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Alzheimer's & Dementia 6 (2010) 257–264

Alzheimer's & Dementia

The Alzheimer's Disease Neuroimaging Initiative: Annual change in biomarkers and clinical outcomes

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Abstract

Background: The Alzheimer's Disease Neuroimaging Initiative Phase 1 (ADNI-1) is a multisite prospective study designed to examine potential cerebrospinal fluid and imaging markers of Alzheimer's disease (AD) and their relationship to cognitive change. The objective of this study was to provide a global summary of the overall results and patterns of change observed in candidate markers and clinical measures over the first 2 years of follow-up.

Methods: Change was summarized for 210 normal controls, 357 mild cognitive impairment, and 162 AD subjects, with baseline and at least one cognitive follow-up assessment. Repeated measures and survival models were used to assess baseline biomarker levels as predictors. Potential for improving clinical trials was assessed by comparison of precision of markers for capturing change in hypothetical trial designs.

Results: The first 12 months of complete data on ADNI participants demonstrated the potential for substantial advances in characterizing trajectories of change in a range of biomarkers and clinical outcomes, examining their relationship and timing, and assessing the potential for improvements in clinical trial design. Reduced metabolism and greater brain atrophy in the mild cognitive impairment at baseline are associated with more rapid cognitive decline and a higher rate of conversion to AD. Use of biomarkers as study entry criteria or as outcomes could reduce the number of participants required for clinical trials.

Conclusions: Analyses and comparisons of ADNI data strongly support the hypothesis that measurable change occurs in cerebrospinal fluid, positron emission tomography, and magnetic resonance imaging well in advance of the actual diagnosis of AD.

Keywords: Alzheimer's disease; Cerebrospinal fluid; Neuroimaging; FDG PET; MRI; Biomarkers; Clinical trial design; Mild cognitive impairment; Cognitive decline

1. Background

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and a substantial burden to patients, caregivers, and the health care system [1]. Approved treatments are few and of limited efficacy, serving mostly to slow or delay progression and not to cure the disease, despite significant research efforts by the National Institutes of Health and the pharmaceutical industry. A major barrier is that clinical disease assessment yields measures of limited value for characterizing diagnosis and quantifying disease progression and drug efficacy: clinical measures have substantial between- and within-person variation [2], and they

[1]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf.

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doi:10.1016/j.jalz.2010.03.002

likely lag far behind the underlying pathology onset and progression [3]. Evidence to date suggests that the neurobiological development of AD affects brain physiology and function at multiple levels and across multiple locations. Researchers have proposed several potential in vivo biomarkers based on either fluid samples or neuroimaging, to ascertain the current status and track the progression of AD-related brain change. Many published articles have shown association with disease progression for potential biomarkers; examples include serum and cerebrospinal fluid (CSF) markers for $A\beta_{42}$, tau, and phosphorylated tau (P-tau) at residue 181 [4]; positron emission tomography (PET) imaging for amyloid burden [5] and for glucose metabolism [6,7]; and structural magnetic resonance imaging (MRI) for brain tissue volumetric changes [8].

The primary goal of the Alzheimer's Disease Neuroimaging Initiative Phase 1 (ADNI-1) was to validate and compare biomarkers for potential use as outcome measures in clinical trials; thus three quarters of the ADNI-1 participants were enrolled from narrowly defined amnestic mild cognitive impairment (MCI) and mild-to-moderate AD groups, and the remaining participants were clinically defined normal controls (NCs) [9]. All participants had repeated clinical evaluation, including cognitive and functional assessments, neurological examination, and MRI, approximately every 6 months for 2 years. In addition, about half of the participants had CSF samples at baseline and 12 months, and, independently selected, about half had PET imaging for glucose metabolism. Supplemental funding later supported PET imaging for amyloid burden in a subset of the cohort. Six MRI laboratories and three PET laboratories then developed summary measures on the sequential images. This process yielded a rich, multidimensional dataset with longitudinal data on many candidate biomarker summaries and on multiple aspects of clinical outcome, finally allowing the testing of many existing hypotheses about markers for AD [10,11]. This article summarizes work of the ADNI Biostatistics Core in preparing a global summary of the overall results and patterns of change observed when ADNI-1 participants had all completed at least 12 months of follow-up.

2. Methods

2.1. Study design and participants

ADNI study design and participants are described in greater detail in other articles in this special issue. Briefly, the study recruited 192 participants with mild-to-moderate AD, 398 with amnestic MCI, and 229 NCs, aged 55 to 90 inclusive. The MRI and PET laboratories prepared summary measures of imaging characteristics, based either on prespecified regions of interest (ROI) or on data-driven regions. For the data-driven regions, a standard, pre-planned, randomly chosen training set of 40% of participants, blocked by study arm and age, was used to train the method and develop the region. A separate evaluation sample of the remaining 60% of participants was used to assess the performance of the metric and for comparison with other measures. A single laboratory carried out CSF measurement, with all samples batched for analysis and quality control at each batch. All imaging summary data for statistical analysis were submitted to the Clinical Core and transmitted, along with clinical and biomarker data, to the Laboratory of Neuroimaging Web site as de-identified files.

2.2. Measures

Biomarkers from three domains were considered in the global analysis: CSF, PET, and MRI. Baseline CSF samples were batch-processed using a standardized protocol, under the direction of the ADNI Biomarker Core [12]. For analyses of change in CSF biomarkers, samples from baseline and 12-month follow-up were batch-processed together. CSF measures of $A\beta_{42}$ and tau were considered. Amyloid deposition was measured using ^{11}C Pittsburgh compound B (PIB) PET imaging (available at: *http://www.loni.ucla.edu/twiki/bin/view/ADNI/ADNIPostProc*). The average standard uptake value ratio across the anterior cingulate, parietal, precuneus, and frontal regions was used as a measure of cortical amyloid burden. Each regional standard uptake value was normalized to the cerebellum standard uptake value to get the standard uptake value ratio. Metabolism was assessed using ^{18}F fluorodeoxyglucose (FDG-PET) uptake, and structural changes were measured by MRI. Additional details of the ADNI protocols for PET and MRI acquisition and standardization are publicly available on the UCLA Laboratory of Neuroimaging Web site (*http://www.loni.ucla.edu/ADNI/Data/index.shtml*). Standardized images were subsequently analyzed by ADNI laboratories to produce summary measures. A subset of measures from the three FDG-PET processing laboratories and from three of the six MRI processing laboratories was considered as potential imaging markers. The FDG-PET measures include a measure of average glucose metabolism across the left and right angular, left and right temporal and posterior cingulate regions (ROI-avg) [13], a measure of spatial extent of hypometabolism defined by the sum of *Z*-scores more than 2 standard deviations below the normal mean using stereotactic surface projection analysis normalized by pons (SumZ2PNS and SumZ2PR), and a data-driven functional ROI (DD-fROI) [14]. The MRI measures include hippocampal and ventricular volumes measured using FreeSurfer [15], boundary shift integral, and ventricular boundary shift integral [16], and a data-driven measure of temporal lobe atrophy (DD-ROI) [17]. Apolipoprotein E genotype was determined by the ADNI Biomarker Core. Four cognitive performance tests were considered for measurement of longitudinal change: the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating Sum of Boxes (CDR-SB), the Rey Auditory-Verbal Learning Test (RAVLT) total of five trials, and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). The Functional Activities Questionnaire (FAQ) was used as

a measure of daily function. For participants classified as MCI at baseline, time from baseline to first diagnosis of AD was considered as time to conversion or if conversion did not occur by the last clinical examination the time to conversion was defined to be censored (i.e., to occur at an unknown point beyond the end of the study).

2.3. Statistical analysis

The primary analytic goals were to characterize longitudinal trajectories of change and their variation in each of the measures of interest, to test systematically an a priori set of hypotheses about the predictors of change in the NC, MCI, and AD groups, and to assess the potential for improving the efficiency of clinical trials. There were three main categories of imaging summary measures: single number summaries that captured change between two scans, summary measures calculated separately for each scan, and summaries from data-driven voxel-based techniques. The data-driven methods used a training-set, test-set approach to develop optimal ROI. These optimal ROIs were generated from the training dataset for a particular imaging technique/processing method by comparing baseline to follow-up scans and thresholding at a particular P value. The supra-threshold regions were then used as data-generated ROIs that were applied to an independent test dataset. Although there are issues in using P value thresholds to generate optimal ROIs in this manner, the optimal pattern was found to be robust to the choice of threshold value [17]. For summaries calculated separately for each scan, annualized change was estimated through the two-point differences divided by the time (in years) between the scans. These annualized change measures were used to compare across markers and across diagnostic groups.

To test hypotheses about predictors of change in either an imaging or cognitive outcome, the baseline and all follow-up assessments for a given subject were used to give added information about between and within subject variation. Random effects repeated-measures models were fitted [18] separately for each diagnostic group. We began with univariate models in which each predictor's effects on baseline level and rate of change per year were assessed. Next, we examined the joint effects of selected CSF, PET, and MRI measures (for ADAS-cog), on baseline level and rate of change in models also including years of formal education (centered at 12) and an indicator for presence of one or more *APOE* $\varepsilon 4$ alleles. In these joint models, all biomarkers were transformed to Z-scores centered at the mean in the NC and scaled to the SD for the NC. Thus, a one-unit change in the biomarker corresponds to an increase or decrease of 1 SD among the NC. Assumptions of the models were assessed and were met by the data.

Predictors of time to conversion to AD from MCI were assessed using an interval-censored accelerated failure time model [19]. Initial models considered only one biomarker at a time to assess its association with time to conversion. Multivariate models were then built using variables that were associated with conversion in the univariate models at $P < .15$. Ridge regression [20] was used to shrink coefficients for weaker effects. Model fit was assessed by comparing estimates of the accelerated failure time estimated survival curves with nonparametric maximum likelihood estimates of survival [21], analogous to Kaplan–Meier estimates appropriate for interval censored data.

Potential for improving clinical trials was assessed by comparison of precision of the measurement for capturing change in a clinical trial. Precision is closely associated with sample size calculations. Therefore, sample sizes required to detect a 25% reduction in annual rate of decline were calculated for a two-arm, 1-year clinical trial with 80% power. To compare across markers, we computed subject-specific measures of precision, by calculating the squared deviation from the mean change and dividing it by the square of the mean change. The square root of this value was used in our analyses, which were restricted to individuals for whom complete data (across all imaging biomarkers) were available and who were assigned to the independent test set for the data-driven measures. Friedman's rank test was used to test the hypothesis that the precision was the same across all measures. If this global test was found to be significant, post hoc pairwise tests adjusted for multiple comparisons were performed. Clinical trial designs with entry restricted to people with biomarker levels worse than a cut-off value predictive of more rapid decline were also considered.

All significance tests were at level .05 and all analyses carried out in SAS [22] and *R* [23].

3. Results

The study sample included 210 NCs, 357 MCI, and 162 AD subjects with baseline and at least one cognitive follow-up assessment. Of these, 83 NCs, 175 MCI, and 76 AD had serial PET images including baseline and month 12 (47 NCs, 89 MCI, and 38 AD in the independent test set), and 96 NCs, 155 MCI, and 74 AD subjects had baseline and month 12 CSF measures. Sample sizes for the measures from the serial MRI depended on the different laboratories generating data, so measures were available for 178–200 NCs, 297–334 MCI, 132–147 AD (123 NCs, 196 MCI, 86 AD in the independent test set). A total of 14 NCs, 40 MCI, and 11 AD subjects had two PIB scans approximately 12 months apart as part of the PIB add-on study.

3.1. Annualized change in CSF, imaging, and cognitive tests

Table 1 shows the mean and SD of annualized change for key summary measures. The rate of change for measures hypothesized to show early change (CSF, PIB) is greater in NC than in AD, with MCI intermediate. For the measures hypothesized to change later in the course of AD development, however, the rate of change is greatest in AD and less in NC than

in MCI (FDG-PET, MRI, cognitive measures). These estimates are helpful to us in study design and power calculations for future studies.

3.2. Longitudinal models predicting trajectories for change in hippocampal volume

In univariate analyses, lower baseline values of CSF $A\beta_{42}$ and higher values of CSF tau were associated with more rapid hippocampal atrophy in all three participant groups (Table 2). In addition, in the MCI group, presence of an E4 allele, less years of education, and lower metabolism as measured by the ROI-avg region were also associated with more rapid atrophy. Multivariate analyses, however, suggested that some variables might not predict independently, although it should also be noted that the sample size was reduced considerably, typically by three quarters, when individuals were required to have data on all predictors. For NC, no single variable was a significant predictor of hippocampal decline when all variables were included in the same model, although the coefficients were generally in the expected direction. The typical E4− MCI participant experienced hippocampal atrophy at a rate of 33 mm^3 per year, on average. MCI who were E4+ had estimated hippocampal atrophy approximately twice as fast as those who were E4−, other variables being equal. An MCI participant with baseline PET ROI-average score one NC-SD better than the average MCI had atrophy about 30% less rapid than an average MCI participant. Among the AD group, the typical E4− participant lost 68 mm^3 per year in hippocampal volume. Every one NC-SD higher baseline CSF tau level was associated with nearly a 30% faster hippocampal atrophy rate. Taken together, these findings suggest that abnormal values of the CSF biomarkers are indeed associated with more rapid atrophy, in all diagnostic groups. Our findings are limited, however, by the fact that only half of the participants had PET and half had CSF biomarkers, and thus only 25% had both. Further analysis with the larger samples and longer follow-up of ADNI-2 is needed to determine whether the lack of significance in multivariate analyses reflects mediation or partial mediation through other processes, or is due to the small sample sizes available in ADNI-1 to study all markers simultaneously.

Table 1
Mean (standard deviation) of annualized change for selected ADNI variables

Variable name	Annualized mean change by diagnosis		
	NC	MCI	AD
CSF $A\beta_{42}$	−0.94 (18)	−1.4 (17)	−0.1 (14)
CSF Tau	3.45 (13)	2.34 (21)	1.24 (24)
PIB	0.098 (0.18)	−0.008 (0.18)	−0.004 (0.25)
FDG-PET: SumZ2PNS	−177 (1532)	752 (2950)	2993 (4040)
FDG-PET: ROI-avg	−0.006 (0.06)	−0.015 (0.064)	−0.055 (0.067)
FDG-PET: DD-fROI	−0.019 (0.037)	−0.047 (0.030)	−0.081 (0.047)
Hippocampus	−40 (84)	−80 (91)	−116 (93)
Ventricles	848 (973)	1551 (1520)	2540 (1861)
ADAS-cog total	−0.54 (3.05)	1.05 (4.40)	4.37 (6.60)
MMSE	0.0095 (1.14)	−0.64 (2.5)	−2.4 (4.1)
CDR-SB	0.07 (0.33)	0.63 (1.16)	1.62 (2.20)
RAVLT 5-trial total	0.29 (7.8)	−1.37 (6.6)	−3.62 (5.6)

Table 2
Predictors of longitudinal change in hippocampal volume (Freesurfer), based on repeated measures regression models, showing results for coefficient of effect on annual change

Predictor of change/y	Univariate model		Joint model	
	Coefficient	*P* value	Coefficient	*P* value
Normal controls				
APOE ε4+	−12	.095	−27	.082
Yrs of education	1.1	.36	0.85	.68
CSF $A\beta_{42}$	0.25*	.001*	6.1	.38
CSF tau	−0.35*	.031*	−6.6	.40
FDG-PET ROI-avg	13	.72	5.4	.34
Mild cognitive impairment				
APOE ε4+	−32*	<.001*	−36*	.002*
Yrs of education	1.9*	.040*	−2.7	.12
CSF $A\beta_{42}$	0.26*	<.001*	−0.66	.91
CSF tau	−0.31*	<.001*	−4.4	.15
FDG-PET ROI-avg	78*	.005*	9.3*	.026*
Alzheimer's disease				
APOE ε4+	−15	.087	−29	.18
Yrs of education	0.37	.79	−3.4	.18
CSF $A\beta_{42}$	0.45*	.002*	−1.3	.92
CSF tau	−0.22*	.031*	−8.7*	.046*
FDG-PET ROI-avg	18	.73	10.2	.75

NOTE. Univariate models were not adjusted for other predictors; joint models included *APOE* ε4 status (any E4 allele), education, baseline CSF $A\beta_{42}$ and Tau, and FDG PET ROI-avg unless otherwise specified. In the joint models, all markers were transformed to *Z*-scores using the mean and standard deviation in the normal controls.

* Predictors significant at .05.

3.3. Longitudinal models predicting trajectory of change in ADAS-cog scores

In Table 3, we examined prediction of change in the ADAS-cog total score. ADAS-cog increases, representing cognitive impairment, were associated in the NCs with smaller baseline hippocampal volume, in univariate models, and with presence of *APOE* ε4 in the joint model. In the MCI group, lower baseline CSF $A\beta_{42}$, higher tau, lower FDG-PET metabolism, smaller baseline hippocampal volume, and larger ventricles were all associated with more rapid cognitive function worsening, in univariate models. The typical E4− MCI participant with marker levels comparable with an average NC had an estimated increase of half a point per year ADAS-cog score. In joint models, only the FDG-PET measure remained significant, and each one NC-SD worse metabolism was associated with a .40 point faster annualized rate of worsening on the ADAS-cog. Among AD patients, a typical reference person had an average increase of 2 points per year in ADAS-cog; higher CSF tau was associated in univariate models with faster ADAS-cog decline, but not after adjusting for covariates. Lower baseline metabolism, however, remained significantly associated, with each one NC-SD worse metabolism associated with a two-point worse annualized rate of cognitive performance decline. Results for

other cognitive outcomes and FDG-PET and MRI summaries are in general agreement (not shown).

3.4. Predictors of time to conversion from MCI to AD

A third set of univariate and multivariate analyses examined predictors for conversion from MCI to AD. Table 4 shows results from survival models for time to conversion; we examined not only fluid and imaging biomarkers, but also baseline cognitive function as a potential predictor, and adjusted for whether participants were already taking cholinesterase inhibitors. Univariate models (not shown) suggested that many baseline fluid and imaging biomarkers were associated with shorter time to conversion, including hippocampal and ventricular volume and brain size; complex summaries of FDG-PET hypometabolism from the University of Utah; and the P-tau/Aβ_{42} ratio. In addition, baseline cognition and functional measures were predictive. People who were on acetylcholinesterase inhibitors were also more likely to convert. Multivariate analyses showed that only acetylcholinesterase inhibitors (ACHEI), cognition, and function achieved statistical significance when all variables were included, suggesting that most of the effect of the biomarkers on conversion can be explained through the baseline cognitive and functional scores. When cognitive and functional scores and redundant brain volumetrics were removed, hippocampal volume and FDG-PET hypometabolism were significant.

Table 3
Predictors of longitudinal change in ADAS-cog total 11 score, based on repeated measures regression models, showing results for coefficient of effect on annualized change

	Univariate model		Multivariate model	
Predictor of change/yr	Coefficient	*P* value	Coefficient	*P* value
Normal controls				
APOE ε4+	0.22	.22	1.06*	.020*
Yrs of education	−0.04	.19	−0.026	.64
CSF Aβ_{42}	−0.0005	.82	0.10	.63
CSF tau	0.001	.75	0.33	.19
FDG-PET ROI-avg	−1.9	.076	0.05	.77
Hippocampal volume	−0.0004*	.016*	−0.25	.27
Ventricular volume	0.000006	.45	0.18	.31
Mild cognitive impairment				
APOE ε4+	0.83	.005	0.57	.24
Yrs of education	−0.01	.82	−0.004	.96
CSF Aβ_{42}	−0.01*	<.001*	0.058	.83
CSF tau	0.01*	<.001*	0.20	.16
FDG-PET ROI-avg	−4.2*	<.001*	−0.40*	.040*
Hippocampal volume	−0.001*	<.001*	−0.014	.94
Ventricular volume	0.00005*	<.001*	0.38	.070
Alzheimer's disease				
APOE ε4+	0.85	.30	−0.39	.82
Yrs of education	0.17	.15	0.050	.79
CSF Aβ_{42}	−0.01	.26	−1.39	.12
CSF tau	0.02*	.04*	0.43	.17
FDG-PET ROI-avg	−14*	<.001*	−2.12*	.005*
Hippocampal volume	0.0002	.79	−0.08	.90
Ventricular volume	−0.000002	.95	0.43	.47

Univariate models were not adjusted for other predictors; joint models included *APOE* ε4 status (any E4 allele), education, baseline CSF Aβ_{42} and Tau, FDG PET ROI-avg, and hippocampal and ventricular volume (Freesurfer) unless otherwise specified. In the joint models, all markers were transformed to *Z*-scores using the mean and standard deviation in the normal controls.

* Predictors significant at .05.

3.5. Precision of imaging markers and implications for clinical trials

Finally, we examined the potential of the fluid and imaging biomarkers to improve clinical trials in several different ways. We considered the possibility that they might be used as outcome measures, and calculated the sample size that would be required in a two-arm, 1-year clinical trial, with 80% power to detect a 25% improvement in annual rate of decline. Fig.1. shows the results of the comparisons of sample size estimations for a trial in MCI subjects across the most promising MRI and PET biomarkers based on data obtained from 69 MCI subjects. Each different shade in the Figure identifies a group of measures that were not significantly different from one another. In particular, measures of brain change and hippocampal atrophy required the fewest subjects. The data-driven functional ROI required the fewest subjects out of the PET measures and was comparable with many of the top MRI measures.

An alternative strategy for improving clinical trial design is enrichment of the study population. A trial restricting participation to an enriched MCI population with CSF Aβ to less than 192 pg/mL would only require 225 per group to detect a 25% reduction in rate of change in ADAS-cog, whereas an unrestricted study would require 375 people per arm. These sample sizes are based on linear mixed effects models of rate of change over 2 years of visits every 6 months, and simulations that replicate ADNI's missing data.

4. Discussion

The first 12 months of complete data on ADNI participants demonstrated the potential for substantial advances in characterizing trajectories of change in a range of biomarkers and clinical outcomes, examining their relationship and timing, and assessing the potential for improvements in clinical trial design. Entry criteria for the ADNI, NC, MCI, and AD groups were well defined and yielded groups that were distinctly different not only in their initial characteristics, but also in their average trajectories across a range of CSF, PET, MRI, and clinical measures. These findings were consistent with the previous published data reporting that the onset and progression of neurobiological changes precedes (by a considerable time) the actual diagnosis of AD [24,25]. The levels and rates of change of CSF, PET, and MRI summary measures showed considerable variation within diagnostic group, with substantial overlap between the NC and the MCI groups, and between the MCI and AD groups. One possible explanation of the high degree of variation is the presence of different degrees or types of underlying neuropathology

Table 4
Results of survival models for time to conversion from MCI to AD

Predictor variable	Coefficient	*P* value	*P* value*
Entire MCI cohort with MRI			
Baseline ADAS-cog	−0.101†	.002†	
Baseline FAQ	−0.092†	.002†	
Using ACH El	−0.060†	.046†	
Baseline hippocampus	0.058	.078	.003†
Baseline MMSE	0.053	.083	
MCI cohort with MRI, FDG PET			
Baseline FAQ	−0.073†	.043†	
Baseline ADAS-cog	−0.074	.059	
Baseline hippocampus	0.070	.070	.025†
Baseline FDG-PET ROI-avg	0.071	.091	.015†
MCI cohort with MRI, CSF			
Baseline FAQ	−0.118†	.015†	
Using ACH El	−0.090	.055	
Baseline ADAS-cog	−0.091	.065	

Table shows predictors that had *P* values less than .10 in model. Ridge regression used to shrink coefficients for smaller values. The rightmost column (*P* value*) displays *P* values from models excluding all clinical variables.
† Results significant at .05.

among participants with the same clinical classification; consistent with this idea, reduced metabolism and greater brain atrophy in the MCI at baseline are associated with more rapid cognitive decline and a higher chance of conversion to AD. Results from univariate regression models confirmed that cognitive decline in MCI was associated with several biomarkers. Multivariate models suggested that they are likely not operating independently but instead may either represent part of a sequence in which some mediate others at least in part, or may reflect several aspects of a common progression of underlying neurobiological damage. The moderate number of people with data on all markers limited the power of multivariate models. Larger sample sizes, especially of people with all modalities of fluid and imaging biomarkers, and longer follow-up are critical in determining relative contributions at different disease stages. In particular, cognitive decline in the NCs is subtle and requires larger sample sizes and longer follow-up to separate out effects of different risk factors. Results in AD suggest that the hypothesized later changes are likely to play more of a role as predictors than those thought to take place earlier in the disease process. A related possibility is that the longer-term trajectory of biomarker measures may be nonlinear, with some measures showing a steeper rate of change at later stages of disease progression and some at earlier stages. Testing this hypothesis properly will require longer follow-ups than are currently available, to assess within-individual shifts in rates of change. Finally, some measures clearly have more between-person and within-person variation than others. Comparisons of the precision of estimated rates of change identified several promising MRI and FDG-PET measures. These measures have sufficiently stable rates of change that the sample size for a two-arm clinical trial in MCI or AD using the marker as a surrogate endpoint could be reduced considerably, compared with the standard cognitive outcomes. Alternatively, designs using biomarkers to restrict entry to those most likely to decline could improve power of clinical trials even using cognitive scores as the primary outcome measure.

Our findings are broadly consistent with other studies. Analysis of a smaller subset of ADNI participants with data on multiple biomarkers reported that PET and CSF biomarkers of Aβ agreed with each other but were not correlated with cognitive impairment, whereas FDG-PET was more strongly related to cognition and less to other biomarkers [26]. Volumetric changes have been noted to be present even over 6 months to a year in ADNI patients [27]. Numerous studies have noted that baseline levels of biomarkers predict cognitive change and incident AD in people with MCI [8,25,28]. Uniform ascertainment of multiple measures in large samples allowed us to carry out formal comparisons across biomarkers, including those based on ROI that were developed by data-driven methods. The large sample available to ADNI may have permitted detection of more moderate associations than would have been possible with smaller samples in other reports, and also allowed use of more predictors in multiple regression models with either change in cognitive function or time to AD diagnosis as the outcome.

Our analysis of ADNI data has several notable limitations. First, follow-up is limited to 12 months for the CSF and many of the imaging summary measures, and to 2 years on average

Lab	Modality	Variable	Sample Size					
Jagust	PET	ROI-avg	4605					
Foster	PET	logSumZ2PNS[1]	2176					
Foster	PET	logSumZ2PR[1]	1629					
Fox	MRI	VBSI[2]	284					
Schuff (FreeSurfer)	MRI	ventricles	277					
Reiman	PET	DD – fROI[3]	249					
Schuff (FreeSurfer)	MRI	hippocampus	202					
Fox	MRI	BSI[4]	177					
Thompson	MRI	DD - ROI[3]	73					

Fig. 1. 1.5T MRI vs. PET sample size calculations and comparisons: MCI (69 test subjects). Grey-scale bars connect groups of variables for which calculated sample size did not differ significantly under multiple-comparison testing.1 = Measures of glucose hypometabolism, log transformed; 2 = ventricular boundary shift integral as a percentage of baseline brain volume; 3 = data-driven summaries applied to independent test set; 4 = boundary shift integral as a percentage of baseline brain volume.

for clinical outcome data. Many of the questions of greatest interest involve sequences or shifts in the degenerative process, and thus require longer-term follow-up for definitive analysis. Second, although ADNI as a whole includes more than 800 participants, the sample size for CSF, FDG-PET, PIB, and most notably any combination, is substantially smaller. Third, the study is not population-based; ADNI participants are better educated and less ethnically diverse compared with the population as a whole. Fourth, the study recruitment strategy deliberately focused on three well-defined clinical subgroups, but thus omitted people with, for example, early MCI. Finally, the analyses presented include only a very limited, pre-specified subset of the many potential PET and MR imaging summary measures and the detailed cognitive and performance test data collected for ADNI participants.

This broad perspective on ADNI findings thus far, however, has notable strengths. We present an overview of key findings across CSF, PET, and MRI domains, and across multiple cognitive function and clinical progression outcomes. Our analyses have gained strength from having a large sample size of people from more than 50 sites with clear, consistent, clinical entry criteria. All biomarker and clinical data were collected and processed with uniform standard criteria. We used a systematic approach to model building and hypothesis testing, reflecting the careful specification of study goals in the original ADNI proposal, to address the challenges posed by the multiplicity of potential biomarkers of interest.

5. Summary

Analyses and comparisons of ADNI data strongly support the hypothesis that measurable change occurs in CSF, PET, and MR images well in advance of the actual diagnosis of AD. Even in the first 2 years of follow-up, distinct patterns of glucose hypometabolism and hippocampal atrophy, in particular, are associated with increased rates of cognitive decline and with greater risk of conversion from MCI to AD. These changes can be measured with sufficient precision to suggest potential as surrogate markers in clinical trials, provided they are able to capture the effects of treatment on clinical outcomes. More detailed analysis of the rich ADNI database is clearly warranted as well as extension with longer follow-up, more complete CSF and PET participation, and examining the critical transition between NC and MCI.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., and Wyeth, as well as nonprofit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation.

References

[1] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204.

[2] Schneider LS. Assessing outcomes in Alzheimer Disease. Alzheimer Dis Assoc Disord 2001;15(Suppl 1):S8–18.

[3] Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–95.

[4] Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403–13.

[5] Okello A, Koivunen J, Edison P, Archer HA, Turkheimer FE, Nagren K, et al. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. Neurology 2009;73:754–60.

[6] Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 2003;60:1374–7.

[7] Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, et al. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur J Nucl Med Mol Imaging 2003;30:1104–13.

[8] Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000;47:430–9.

[9] Mueller SG, Weiner MW, Thai LJ, Petersen RC, Jack C, Jagust W, Tro janowski JQ, Toga AW, Beckett L. The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin N Am 2005;15:869–77.

[10] Hampel H, Burger K, Teipel SJ, Bokde ALW, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. Alzheimers Dement 2008;4:38–48.

[11] Mueller SG, Weiner MW, Thai LJ, Petersen, Jack CR, Jagust W, et al. Ways toward an early diagnosis in Alzheimers disease: the Alzheimers Disease Neuroimaging Initiative (ADNI). Alzheimer's Dement 2005;1:55–66.

[12] Shaw LM. PENN Biomarker Core of the Alzheimer's Disease Neuroimaging Initiative. Neurosignals 2008;16:19–23.

[13] Landau SM, Harvey DH, Madison CM, Koeppe RA, Reiman ER, Foster NL, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol Aging (in press). doi:10.1016/j.neuorbiolaging. 2009.07.002.

[14] Chen K, Langbaum JBS, Fleisher AS, Reschke C, Lee W, Liu X, et al. Twelve-month metabolic declines in probable Alzheimer's disease and

amnestic mild cognitive impairment assessed using an empirically predefined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. Neuroimage (in press).
[15] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–55.
[16] Evans MC, Barnes J, Nielsen C, Kim LG, Clegg SL, Blair M, et al. Volume changes in Alzheimer's disease and mild cognitive impairment: cognitive associations. Eur Radiol 2010;20:674–82.
[17] Hua X, Lee S, Yanovsky I, Leow AD, Chou Y-Y, Ho AJ, et al. Optimizing power to track brain degeneration in Alzheimer's disease and mild cognitive impairment with tensor-based morphometry: an ADNI study of 515 subjects. Neuroimage 2009;48:668–81.
[18] Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963–74.
[19] Cox DR, Oakes D. Analysis of Survival Data. London; New York: Chapman and Hall; 1984.
[20] Gray RJ. Flexible methods of analysing survival data using splines, with applications to breast cancer prognosis. J Am Stat Assoc 1992;87:942–51.
[21] Wellner JA, Zhan Y. A hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. J Am Stat Assoc 1997;92:945–59.
[22] SAS Institute, Inc. SAS/STAT(R) Version 9.0. Cary, NC: SAS Institute, Inc; 2004.
[23] R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2009. ISBN 3-900051-07-0.
[24] Jack CR, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain 2009;132:1355–65.
[25] Petersen RC, Jack CR. Imaging and biomarkers in early Alzheimer's disease and mild cognitive impairment. Clin Pharmacol Ther 2009;86:438–41.
[26] Jagust WJ, Landau SM, Shaw LM, Trojanowski JQ, Koeppe RA, Reiman EM, et al. Relationships between biomarkers in aging and dementia. Neurology 2009;73:1193–9.
[27] Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, et al. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain 2009;132(Pt. 4):1066–77.
[28] Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006;5:228–34.