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A focus on structural brain imaging in the Alzheimer's Disease Neuroimaging Initiative

Meredith N. Braskie[1,2] and **Paul M. Thompson**[1,2,3,4]

[1]Imaging Genetics Center, Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Marina del Rey, CA 90292, USA

[2]Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

[3]Departments of Psychiatry and Behavioral Sciences, Radiology, and Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

[4]Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90089, USA

Abstract

In recent years, there has been a wealth of laboratories and consortia that use neuroimaging to evaluate the risk for and progression of Alzheimer's disease (AD). One such consortium is the Alzheimer's Disease Neuroimaging Initiative (ADNI) - a longitudinal, multi-center study that evaluates a range of biomarkers for use in AD diagnoses, predicting patient outcomes, and for clinical trials. These biomarkers include brain metrics derived from magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, and metrics derived from blood and cerebrospinal fluid (CSF). Here we focus on ADNI studies, published between 2011 and March 2013, for which structural MRI was a major outcome measure. Our main goal here was to review key papers offering insights into AD progression, and the relationships of structural MRI measures to cognition and to other biomarkers in AD. In the Supplemental Materials, we also discuss genetic and environmental risk factors for AD, and exciting new analysis tools for the efficient evaluation of large scale structural MRI data sets such as ADNI.

Keywords

biomarkers; Alzheimer's disease; magnetic resonance imaging; MRI; Mild Cognitive Impairment; cognitive decline; dementia; brain volume; hippocampus; temporal lobe; atrophy; conversion; progression; predict; cognition

Please address correspondence to: Paul M Thompson, PhD, University of Southern California, Imaging Genetics Center, Institute for Neuroimaging and Informatics, 4676 Admiralty Way, 4th floor, Marina Del Rey, CA 90292, pthomp@usc.edu.

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Introduction

In recent years, numerous laboratories and multicenter consortia worldwide (e.g., (1-3) have used neuroimaging and other biomarkers to evaluate Alzheimer's disease (AD) risk factors, and disease progression and prediction. Here we review findings from one such consortium - the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large, multicenter longitudinal study designed to test biomarkers for identifying and tracking AD. We occasionally discuss non-ADNI work to provide context for the ADNI findings. We focus specifically on ADNI studies using structural magnetic resonance imaging (MRI) as a main outcome measure, and we compare those measures to other biomarker information when available. We did not review studies that examined only biomarkers derived from cerebrospinal fluid (CSF), plasma, or other non-MRI imaging modalities. Sometimes, other biomarkers not explored here may be the best option for a particular research question.

We emphasize studies published since 2011 through March 2013, although we occasionally cite papers outside that range if they are landmark studies or are needed to explore a line of reasoning. A review of all ADNI work through mid-2012 has been published previously (4). Other recent AD review articles not specific to ADNI focused on AD-related genetic findings (5; 6), and brain imaging (7-10). Here we survey how ADNI has improved our understanding of AD progression, and the relationships of structural MRI measures to cognition and other AD biomarkers. In the Supplemental Materials, we examine genetic and environmental risk factors for AD, and report on analysis tools that improve our ability to analyze large-scale structural MRI data sets such as ADNI.

Although the ADNI studies discussed here included subjects drawn from the same subject pool, they had various goals and were performed using different software and statistical models with a variety of variables included. Therefore, the resulting findings may not be directly comparable. A detailed discussion of all these results is beyond the scope of this article. Instead, we have focused on the most common findings across studies with the understanding that results replicable using different methods have attained a higher standard of credibility. We also have presented differences in findings that correspond to a particular study attribute. For instance, certain results may be found more often in a particular diagnostic group. We have presented these findings in the context of disease progression.

AD progression - the temporal sequence of changes in biomarkers

Understanding how AD biomarkers change over time throughout disease progression is crucial to evaluating AD prevention and treatment efforts. To determine whether a treatment is working, it is important to choose biomarkers that are most relevant and specific to AD. It is also important to choose biomarkers that are in a state of change for the study sample being evaluated. The biomarkers that are most dynamic (in terms of their rate of change over time) will likely not be the same ones at various stages of the disease, since each may eventually reach a maximum (11). The apparent sequencing of biomarkers depends both on the order of true biological changes, and on the precision and sensitivity with which the assessment methods can detect those true biological processes. The true biological ordering

of brain changes may be obscured if some changes remain below the detection threshold for a period of time.

In 2010, Jack and colleagues proposed a model of biomarker change in which each type of AD biomarker became more dynamic (i.e., began to change more rapidly over time) at a somewhat different point in disease progression. Preclinical *in vivo* changes in beta-amyloid (Aβ) in the brain or CSF tended to be detectible first. These biomarkers are specific to AD and indicate that disease processes are underway. CSF Aβ changes were followed by changes in detectible levels of tau-mediated neuronal injury (measured using CSF tau levels) and fluorodeoxyglucose positron emission tomography (FDG-PET). Brain structure measured using MRI was proposed to change next, shortly before measurable changes in memory and then other functional measures assessed clinically. These later changes in measures associated with neuronal death and cognitive impairment may serve well as markers of disease progression. Once they are detectable *in vivo*, AD pathological processes have already been initiated. The authors postulated that the maximum rate of change moves sequentially from one biomarker to the next, following a non-linear time course that may be sigmoid-shaped with time (12). A later revision of that model acknowledged that ordering of MRI and FDG-PET biomarkers remains ambiguous (13). Additionally, some evidence suggests that tau and Aβ pathophysiology may arise independently in many individuals (14), with abnormal tau remaining initially at levels not detectible *in vivo* and accelerating to detectible levels only after detectible Aβ changes have occurred (13; 15).

Evidence has accumulated (16-25) that amyloid biomarkers are among the earliest AD biomarkers to begin changing. In one study, brain atrophy in the default mode network (including the precuneus) and medial temporal lobe occurred after CSF Aβ42 and tau changes, but appeared to precede frontal atrophy (24). Similarly, in another study, Alzheimer's Disease Assessment Scale - Cognitive (ADAS-cog) scores were plotted against *Z* scores in other biomarkers relative to healthy controls (CTLs) (19). CSF Aβ1-42 *Z* scores changed the fastest in correlation with declining cognition in CTLs and in those with mild cognitive impairment (MCI), before leveling off in AD patients. CSF tau appeared to change next (with greatest rates of change largely in those with MCI), then hippocampal volume (with greatest rates of change in MCI and early AD). Finally, FDG-PET metabolism became more dynamic (19). These results suggest that early indicators of AD such as detectable changes in CSF Aβ1-42 and CSF tau precede markers of AD progression such as hippocampal volume and glucose metabolism.

Ewers and colleagues' results may support hippocampal atrophy occurring before changes in FDG-PET metabolism. In control subjects, the presence of brain Aβ at baseline (PIB-PET+ scans) was associated with faster subsequent rates of atrophy over two years only in the hippocampus and precuneus (20). In PIB+ MCI patients (compared with PIB- MCI patients), subsequent rates of atrophy over two years were higher in the hippocampus and other temporal and parietal regions, with an additional trend toward faster decline in parietal FDG-PET metabolism (20). This suggests that presymptomatically, brain Aβ is elevated prior to or along with atrophy in the hippocampus and precuneus, but that it does not herald acceleration of atrophy in other regions in the near term. As the disease progresses and cognitive impairment becomes evident, baseline brain Aβ is associated with continued

atrophy in the hippocampus and precuneus, but also predicts a faster rate of atrophy in other regions and a trend-level faster decline in FDG-PET metabolism. This suggests that these changes occur later than the atrophy in the hippocampus and precuneus. However, there were more MCI subjects than controls in this study, so it is also possible that statistical power differences contributed to the differing results. Examining how brain Aβ predicts changes in other biomarkers in larger control samples and over longer time periods may help clarify the shape and ordering of the biomarker curves. Others found that the rate of change in FDG-PET metabolism and hippocampal volume was slowest in CTLs and fastest in AD, while the rate of change in CSF Aβ was fastest in CTLs (although not significantly so). This may support changes in Aβ as an initial stage of AD followed by hippocampal atrophy and FDG-PET hypometabolism with unclear ordering of the latter two (16). That atrophy may then mediate changes to episodic memory (26).

Known genetic risk factors for AD, including the ε4 allele of AD genetic risk factor apolipoprotein E (*APOE*4) (27), may offer insights into AD progression. In the Lo et al. 2011 study, *APOE*4 was associated with lower baseline CSF Aβ42 and less FDG-PET metabolism in CTLs, but was not significantly associated with baseline hippocampal volume. In MCI, *APOE*4 was associated with lower CSF Aβ levels and FDG-PET metabolism, and smaller hippocampi at baseline (16). This suggests that FDG-PET metabolism is affected earlier than hippocampal volume in *APOE*4+ subjects. Similarly, a non-ADNI paper found that in late middle-aged CTLs, *APOE*4 dose was associated with FDG-PET hypometabolism in the posterior cingulate, but not with the volume or FDG-PET metabolism of the hippocampus (28). However, there are already differences in FDG-PET between *APOE*4+ and *APOE*4- subjects in their 20s and 30s (29), while *APOE*4 is not associated with brain amyloid positivity (measured with florbetapir) until approximately age 56 (30). This suggests that although altered glucose metabolism may affect AD risk in *APOE*4+ adults, the vulnerability to AD may be distinct from the AD-related amyloid cascade outlined by Jack and colleagues (12; 13; 31). Lo and colleagues found that *APOE*4 was associated with a higher hippocampal atrophy rate (but not rate of change for FDG-PET metabolism or CSF Aβ) only in AD and MCI subjects (16). This suggests that FDG-PET differences associated with *APOE*4 may be long-standing, and may not relate directly to disease progression. In contrast, another cross sectional non-ADNI study of AD progression found that in those with autosomal dominantly inherited forms of early onset AD, CSF tau changes and hippocampal atrophy occurred before FDG-PET metabolism changes and episodic memory (32). In that study, biomarker values were similar in young mutation carriers and young non-carriers, but differences between carriers and non-carriers emerged with age (32). This suggests that the relationships of biomarkers to the time until the expected AD onset age were related to AD pathological changes rather than to unrelated genetic effects. Early onset AD and *APOE* genetic findings may or may not all generalize to late-onset AD risk, but they underscore the importance of controlling for *APOE* genotype and understanding its effects in AD neuroimaging studies. To determine whether hippocampal atrophy or FDG-PET hypometabolism occurs first in AD, it would be useful to follow CTL subjects with Aβ abnormalities to determine which other biomarkers increase earliest or fastest. The addition of early MCI subjects from ADNI-2 to these studies may help elucidate the ordering of biomarkers.

Several studies have supported a non-linear shape for biomarker curves (13; 22; 33-35). However, fully modeling biomarker curve shapes in ADNI is difficult given the short follow-up period thus far. “Trajectories” of biomarkers are commonly inferred based on a cross-sectional data. Cross-sectional designs may be misleading due to cohort effects, including differing ages of disease onset in AD patients and healthy survivor effects (36). Rates of atrophy and clinical decline may differ with advancing age within diagnostic group, becoming less aggressive in relatively older late-onset AD patients. This may obscure true biomarker shapes when viewed in cross-section (37).

Relationships of structural MRI to cognition

To be useful, a biomarker must ultimately be linked to cognition, or must predict future changes in cognition. In other words, following an intervention, would a given biomarker inform researchers about whether the rate of cognitive decline is now slower or will be in the future? As such, many studies have sought to establish a link between various AD biomarkers and cognition at different disease stages. Here we focus on studies that related structural MRI measures to cognitive change.

In aging, the processes of neuronal atrophy, cell death, and vascular changes all reduce regional brain volumes and may impair cognition, leading to a correlation between the two. In fact, hippocampal and ventricular volume along with the number of years since disease onset are the best predictors of ADAS-cog scores in AD patients (38). Additionally, the rare subjects who show longitudinal “improvements” in brain structure (apparent volumetric gains) are also likely to show cognitive improvement that may arise partly from practice effects (39). The apparent volumetric gains may relate to mechanisms such as axonal sprouting, white matter repair, or neurogenesis (39), but a relative lack of atrophy and measurement noise may also play a role.

Several studies report correlations between regional brain volume or atrophy and various types of cognitive test. As expected, memory measures correlate best with temporal lobe structures, while executive function and general cognitive functioning measures typically correlate more strongly with more global measures such as whole brain atrophy, ventricular enlargement, and cortical thickness across multiple brain regions (40-43).

Lo et al. found that the rate of change for CSF Aβ42, FDG-PET metabolism, and hippocampal volume in MCI all correlated significantly with the rate of change in ADAS-cog scores. Highest correlations of ADAS-cog scores in MCI were with both FDG-PET and hippocampal changes (roughly equally). In mild AD, however, only changes in FDG-PET metabolism and hippocampal volume were related to changes in cognition, with the strongest association being with FDG-PET (16). This suggests that hippocampal atrophy may begin to become less important than global function to cognition as AD progresses. Hippocampal atrophy, although not cortical atrophy, may continue to accelerate in subjects with a Mini-Mental State Exam score (MMSE) at least as low as 15 (22), and the MMSE scores for AD subjects averaged 23.3 in the Lo et al., study (16), suggesting that a floor effect is not responsible for their shift in relative importance toward FDG-PET influencing the cognitive decline. The shift may reflect a breakdown of information flow between the

hippocampus and cortex, which would render hippocampal volume irrelevant if its functionality were already disabled by limited communication with the rest of the brain in dementia. Rowe and colleagues also identified this shift: in controls and MCI subjects, hippocampal volume was associated with cognitive measures, but in AD patients, global gray matter volume was more strongly correlated with cognitive functioning, although sample sizes for MCI and AD were similar (44). Others found correlations between hippocampal or temporal lobe structure and memory in cognitively impaired subjects, but not in CTLs alone (43; 45; 46).

Consistent with prior work (26), some found that changes in MRI and FDG-PET neuroimaging mediated the relationship between brain Aβ and cognitive changes (20). CSF Aβ and tau independently predicted longitudinal hippocampal atrophy and ventricular expansion, and CSF tau predicted a change in FDG-PET metabolism. However, CSF measures did not explain changes in cognition after controlling for the changes in imaging measures (21). This suggests that changes in atrophy and glucose metabolism (markers of disease progression) mediate the relationship between indicators of the presence of AD (abnormal levels of Aβ and tau) and cognitive impairment. Likewise, others found that ventricular expansion, but not PIB change over ~12 months was associated with worsening cognition (34).

Relationships of structural MRI to other AD biomarkers

To establish that changes in a given biomarker are moderately specific to AD, it is helpful to link that measure to abnormal levels of AD-related markers such as amyloid or tau. Some studies reported relationships between hippocampal volumes and either cortical amyloid burden (inferred from PIB-PET scans) or CSF Aβ42 in CTL and MCI subjects, but not in AD (44; 47). Others who examined only non-demented subjects likewise found correlations between hippocampal volumes and CSF Aβ (26; 48). Baseline cortical thickness in several brain regions was also correlated with CSF Aβ only in CTLs (49). One study found that the relationship with CSF Aβ was strongest in CTLs in the inferior-anterior hippocampal head and superior and inferior hippocampal body, but in MCI, the relationship was limited to the superior body (47). This relationship may therefore become weaker with disease progression. Rowe and colleagues found a correlation between CSF Aβ and hippocampal volume only in CTLs and between PIB-PET cortical binding and hippocampal volume only in MCI patients (44). This suggests that, as in purely genetic early onset forms of AD, abnormal CSF Aβ may be detectable earlier in the disease process than is brain amyloid (32). However, other studies found that, when data from all diagnostic groups were pooled together, hippocampal structure related to either CSF t-tau levels (47) or to both CSF Aβ and tau levels, especially p-tau181 (50). Trends toward significance for some tau measures also existed in the MCI and AD groups individually (50). These results may be explained by tau measures having subtle effects that are continuous across groups, but sub-threshold within diagnostic groups in the available sample sizes. In contrast, CSF Aβ appears to be related to hippocampal volume most strongly before frank dementia is present. However, one study found no significant relationship between CSF Aβ and baseline hippocampal volume in any diagnostic group (51). These findings may differ from others (26; 44; 47; 48) because only Stricker and colleagues included *APOE* genotype as a covariate in their

analyses (51). *APOE*4+ CTLs have greater detectable brain amyloid (44) and lower CSF Aβ (52; 53) than *APOE*4 non-carriers. Although *APOE*4+ controls do not typically have lower baseline whole hippocampal volume than *APOE*4- controls (54-56), *APOE*4 is associated with differences in hippocampal subfield structure (55; 57) and hippocampal atrophy rates (58) in healthy adults. It is possible that part of the apparent relationship between CSF Aβ and baseline hippocampal volume in non-demented adults was diminished after controlling for that allele.

When atrophy rate was considered rather than baseline volume, a decline in hippocampal volume correlated with CSF Aβ, but not tau measures, in CTLs only (51). In MCI subjects, AD-related temporal and parietal cortical atrophy (49) and hippocampal atrophy rates were associated with both CSF Aβ (49; 59) and p-tau181 (49; 51). In AD patients, hippocampal atrophy rates were correlated with CSF p-tau 181 (51) and temporal lobe atrophy rates were correlated with both p-tau 181 and the ratio of tau/Aβ42 (46), but neither was related to CSF Aβ levels alone. These data support the notion that baseline CSF Aβ is more tightly linked to brain structural integrity in preclinical AD. CSF tau levels may relate more to brain atrophy rates later in the disease process.

Predicting cognitive decline

Although some rare, early-onset forms of AD are inherited in a fully penetrant, autosomal dominant manner, typically, AD onset is unpredictable. Identifying biomarkers that accurately determine who will eventually develop AD symptoms, and when, would be invaluable. Clinically, predictive biomarkers would help physicians to identify individuals who may benefit from presymptomatic treatments. In research, predictive biomarkers would allow researchers to stratify clinical trial evaluations based on likely rates of decline and preferentially select subjects who are most likely to decline cognitively, boosting the power to detect intervention effects.

ADNI data have been used to model brain structure changes in normal healthy controls (60) and to relate these changes to longitudinal memory decline (61-65). Most of these studies predicted cognitive decline based on MRI measures selected *a priori* for their relevance to AD (62; 64; 65), although one study combined MRI and CSF measures as predictors using unsupervised clustering of baseline variables to identify subjects with similar profiles (63). Membership in an AD-like profile (defined best by hippocampal volume and CSF tau markers) was associated with greater cognitive decline over three years. Other MRI markers - ventricular volume, white matter hyperintensities, and entorhinal cortex thickness - were less able predictors (63). Two other studies combined measures from several MRI regions to predict memory decline. In one of these, the best predictive model of memory decline included hippocampal volume (but not entorhinal cortex volume), other temporal regions, superior parietal lobe, and the posterior cingulate (61). The second study examined 6-month brain structure changes as predictors of cognitive decline over two years. Ventricular expansion and atrophy of the fusiform and inferior temporal cortices best predicted memory decline (64). Together, these studies suggest that CSF tau changes and measures of temporal lobe integrity loss most reliably predict cognitive decline in CTLs.

Most ADNI predictive studies examined cognitive decline in MCI patients. Of those, several focused solely on baseline MRI features, assessing individual candidate regions of interest selected for their relationship to AD (66-69). Others compared MCI scans with an "AD signature" that included multiple candidate regions or voxels identified as AD-like based on previous work (70-73), or trained on AD-CTL differences in the same study (74-78). Some researchers instead assessed a network of regions derived from a "progression" signature either created by comparing the baseline brains of stable versus progressive MCI patients, or by identifying regions in which atrophy progressed across earlier time points (79-81). Such studies used cross validation, and performed training and testing repeatedly on a variable subset of subjects.

When only MRI measures were evaluated, the best baseline and longitudinal predictors of cognitive decline in MCI patients typically included measures of the medial temporal lobe regions, especially the entorhinal cortex, hippocampus, and amygdala (66; 68; 69; 74-77; 79-81). Baseline measures or atrophy rates in the parahippocampal cortex or posterior regions (posterior cingulate cortex and precuneus) were associated with conversion to AD in a smaller number of studies (74; 76; 78-80). However, when atrophy rate was considered within MCI patients, medial temporal atrophy was a better predictor of conversion than posterior atrophy (66; 81). One study found that the expansion rate of the temporal horns of the lateral ventricles predicted conversion to AD even better than the hippocampal atrophy rate (67). Some studies found that including multiple types of structural measures (e.g., cortical thickness, volume, and atrophy rate) predicted AD better than any one measure alone (73; 78).

Several studies predicted cognitive decline in MCI patients using both structural MRI measures and other biomarkers such as cognitive testing, CSF Aβ42 or tau, FDG PET, and *APOE* genotype (71; 82-99). In most studies, the model that combined information from multiple modalities, including MRI, predicted decline better than any one biomarker alone (71; 82; 83; 85; 87; 89; 92; 95-97), underscoring the importance of tools flexible enough to accommodate information from multiple sources. Even so, several studies that examined multiple types of biomarkers found that baseline cognitive measures were the best single predictors of future conversion to AD (88; 90; 92-95). This may be because ADNI-1 and ADNI-GO, from which most published ADNI papers to date are derived, recruited only MCI subjects who were close to dementia. As cognitive decline may have a steeper slope than other biomarkers close to AD conversion (13), cognitive markers are likely to be more informative at that point. ADNI-2 recruits subjects known as "early MCI", for whom CSF and MRI biomarkers may prove to be more informative. In studies of CTLs or those with early MCI, evaluating disease progression without relying on conversion to a different diagnostic category would be useful. This may mean comparing baseline biomarkers to AD-like changes in other biomarkers such as cognition, CSF Aβ or tau, and MRI (76; 84). A few studies showed FDG-PET to be more useful than MRI measures for predicting conversion from MCI to AD within a few years (96; 98). This suggests that FDG-PET either changes later or for longer than MRI measures, as is the case in early onset autosomal dominantly inherited forms of AD (32).

Conclusion

ADNI has helped elucidate how AD progresses. This information is crucial to choosing measures of interest in interventional and prevention trials. Here we evaluated AD biomarkers derived from structural MRI scans. We discussed how useful these biomarkers are for understanding disease progression, and compared structural MRI measures to changes in cognition and to biomarkers from other modalities.

Structural MRI is only one of several biomarkers that could be selected for monitoring AD changes in the brain. Among its benefits are its ease of use, non-invasiveness, and relatively low cost (compared with PET). It can therefore be administered in large-scale, multi-site studies and many clinical settings. Ongoing efforts to standardize MRI measures and pool standardized data have been quite successful, creating larger samples and higher statistical power (100). However, structural MRI measures are not as specific to AD as amyloid measurements and may include effects of aging and other neurodegenerative diseases and processes.

Structural measures of the medial temporal lobe structures do an able job of predicting cognitive decline (66; 68; 69; 74-77; 79-81). However, biomarkers from multiple modalities examined together tend to predict cognitive decline better than any single biomarker (71; 82; 83; 85; 87; 89; 92; 95-97). Choosing appropriate biomarkers for the disease stage studied and consistently controlling for confounding covariates will empower future studies to more efficiently detect the effects of treatment and prevention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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