical symptoms, while late-onset AD generally features medial temporal symptoms.

These studies zero in on abnormal cortical systems contributing to specific functional deficits - revealing pathophysiological differences underlying the different symptoms of dementia or dementias with differences in the age of onset.

3. Methods to Track Brain Changes in Alzheimer's Disease

Methods to track structural brain changes with conventional MRI fall into 3 main categories: (1) volumetric measurement of specific structures, such as the hippocampus or entorhinal cortex; (2) image

processing techniques that estimate rates of whole brain atrophy as a percentage volume loss per year (Fox et al., 2000, Smith et al., 2002); and (3) map-based techniques that visualize the 3D profile of group differences in gray matter loss (Baron et al., 2001), atrophic rates (Fox et al., 2001; Leow et al., 2005), white matter integrity (Medina et al., 2005) or cortical gray matter thickness (Fischl et al., 2000; Salat et al., 2004; Thompson et al., 2005; Sowell et al., 2006). The main measures used in drug trials today are typically simpler ones that produce single numeric measures of disease burden, such as total hippocampal volume, or whole brain atrophic rates, which can all be expressed in cubic centimeters per year (or as a percentage change per year). The more exotic techniques that produce 3D maps of degenerative changes (reviewed below) have yielded substantial neuroscientific information on the disease trajectory, but have yet to gain acceptance in drug trials. Drug trials have not yet used these measures partly due to their complexity but also due to the pressure to express outcomes in a simple way, ideally using a small number of summary measures. Large-scale neuroimaging efforts (e.g., the Alzheimer's Disease Neuroimaging Initiative, www.loni.ucla.edu/ADNI) are now comparing the power of these map-based imaging measures, together with biomarkers and other clinical/functional measures, to differentiate MCI and AD from healthy aging, to predict future cognitive decline, and to predict conversion from MCI to AD. This is a vital effort – currently, given that in individual subjects assessed with MRI, MCI is not readily distinguished from AD or from normal aging, except when groups of subjects are compared in aggregate – individuals in each of these categories overlap substantially for all known MRI measures.

3.1. Hippocampal Volumes and Maps. AD pathology emerges first in the entorhinal cortex and hippocampus, so most volumetric MRI studies of MCI and AD patients have focused on the medial temporal lobe structures. Neuronal atrophy, decreased synaptic density, and overt neuronal loss is evident on MRI as progressive cortical gray matter loss, reduced subcortical gray and white matter volumes, and expanding ventricular and sulcal CSF spaces (Thompson et al., 2004).

Patients with mild AD have roughly 25% smaller hippocampal volumes than matched healthy elderly controls (De Santi et al., 2001; Callen et al., 2001, Du et al., 2001) whereas MCI patients show a mean reduction of around 11% (Du et al., 2001). Early studies by Jack et al. (1997) found that some 97.2% of the patients they studied with very mild AD – i.e., with Clinical Dementia Rating 0.5 – had hippocampal volumes below the healthy normal average. In MCI, mean hippocampal volumes are variously reported as being roughly half way between AD and normals (Soininen et al., 1994; Jack et al., 1999; Visser et al. 2002; Pennanen et al., 2004), or as being more similar to AD patients (Dickerson et al., 2004; Killiany et al., 2002). Xu et al. (2000) found that entorhinal cortex and hippocampal volume measures provided roughly equal intergroup discrimination ability in 30 control, 30 MCI, and 30 AD subjects; even though the entorhinal cortex typically atrophies earlier, it is harder to delineate reliably on MRI. Many groups have also used pre-morbid hippocampal atrophy, rated visually (de Leon et al., 1993) or using volumetry (Visser et al., 1999; Laakso et al., 2000; Killiany et al., 2000), to predict subsequent crossover to AD. Jack et al. (1999) also found that hippocampal atrophy at baseline was associated with conversion from MCI to AD at a 33-month follow-up (relative risk: 0.69, p=0.01; 27 of 80 MCI subjects had become demented).

3D modeling techniques (**Figure 3**) have localized specific regions of atrophy within the hippocampus in MCI. For example, Becker et al. (2006) used 3D surface reconstruction techniques to model the shape of the hippocampus, creating average shape models for cohorts of subjects with amnestic MCI, non-amnestic MCI, AD, and healthy controls. These techniques can localize tissue atrophy or shape alterations (Csernansky et al., 2000) and can map the average pattern of hippocampal thickness reductions in millimeters (Thompson et al., 2003). Amnestic MCI patients showed diffuse hippocampal atrophy (Becker et al., 2006), and reduced volumes in the mesial temporal lobe including the hippocampus, entorhinal cortex, and amygdala (Bell-McGinty et al., 2006). Non-amnestic MCI patients – who show cognitive impairments in single or multiple domains other than memory - typically have greater atrophy outside of the hippocampus, specifically in multi-modal association cortices.

These methods provide, at each location on the hippocampal surface, a measure of how much radial atrophy there is, as either a proportion of average control values, or as a *Z*-score, or a significance map comparing one group with another. These methods have been used to detect structural differences in the hippocampus that are associated with Alzheimer's disease (Thompson et al., 2004; Frisoni et al., 2006), MCI (Becker et al., 2006; Apostolova et al., 2006), schizophrenia (Narr et al., 2004), normal development (Gogtay et al., 2006), methamphetamine abuse (Thompson et al., 2004), epilepsy (Lin et al., 2005), bipolar illness (Bearden et al., 2006), depression (Butters et al., 2006), and HIV/AIDS (Becker et al., 2006). Frisoni et al. (2006) also used this method to compare a group of 28 AD patients and 40 elderly controls, and found significant tissue loss (20% or more) in the hippocampal CA1 fields and part of the subiculum. As expected from pathological studies (van Hoesen et al., 2000), regions corresponding to the CA2-3 fields were relatively spared. This atrophy distribution largely corresponds to the known selective involvement of hippocampal regions by AD pathology, and supports the possibility of carrying out *in vivo* macroscopic neuropathology of the hippocampus with MR imaging in the dementias.

Predicting Outcomes in MCI. Hippocampal surface maps have also been used to predict outcomes in MCI. In 20 MCI subjects followed neuropsychologically for 3 years, maps of hippocampal atrophy at the start of the study successfully differentiated the 7 patients who later converted to AD from 6 who stayed stable and 7 who improved. CA1 and subicular degeneration were associated with conversion to AD; these areas were intact in MCI patients who improved and no longer met MCI criteria at follow-up (Apostolova et al., 2006).

Accelerated Hippocampal Atrophy in Those at Genetic Risk. The same hippocampal mapping technique has been used to detect accelerated atrophy in healthy elderly people at genetic risk for Alzheimer's disease. In a longitudinal study (Roybal et al., 2005), 3D hippocampal surface models were generated from volumetric brain MRI scans of 54 subjects (27 men, 27 women), scanned at two different timepoints (mean age at baseline=68.6, mean interval: 1.6 yrs, 19 ApoE4 carriers: 2 homozygous, 17 heterozygous).

We found a strong correlation (P=0.024) between the left hippocampal rate of atrophy and the ApoE genotype, with E4 carriers showing a greater average atrophic rate than non-E4 carriers (left hippocampus –2.4%/yr vs. 0.36%/yr). Progressive hippocampal head atrophy occurred in healthy ApoE4 carriers, an atrophic pattern that is accelerated in AD. The maps showing greater average annualized loss and faster left hippocampal atrophy for ApoE4 carriers indicates that, in those at genetic risk for AD, abnormally accelerated structural changes are detectable prior to cognitive decline.

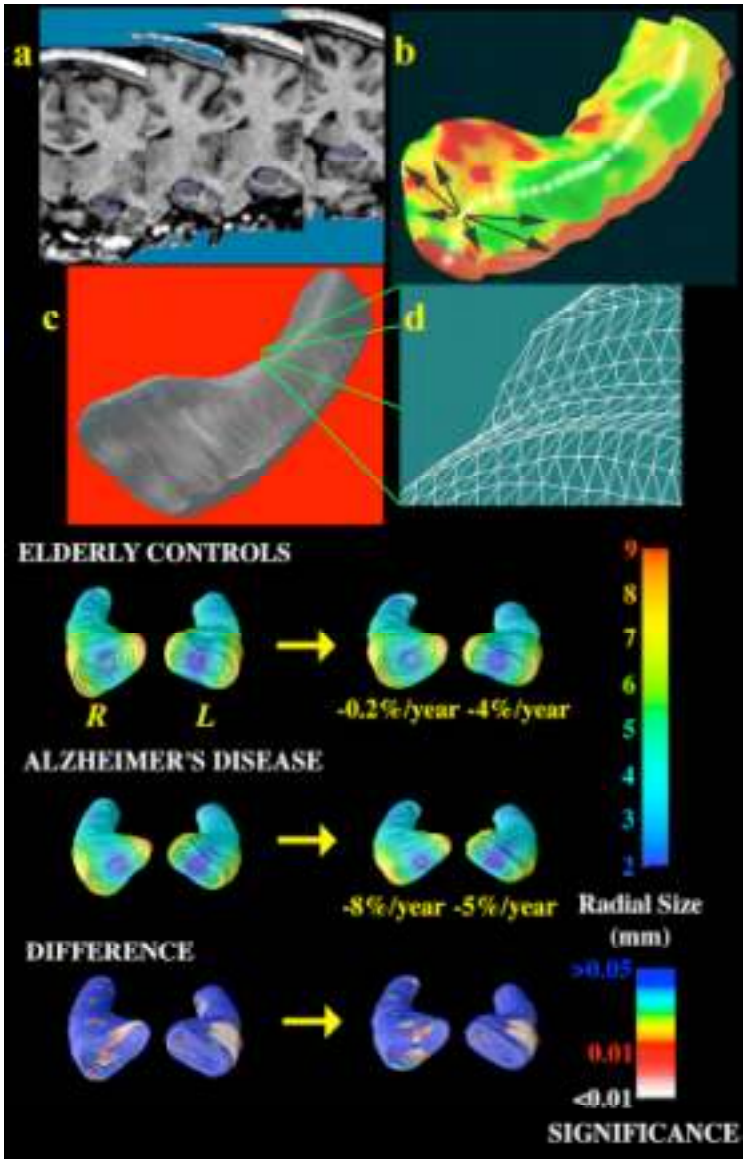

Figure 3. Mapping Hippocampal Atrophy. The 3D profile of hippocampal atrophy in disease can be mapped using surface-based modeling methods (Thompson et al., 2004). The hippocampus is traced (a) either by hand or automatically, in serial coronal sections. After converting the traces to parametric surface mesh format *[(c) and (d)],* a medial core (i.e., a curve threading down the center of the hippocampus) is computed for each hippocampus. The distances from the medial core to each surface point are estimated and used to generate first individual and later average group distance maps. Here, group distance maps for elderly controls and patients with moderate Alzheimer's disease are compared at baseline (*left column*), and after an approximately 2-year follow-up interval (*right column*). The significance maps show regions with significant atrophy at each time point (white colors). Similar maps can be made to plot regions where there is evidence for progressive atrophy over time or changes that link with cognitive test performance or clinical outcomes (Lin et al., 2005).

3.2. Automated Mapping of Gray Matter Changes: Voxel-Based Morphometry. Conventional region-of-interest approaches, which use manual tracing to determine the volume of the structures, are ubiquitous but are gradually being replaced by more automated techniques for rapid large-scale processing of scans (Good et al., 2001; Leow et al., 2006; see Ashburner et al., 2003, for a review). Automated image registration approaches can align groups of images into a common space and inter-group differences can be assessed using voxel-by-voxel statistics. 3D statistical maps of group differences in brain structure can be visualized, identifying regions where atrophy correlates with diagnosis, as well as clinical, therapeutic, genetic or functional measures. Chetelat et al. (2002) used an automated technique known as *voxel-based morphometry* (VBM; Ashburner and Friston, 2000, 2001) to map gray matter changes in amnestic 18 MCI patients. In a follow-up scan 18 months later, subjects who had converted to Alzheimer's disease showed significantly greater GM loss - relative to non-converters - in the hippocampus, inferior and middle temporal gyri, posterior cingulate, and precuneus. All of these regions show severe deficits in mild AD (cf. **Figure 1**).

3.3. Optimized Voxel-Based Morphometry. Brief comment is warranted regarding a controversy that arose in the literature regarding the use of VBM (Ashburner and Friston, 2000; Bookstein, 2001; Davatzikos et al., 2001; Thacker, 2003; Crum et al., 2003). This debate generated some confusion regarding the validity of VBM. VBM is an extremely popular approach for comparing structural brain images, partly due to its high automation, and it is implemented in the *Statistical Parametric Mapping* image analysis package (SPM; www.fil.ion.ucl.ac.uk/spm/). Prior to 2000, the most commonly used implementation of VBM involved warping all tissue class images (i.e., 3D maps of gray and white matter probabilities) to match the same standardized brain atlas, and preserving the probability values in the spatially transformed images. These data were typically then smoothed and statistical analyses performed. This approach was criticized by Bookstein (2001) and Thacker (2003), who noted that this method only detects registration errors, because if the warping was 100% exact, there would be no residual differences.

Bookstein noted that the results of such studies depend heavily on the registration strategy used, and therefore VBM should not be used. In response to this criticism, the authors of VBM developed a modified approach, known as "modulated VBM" (Ashburner and Friston, 2001). This approach warps the tissue class images, but preserves information on the total volume of tissue by scaling the image intensities according to the amount of expansion or contraction. This approach was independently suggested by Davatzikos et al. (2001), where it was termed 'RAVENS' (*Regional Analysis of Volumes Examined in Normalized Space*); the same approach is known as "modulated VBM" by SPM users. Here the comparisons are volumetric, and the resulting 'optimized' VBM approach is now similar in many respects to the tensor-based morphometry methods described below (**Section 3.6**).

3.4. Surface-Based Analysis of Cortical Thickness. Cortical modeling techniques (Thompson et al., 2004) may also be used to map the profile of gray matter thickness across the cortical mantle, providing better localization and statistical power by matching data from corresponding gyri, as far as possible, across subjects. These cortical modeling approaches can be considered as a variant of voxel-based morphometry, but offer several benefits. First, parameters such as cortical thickness can be computed in 3D, displayed on the cortical models, and averaged across subjects for group comparisons. Second, the explicit modeling of the cortical surface geometry allows one cortex to be precisely aligned with another before multi-subject comparisons are made. This greatly reduces registration errors when comparing data across subjects and groups. An additional step known as *cortical pattern matching* can be used to fluidly match the entire gyral pattern from subject to subject, using a 3D deformation field to drive sulcal landmarks into correspondence (Thompson et al., 2004). This very high-order matching of anatomy can improve the power to detect subtle gray matter differences between groups or over time, and localizes effects relative to known cortical landmarks. In this process, clear anatomic divisions often emerge in the regions affected (e.g., the degree of cortical degeneration differs substantially on either side of the cingulate sulcus in **Figure 1(c),** a feature corroborated by the *post mortem* maps).

Composite maps of cortical thickness, based on MRI, have revealed a complex shifting pattern of cortical atrophy over the human lifespan, which is thought to primarily reflect neuronal shrinkage rather than overt neuronal loss (Sowell et al., 2003, *N*=176; Salat et al., 2004, *N*=106 subjects). These cortical mapping techniques show great promise, but have yet to be applied in MCI.

Cortical gray matter thickness is a powerful neuroimaging marker of cortical integrity, and a reasonable question is: 'What exactly is it measuring?' It is sensitive to subtle disease-related changes, and correlates with cognitive decline in Alzheimer's disease and schizophrenia (Thompson et al., 2001, 2003). Cortical thickness on MRI may be related to regional neuronal density in the cortical mantle (Selemon et al. 1995), but it may also depend on unknown vascular factors, glial cell numbers, and the extent and integrity of cortical myelination. We recently developed an approach to measure the thickness of the cortex from MRI, and mapped how it changes over the human lifespan. This approach has now been used in over 30 studies, to compile composite maps of average cortical thickness and compare them between specific populations (see Thompson et al., 2004 for an overview – **Figure 4** shows the main steps). Regions with systematic differences in cortical thickness can be detected and displayed on the cortex, as can the trajectory of changes in development or disease.

Cortical thickness can be defined in several different ways, but the simplest approach computes the 3D distance from the inner cortical gray-white matter boundary in tissue-classified brain volumes to the outer cortical surface (gray-CSF boundary) in each subject (see Thompson et al., 2004). Neuroimaging and histological studies have found significant changes in cortical thickness with normal aging (Raz et al., 1997; Magnotta et al., 1999; Sowell et al. 2003; Gogtay et al., 2004). In one study, we examined a large sample (*N*=176) of normal individuals across the span of life between 7 and 87 years (Sowell et al., 2003, 2006). Cortical thickness decreased quadratically with age from an average thickness of ~2.6mm at age 20 to less than 2 mm in the age range 80-90. Perhaps surprisingly, scatterplots of these effects revealed a dramatic decline in gray matter density between the ages of 7 and 60 years with a slower decline thereafter, in most

brain regions (the most dramatic changes occurring in the frontal cortex during late adolescence, where gray matter thickness falls rapidly). A second surprise was that the most lateral aspects of the brain in the posterior temporal and inferior parietal lobes bilaterally showed a distinct pattern of gray matter change, one in which the non-linear age effects were inverted relative to the age effects seen in more dorsal cortices, i.e., cortical atrophy accelerated rather than remaining linear or slowing down with age.

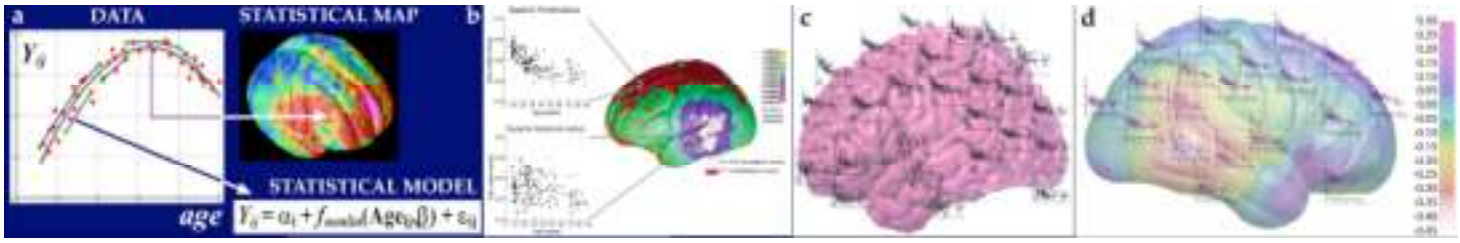

Figure 4. Mapping Cortical Changes. Several recent studies have examined the effects of age on the thickness of the cortex, measured in MRI scans of the brain (Sowell et al., 2003, 2006; Thompson et al., 2004; Shaw et al., 2006). This figure shows a general approach we developed to map cortical gray matter changes over time; it has also been used to produce time-lapse animations of the trajectory of cortical thinning with age, and to map the progression of diseases such as childhood-onset schizophrenia and Alzheimer's disease (Thompson et al., 2001, 2003; Vidal et al., 2006). First, measures (Y_{ij}) of gray matter thickness are obtained longitudinally (*green dots*) or once only (*red dots*) in a group of subjects at different ages. Fitting of statistical models to these data (*Statistical Model, lower right*) produces estimates of parameters that can be plotted onto the cortex, using a color code. These parameters can include age at peak (see arrow at peak of the curve), significance values, or estimated statistical parameters such as rates of change, and effects of drug treatment or risk genes. (b) and (c): We estimated the trajectory of gray matter loss over the human lifespan in a cohort of 176 normal subjects (Sowell et al., 2003). After cortical pattern matching was used to associate data from corresponding cortical regions, we developed software to fit a general nonlinear statistical model to the gray matter data from the population. This revealed significant nonlinear (quadratic) effects of time on brain structure. To show that it is feasible to pick up very small systematic differences using this technique, Sowell et al. (2006) found a sex difference in the trajectory of cortical thinning (d). There was an absolute excess in cortical thickness in women relative to men, of around 0.3mm, mainly in the perisylvian language areas (even without brain size adjustments). Our other cortical thickness studies provide evidence for this sex difference (Luders et al., 2006), which is important to consider if cortical thickness is used to gauge degenerative brain changes. For full details of the approach, see Thompson et al., 2004 and Sowell et al., 2006**.**

Gender differences in other markers of cortical atrophy are also apparent. In Kochunov et al. (2005), we studied age-related trends for the width and the depth of major cortical sulci in 90 healthy subjects (47 males, 43 females) aged 20-82 years. The average sulcal width increased by ~0.7 mm/decade, while the average sulcal depth decreased by ~0.4 mm/decade. Greater age-related decline was found in men relative to women, and in multimodal relative to unimodal cortical areas.

The rate of cortical thickness reduction in abnormal aging and degenerative disorders has also been shown to be different from that in healthy aging, making it a useful biomarker of neurodegeneration in a variety of illnesses (Thompson et al. 2003, 2004; Lerch et al., 2005). Our cortical mapping approach has been used to detect unsuspected alterations in gray matter distribution in Alzheimer's disease (Thompson et al., 2001, 2003; Pievani et al., 2006; Apostolova et al., 2006), Lewy Body dementia (Ballmeier et al., 2004), MCI (Apostolova et al., 2006), late-life depression (Ballmeier et al., 2004), HIV/AIDS (Thompson et al., 2005), methamphetamine users (Thompson et al., 2004), childhood and adult onset schizophrenia (Thompson et al., 2001; Narr et al., 2005; Vidal et al., 2006), normally developing children (Sowell et al., 2004; Gogtay et al., 2004; Lu et al., 2006), fetal alcohol syndrome (Sowell et al., 2002), individuals at risk for schizophrenia (Sun et al., 2006), adult- and adolescent-onset bipolar illness (Bearden et al., 2006; Gogtay et al., 2006), velocardiofacial syndrome (VCFS; Bearden et al., 2006), Williams syndrome (Thompson et al., 2005), epilepsy (Lin et al., 2006), attention deficit hyperactivity disorder (Sowell et al., 2004), genetic influences on brain structure (Thompson et al., 2001; Cannon et al., 2005), and lithium effects on brain structure (Bearden et al., 2006). The most general review of these methods is in Thompson et al. (2004).

One of the most provocative recent findings is that significant cortical thinning is detectable in asymptomatic carriers of the high-risk allelic variant, apolipoprotein E e4 (APOE e4). This allele is quite prevalent in the general population, and results in a three-fold increased risk of developing Alzheimer's disease. Using a technique to unfold the convoluted geometry of the hippocampus (see Zeineh et al., 2003 for details), Burggen et al. (2006) found that 9 (heterozygous) APOE e4 carriers with normal memory performance showed significantly reduced cortical thickness compared to 14 non-carriers in entorhinal cortex and the subiculum (by 10.6% and 7.5% respectively; p=0.005, 0.003), but not in the main body of the hippocampus or perirhinal cortex. Such a pattern of cortical thinning is consistent with the known progression of AD pathology and may reflect either a pre-existing reduction in cortical thickness, or early dynamic changes in cortical structure that diminish the processing capacity of the cortex. These early changes may contribute to accelerated disease

onset.

3.5. Imaging White Matter with DTI. White matter changes in MCI and AD are also of interest. Conventional MRI has insufficient contrast to discriminate fiber tract organization within the white matter, but diffusion tensor imaging (DTI), a newer MRI variant introduced in the mid-1990's (Le Bihan et al. 1986; Moseley et al. 1990; Basser et al. 1994) is sensitive to myelin breakdown, as well as fiber integrity and orientation. Medina et al. (2005) found that groups of MCI and AD subjects showed abnormal reductions in fractional anisotropy, a DTI-based measure of fiber integrity, in multiple posterior white matter regions. Rose et al. (2006) found that relative to normal controls, AD patients showed a significant reduction in the integrity of the association white matter fiber tracts, including the splenium of the corpus callosum, the superior longitudinal fasciculus, and cingulum but not the pyramidal tracts. This is consistent with the typical clinical presentation of AD, i.e. global cognitive decline but no motor disturbances. Other measures of water diffusion, such as the apparent diffusion coefficient (ADC), are abnormally elevated in the hippocampus in MCI (Kantarci et al., 2000a, 2001), and in broader areas - including the parietal white matter - in established AD (Sandson et al., 1999). Abnormal white matter changes can therefore be detected in MCI, prior to the development of dementia.

3.6. Tensor-Based Morphometry.

The best MRI measure to monitor disease progression in dementia depends, to some degree, on the follow-up interval after which patients are re-assessed. At relatively short follow-up intervals (6 months), ventricular measures are 3 times more powerful than whole brain atrophic rates for distinguishing AD from controls; this advantage dissipates if the follow-up interval is extended to one year (Schott et al., 2005).

Demonstration of *deteriorating* brain structure during the transition from MCI to AD has significant prognostic value as such changes over time almost certainly reflect the progression of underlying brain pathology. For tracking brain changes in exquisite detail, *tensor-based morphometry* (TBM) - also known as *deformation morphometry* or *voxel compression mapping* - has emerged as a powerful method to track brain

change (Thompson et al., 2000; Fox et al., 2001; Janke et al., 2001; Studholme et al., 2001; Leow et al., 2006; Chiang et al., 2006). TBM is a more complex image analysis approach; it quantifies tissue growth or atrophy throughout the brain, based on elastically warping sequentially collected MRI scans. It visually indicates the local rate at which tissue is being lost, or expanding, throughout the anatomy of the brain (see **Figure 5** for an illustration). It surveys the whole brain at once, but detects localized changes occurring at a regional level, without having to specify the regions of interest in advance. This approach may ultimately offer the greatest power for clinical trials. Deformation morphometry can detect subtle medication-related changes over a period of less than a month, such as effects of lithium on brain structure (Leow et al., 2006), and is automated enough to apply to large cohorts of subjects efficiently, without the need for laborious interaction with images to identify regions of interest. The brain changes are then compared across subjects or groups. Correlations can be mapped between these changes and demographic or clinical measures such as age, sex, diagnosis, cognitive scores, treatment outcomes, or biological serum measures (see Chiang et al., 2006, for examples of this approach in a study of HIV/AIDS).

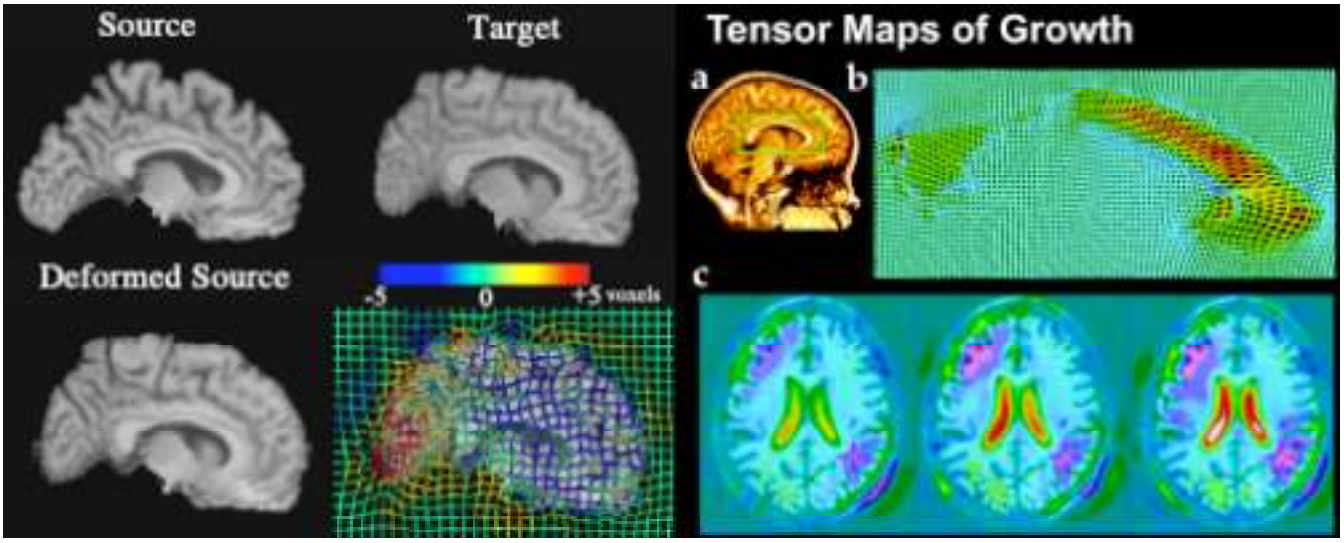

Figure 5: Tensor-Based Morphometry Maps Rates of Tissue Gain or Loss. Tensor-based morphometry, or TBM, can automatically map brain changes in large groups of subjects. Here, an example MRI image (*top left*) is aligned to a target image, and the shape of gyri, corpus callosum, and ventricles are well-matched (data from Chiang et al., 2006). To better visualize the applied 3D deformation field, a colored grid is superimposed on the registered image – red and blue colors represent deformation orthogonal to the midsagittal plane (out of the page). **(a) and (b):** In Thompson et al. (2000), we used TBM to map growth rates (b) in the corpus callosum (a) of a young girl scanned at age 3 and again at age 6 – the anterior corpus callosum grows the fastest at this age (~20% local volume gain per year, mostly likely due to progressive myelination). Rates of tissue expansion are inferred from the derivatives of the warping field that aligns baseline to follow-up scans. (c): Progressive gray and white matter atrophy (*purple colors*) and ventricular expansion (*red and white colors*) are mapped in a patient with posterior cortical atrophy scanned 1, 1.5, and 2 years after diagnosis. After registering growth rate maps to a common neuroanatomical template, group differences in rates of brain change can be tested statistically (see Leow et al., 2006, and Lu et al., 2006, for examples of studies comparing groups cross-sectionally and longitudinally).

How TBM Detects Brain Changes. If two brain images, acquired over time, are rigidly overlaid, brain changes cannot be localized: no information is available on exactly where atrophy is occurring. To localize changes within the brain, matching needs to be performed with a non-linear 'warping' algorithm. Over the last 15 years, many groups have developed nonlinear image warping techniques that align brain images with a compressible elastic or fluid model. This allows localized deformation. How well these approaches perform depends on the mathematical measure of image correspondence used to drive the alignment of the images, how flexible the deformation is (in terms of degrees of freedom), and whether steps are taken to ensure that the mappings are smooth and preserve the topology of the image (see Thompson and Toga, 2003 for a discussion). In one approach (see Leow et al., 2005, and Chiang et al., 2006, for mathematical details), the

follow-up (repeat) image is globally aligned to the baseline scan, and then a 3D elastic or fluid image deformation is used to maximize the mutual information (or a related information-theoretic measure of correspondence) between the two consecutive scans. This fully 3D deformation reconfigures the baseline anatomy into the shape of the follow-up scan. The expansion or contraction at each image voxel is computed from the deformation field (using the Jacobian of the deformation field to produce a '*voxel compression map'* or '*tensor map'*). In this map, contraction implies atrophy; expansion implies local growth or dilation (Fox et al., 2000). A color map then displays these changes on the follow-up scan. As shown in **Figure 3**, the method can be used to map patterns of brain changes in patients scanned longitudinally over short intervals (Leow et al., 2006), in patients with semantic dementia (Leow et al., 2005b, 2006), and has been used to automatically map the profile of brain structural differences in cohorts with HIV/AIDS (Chiang et al., 2006, Lepore et al., 2006), Fragile X syndrome (Lee et al., 2006), Williams syndrome (Chiang et al., 2006b), schizophrenia (Lu et al., 2006), bipolar illness (Foland et al., 2006), in healthy subjects treated with lithium (Leow et al., 2006d), and in twins imaged with DTI (Lepore et al., 2006). TBM has relatively high throughput and sensitivity, making it attractive to use for gauging brain changes in large population studies and clinical trials. New statistical methods are also emerging to increase the sensitivity of TBM. For detecting degenerative brain changes, Lie group and Riemannian manifold methods can provided more statistical power than standard approaches, as they draw upon the full multi-dimensional information available in the deformation tensors (Lepore et al., 2006a,b). Such an approach might be termed 'generalized TBM'.

3.7. Combining Fluid Registration with Anatomical Surface Modeling. Fluid registration can also be combined with surface-based modeling to automatically create maps of anatomical surfaces in large numbers of images, and compare the resulting surfaces statistically. This approach combines the strengths of two very different methods, while providing automation and high-throughput for large population studies. In the largest brain mapping study of MCI to date, Carmichael et al. (2006) delineated the lateral ventricles on a single brain MRI dataset, and fluidly deformed a surface model of these structures, using nonlinear image registration, to match the shape of the ventricles in other MRI scans from 74 MCI, 225 normal, and 40 AD subjects. The

average ventricular shapes were compared using a surface-based modeling approach, which plots the regions with statistical shape differences on the surfaces using a color code (Thompson et al., 2004). MCI subjects showed significant, localized dilations relative to normal subjects in the atrium of the ventricles and in the occipital horns. AD subjects showed a greater extent of enlargement involving the frontal horns. In AD, temporal horn expansion progresses at a rate of 13-18% per year (compared with 2-4%/year in healthy controls; Thompson et al., 2004). By contrast, the mean annual rate of hippocampal volume loss on MRI is much more subtle: 1.73% in stable controls, 3.5% in AD, and 3.69% versus 2.55% in MCI subjects who decline or remain stable at 3-year follow-up (Jack et al., 2000). Strictly speaking, this approach provides similar information to tensor-based morphometry, but surface models are used to constrain the search for significant effects to regions are known to be implicated. This improves statistical power, as well as presenting results in a visually intuitive way.

4. Use of Imaging in Drug Trials

Recent studies also suggest that imaging can be useful as a biomarker for therapeutic efficacy in AD. Refinements are occurring in the measures used, and large-scale projects, such as the Alzheimer's Disease Neuroimaging Initiative (www.loni.ucla.edu/ADNI/) are now comparing and cross-validating different imaging measures for detecting significant brain changes in AD. Even if only conventional volumetric measures are used, Jack et al. (2003) estimated that in each arm of a therapeutic trial, only 21 subjects would be required to detect a 50% reduction in the rate of decline, if the hippocampal volume was used as the outcome measure. This compares with 241 subjects if MMSE scores were used, and 320 if the AD Assessment Scale Cognitive Subscale were used. Imaging measures are not likely to replace cognitive measures as outcome measures in clinical trials, but they are widely regarded as more stable and reproducible across sites. Significant work has been devoted to establishing imaging protocols that are reproducible across imaging centers, and across time (Bernstein et al., 2006) and the detection limits of image analysis techniques has been shown to be greatly

improved if scanner-related factors, such as geometric stability, field homogeneity, RF coil type, and field strength are optimized (Bernstein et al., 2006; Leow et al., 2006).

Automated measures of atrophy are also gaining acceptance in longitudinal studies, although not all studies have yielded the expected conclusions. Fox et al. (2005) applied a powerful image analysis approach, known as the Brain Boundary Shift Integral, to estimate the overall brain volume decrease in registered serial images from 288 AD patients in a Phase IIa immunotherapy trial. Paradoxically, when assessed 11 months later, antibody responders (N=45) had greater brain volume decreases (on average 3.1% versus 2.0%), and greater ventricular enlargement than placebo patients (N=57). Because this atrophy did not correlate with cognitive decline, the authors speculated that these volume changes may be attributed to amyloid removal and associated cerebral fluid shifts.

5. Conclusion

Overall, structural brain scanning with MRI has yielded several measures that help to differentiate mildly impaired patients from controls. MRI can also be used to help predict who will imminently convert to suspected AD, and to gauge how well interventions resist atrophic brain changes, if at all, in clinical trials. Because therapeutic trials require sensitive biomarkers that track the disease process in detail, serial MRI scanning is often combined with powerful, automated analysis methods to compute maps of brain changes, and volumetric measures for brain regions that change early in AD, such as the hippocampus and entorhinal cortex. These efforts now use cutting-edge mathematics to map brain change on MRI and PET, as well as longitudinal datasets that track disease over multi-year time-spans before and after disease onset.

Other innovations in neuroimaging include ongoing developments in diffusion tensor imaging, MR relaxometry, imaging of iron deposition, and high-field MRI scanning. Each of these techniques aims to increase the repertoire of signals available for assessing tissue integrity in early neurodegenerative disease. Perhaps the

most promising development is the recent advent of PET tracer compounds that visualize amyloid plaques and neurofibrillary tangles (NFTs) in the living brain. These pathological features are the defining hallmarks of AD, previously only detectable at autopsy. New tracer compounds for plaque and tangle imaging ([^{18}F]-FDDNP and [^{11}C]-PIB) complement the now-standard PET measures (of perfusion and glucose metabolism) that are the mainstay of differential diagnosis in dementia. Many see in these new tracers the promise to track AD before it is clinically detectable – and assess how therapy resists it before symptoms become irreversible. Amyloid deposition gradually increases in the brain long before detectable symptoms of memory decline, so there is an expectation that amyloid plaque and/or tangle PET tracers can identify and monitor AD progression before any symptoms appear (Klunk et al., 2005; Small et al., 2006). In addition, these tracers quantify pathology objectively, offering a direct means to evaluate anti-amyloid therapies such as secretase inhibitors.

It is not yet known whether these new PET markers correlate more tightly than MRI measures with observable clinical decline in MCI, although both distinguish AD and MCI from controls. A major effort in these analyses is to correlate the trajectory of pathology observed with new PET tracers with dynamic maps of cortical neurodegeneration on MRI. Initial studies in AD reveal a positive correlation between rates of whole brain atrophy and regional [^{11}C]-PIB uptake (N=9; Archer et al., 2006). Each of these measures is tightly correlated with global cognitive function (MMSE; Thompson et al., 2003; Small et al., 2006). It is of interest to relate the two views of the neurodegenerative process. A major goal is to develop joint measures of the disease process with far greater predictive power than either MRI or PET can provide on its own.

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