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The Alzheimer's Disease Neuroimaging Initiative phase 2: Increasing the length, breadth, and depth of our understanding

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Abstract

Introduction: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a multisite study designed to characterize the trajectories of biomarkers across the aging process. We present ADNI Biostatistics Core analyses that integrate data over the length, breadth, and depth of ADNI.
Methods: Relative progression of key imaging, fluid, and clinical measures was assessed. Individuals with subjective memory complaints (SMC) and early mild cognitive impairment (eMCI) were compared with normal controls (NC), MCI, and individuals with Alzheimer's disease. Amyloid imaging and magnetic resonance imaging (MRI) summaries were assessed as predictors of disease progression.
Results: Relative progression of markers supports parts of the amyloid cascade hypothesis, although evidence of earlier occurrence of cognitive change exists. SMC are similar to NC, whereas eMCI fall between the cognitively normal and MCI groups. Amyloid leads to faster conversion and increased cognitive impairment.
Discussion: Analyses support features of the amyloid hypothesis, but also illustrate the considerable heterogeneity in the aging process.

Keywords: Alzheimer's disease; Subjective memory complaints; Amyloid cascade hypothesis

1. Background

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting an estimated 5.2 million people in the United States and costing the nation more than $200 billion per year [1]. Even the few approved treatments have limited efficacy, and many clinical trials have failed to demonstrate any clinical impact [2,3]. One strategy to address the lack of effective treatments is to begin treatment earlier, even before the clinical diagnosis of dementia, into the stage of mild cognitive impairment (MCI) (that precedes AD [4,5]) or even in people with normal cognitive function but prodromal indications [6]. A related strategy is to find and characterize biomarkers that could either identify people at risk during or even before the onset of MCI, or could serve as surrogate markers to detect treatment impact more efficiently [7].

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing multisite cohort study designed to characterize the trajectories of clinical, imaging, and fluid biomarkers across the entire spectrum of aging from clinically normal individuals through MCI to AD, with data

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how to apply/ADNI Acknowledgement List.pdf.

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made available publicly for widespread use [8]. The goal is to identify biomarkers and genetic characteristics that would support the early detection and tracking of AD, and improved clinical trial design. ADNI was initially funded in 2004 and recruited 819 people in this phase (ADNI-1). Additional funding and recruitment were made possible through a Grand Opportunities supplement (ADNI-GO) in 2009 and a competitive renewal (ADNI-2) in 2010.

The ADNI Biostatistics Core was established with the initial funding and has been an integral part of ADNI through all its phases [9]. The Core provides leadership and support for study design, data analysis, and presentation of findings, and guidance for the many outside researchers who want to access and analyze ADNI data. The volume of data made available by ADNI is unprecedented in aging research. ADNI-2 has substantially increased not only the numbers of subjects but also the duration of follow-up of the initial participants, the breadth of our coverage of the spectrum of aging with new cohorts added, and the depth of our understanding with new biomarkers studied. The Biostatistics Core is unique in the ADNI organization in having responsibility for analyses that integrate across the entire length, breadth, and depth of the study. This article will highlight some research accomplishments of the Core that have taken advantage of ADNI-2 data.

2. Methods

2.1. Study design and participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, and lessen the time and cost of clinical trials.

ADNI-1, ADNI-GO, and ADNI-2 study design and participants have been described in detail previously [8,10]. Briefly, ADNI-GO and ADNI-2 added 129 and 782 participants, respectively, to the 819 recruited by ADNI-1, with ADNI-1 normal controls (NC) and MCI participants continuing to be followed. ADNI-GO also added a new cohort of people with early MCI (eMCI), and ADNI-2 added a cohort who were clinically evaluated as cognitively normal, but had subjective memory complaints (SMC) (Fig. 1). All phases of the study collected clinical data (neuropsychological testing, neurologic examination, and diagnosis) and structural MRI on all patients. [18F]fluorodeoxyglucose uptake, measured by positron emission spectrography (FDG-PET) and cerebrospinal fluid (CSF) were each obtained on only about 50% of the participants in ADNI-1, but were collected on everyone participating in ADNI-GO and ADNI-2, and amyloid imaging was added for participants during ADNI-GO and ADNI-2 (Fig. 1).

Thus ADNI-2 expanded the length of potential follow-up for NC and MCI from ADNI-1 and for NC, eMCI, and MCI from ADNI-GO, with data currently available from up to 9 years of follow-up for ADNI-1, and up to 4 years of follow-up for ADNI-GO. The breadth of the MCI span was increased by adding eMCI in ADNI-GO and ADNI-2, and the breadth of the normal span was increased by adding SMC in ADNI-2. The depth of biomarker reach was greatly enhanced by the addition of amyloid imaging, and will be further enriched by a recently funded tau imaging supplement.

2.2. Measures

We considered Mini-Mental State Examination (MMSE) [11]; Clinical Dementia Rating (CDR) Sum of Boxes [12]; 13 item Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) [13]; Rey Auditory Verbal Learning Test [14], Preclinical Alzheimer's Cognitive Composite (PACC) [15], Functional Activities Questionnaire (FAQ) [16], MRI summaries of hippocampal volume and entorhinal cortex [17], ventricular and total brain volume [18] (see [19] and adni.loni.usc.edu for MRI protocol information), CSF assays of Aβ, tau, and pTau [20], and PET summaries of glucose metabolism and amyloid burden [21].

2.3. Statistical analysis

Length: The goal of this analysis was to predict typical long-term disease marker trajectories spanning the range of disease severity, from cognitively normal to dementia. To accomplish this goal, we used a three-step procedure. Step 1 was to transform each outcome measure to a common 100-point scale using a quantile transformation, with 0 representing complete absence of disease symptoms or pathology and 100 representing the maximum observed level, weighted to account for disproportionate sampling of diagnostic categories. Step 2 was to apply a general semiparametric and iterative estimation procedure to derive subject-specific estimates of latent disease-time [22]. This procedure uses information from all outcome measures to place each subject on a long-term continuum of disease, quantified as years into the disease process. For example, if subject A has a latent disease-time estimate that is 5 years greater than subject B, this implies subject A is estimated to be 5 years more advanced toward dementia than subject B. Step 3 was to fit a model estimating the predicted level (on the 0–100 scale) for each outcome measure for a person at a specific latent disease-time, adjusted for

		Base diagnosis at first sample was drawn (or scan was taken)																							
		1:Normal					2:SMC				3:EMCI				4:LMCI					5:AD				
		1.5T MRI	3T MRI	FDG	AV45	CSF	3T MRI	FDG	AV45	CSF	3T MRI	FDG	AV45	CSF	1.5T MRI	3T MRI	FDG	AV45	CSF	1.5T MRI	3T MRI	FDG	AV45	CSF
ADNI1	bl/sc	230	.	105	.	116	.	.	.	.	.	.	.	.	392	.	210	.	196	187	.	100	.	99
	m06	218	52	96	.	.	.	.	.	.	.	.	.	.	361	73	188	.	.	172	41	89	.	.
	m12	274	71	86	.	94	.	.	.	.	.	.	.	.	393	85	180	.	150	153	32	76	.	72
	m18	.	.	.	.	.	.	.	.	.	.	.	.	.	300	66	154	.	.	4	2	1	.	.
	m24	240	67	85	.	27	.	.	.	.	.	.	.	.	308	69	142	.	54	119	27	63	.	17
	m36	179	48	75	.	32	.	.	.	.	.	.	.	.	225	40	118	4	41	2	.	3	3	6
	m48	101	8	64	36	33	.	.	.	.	.	.	.	.	127	4	52	35	35	1	.	16	26	2
	m60	79	10	39	39	20	.	.	.	.	.	.	.	.	83	6	33	21	19	.	.	9	20	.
	m72	36	3	37	30	13	.	.	.	.	.	.	.	.	35	1	32	20	12	.	.	4	17	.
	m84	2	.	29	32	13	.	.	.	.	.	.	.	.	1	.	19	19	7	.	.	4	8	.
	m96	.	.	5	18	6	.	.	.	.	.	.	.	.	.	.	5	7	3	.	.	.	4	.
	m108	.	.	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
ADNIGO2	bl/sc	.	189	187	185	178	106	104	102	90	306	305	303	285	.	163	161	158	158	.	147	145	145	137
	m03	.	173	.	.	.	53	.	.	.	286	.	.	.	.	152	.	.	.	.	118	.	.	.
	m06	.	175	.	.	.	10	.	.	.	262	.	.	.	.	154	.	.	.	.	104	.	.	.
	m12	.	170	.	.	.	22	.	.	.	361	2	2	.	.	142	.	.	.	.	95	.	.	.
	m24	.	140	124	142	81	.	.	.	.	177	159	196	106	.	106	66	110	62	.	24	26	25	14
	m36	.	3	.	.	.	.	.	.	.	21	4	4	.	.	2	.	1	.	.	.	.	.	.
	m48	.	.	.	.	.	.	.	.	.	.	.	20	4	.	.	.	.	.	.	.	.	.	.

Fig. 1. Number of individuals with 1.5T magnetic resonance imaging (MRI), 3T MRI, [18F]fluorodeoxyglucose uptake, measured by positron emission tomography (FDG-PET), AV45, or cerebrospinal fluid (CSF) by diagnosis at the baseline visit (or at the visit when the first sample or scan was taken). Counts are presented by visit within a phase of Alzheimer's Disease Neuroimaging Initiative (ADNI).

age, apolipoprotein E (*APOE*) ε4 allele carriage, sex, and education. We included amyloid and tau as fixed-effects predictors for other measures. We assumed a logistic curve shape. We used the resulting estimates to derive predicted long-term (age 50–90 years) progression curves (on a scale of 0 to 100) for each outcome measure, both for a typical *APOE* ε4 carrier and for normal aging (i.e. latent disease-time = 0 years). The progressive *APOE* ε4 carrier curves were calibrated so that the MMSE curve attains the mean of the ADNI sample at the mean age of the *APOE* ε4 carriers. Additional curves were projected for *APOE* ε4 carriers with elevated amyloid (standardized uptake value ratio [SUVR] of 1.15) at age 50 years. All available panel data were used for these analyses, giving up to 9 years of follow-up for the longest observations. Breadth: We summarized the distribution of key biomarkers by box plots separately for each diagnostic group (NC, SMC, eMCI, MCI, AD) at baseline, with comparison of means by analysis of variance (ANOVA) and Tukey honest significant difference test for multiple comparisons. We present findings for representative imaging and cognitive summary measures (AV45 SUVR, FDG PET mean across all regions of interest, hippocampal volume, ADAS-Cog). We further examined the SMC and NC groups for differences from each other at baseline, using two-sample t-tests and chi-square tests. We quantified biological heterogeneity within the NC and SMC groups, using unsupervised clustering, as in previous work with ADNI-1 NC and MCI data [23,24]. Briefly, each individual began as a cluster of one person. Then individuals were aggregated iteratively to maintain the greatest similarity within clusters (total distance between individuals in the cluster and the cluster center, based on MRI measures and CSF measures without regard to cognitive or functional differences). The choice of number of clusters was based on observed visual separation of the clusters, and on computed within-cluster dissimilarity as the number of clusters decreased, with a goal of obtaining the smallest number of clusters that could capture some separation between clusters and limit spread or dissimilarity within cluster. Depth: We assessed the performance of amyloid imaging as a predictor of disease progression, using both first observed conversion (SMC/NC to MCI) and MMSE trajectory (number of errors) as the outcomes. For conversion, we compared amyloid-positive at baseline (AV45 SUVR >1.1 or CSF Aβ <192 pg/ml) to amyloid negative by log-rank test, illustrated by Kaplan-Meier plots. For this analysis, missing baseline amyloid SUVR was imputed using linear mixed-effects models of all observed SUVRs. This model of SUVR included fixed effects for time from baseline, age, *APOE* ε4 carriage, and baseline PACC; and subject-specific random intercepts and slopes. We imputed missing baseline values with the subject-level predicted baseline SUVR values from this model. We also fitted a Cox model [25] controlling for age and other covariates selected by Akaike Information Criteria from among *APOE* ε4 carriage, education, PACC, and hippocampal volume. For change in MMSE, we used number of errors (30 scores) as the outcome and fitted separate models for comparison in eMCI and MCI. We considered the AV45 and FDG PET composites and hippocampal volume, entorhinal cortex thickness (ERC), total brain volume, and ventricular volume as possible predictors. Each marker was standardized by subtracting the group mean and dividing by the group standard deviation,

so that a one unit increase corresponded to a one standard deviation increase for each marker. Predicted trajectories were estimated by generalized mixed models with log-link, Poisson error, and random intercept, adjusted for age, education, and gender.

3. Results

3.1. Long-term follow-up

General semiparametric estimation based on a composite of all available years of ADNI-1, ADNI-GO, and ADNI-2 data gave estimates of the typical trajectories of two fluid biomarkers (CSF Aβ, Tau), three imaging measures (AV45, FDG, hippocampal volume), and four clinical measures (PACC, MMSE, FAQ, and CDR SB) controlling for *APOE* ε4 carriage, sex, education, amyloid, and tau (Fig. 2). The curves project progression for typical progressive *APOE* ε4 carriers (solid lines, left panel), progressive *APOE* ε4 carriers with elevated amyloid at age 50 years (solid lines right panel), and nonprogressive *APOE*ε4 noncarriers (dashed lines). Nonprogressive estimates showed very stable trajectories over the period from 50 to 90 years of age, remaining close to the lowest percentile, that is, best or healthiest levels. Only hippocampal volume showed a trend toward abnormality with age. High-risk participants, however, were estimated to follow trajectories that became steadily worse in all levels with increasing age. The estimated paths support features of the model hypothesized by Refs. [26,27]. Both CSF Aβ levels and amyloid deposition in the brain precede other abnormalities for the typical progressive individual, followed by CSF tau. FDG PET and MRI volumetric measures were estimated to be near normal at age 50 years for ε4 carriers but already above the normal baseline at age 50 years for people with elevated amyloid at baseline, and increasing rapidly thereafter for both high-risk groups. Functional measures were found to become abnormal after the imaging measures, with FAQ the last of these measures to display problems. In contrast to the Jack model, and of particular importance to the design of therapeutic trials in the earliest stages of AD, cognitive change is evident as early as FDG-PET change, and precedes that of MRI volumetric measures.

3.2. Added subgroups: eMCI, SMC

Box plots of brain imaging and cognitive performance (Fig. 3) show that the eMCI group, as expected, falls in between the late MCI (LMCI) group and the two groups clinically rated as cognitively normal, with fewer individuals overlapping with the AD group. The SMC group, on the other hand, appears very similar to the original NC in amyloid and FDG uptake, baseline hippocampal volume, and cognitive performance. These impressions are confirmed by ANOVA followed by Tukey's Honest

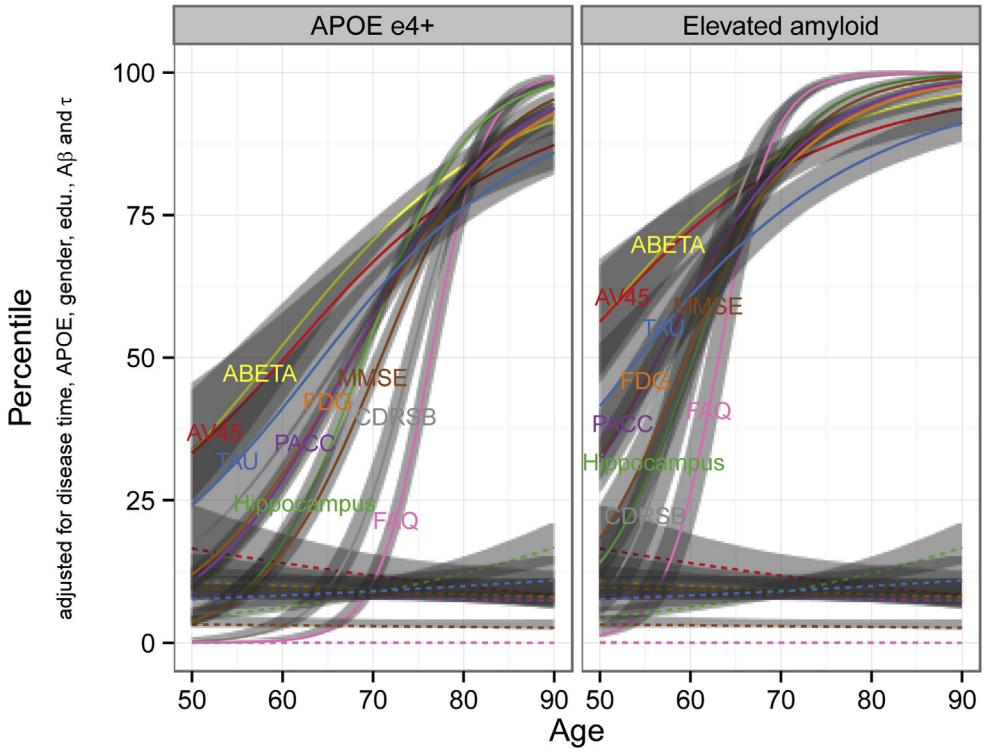

Fig. 2. Long-term trajectories from least affected (0th percentile) to most affected (100th percentile), estimated for high-risk and low-risk patients, from age 50 to 90 years.

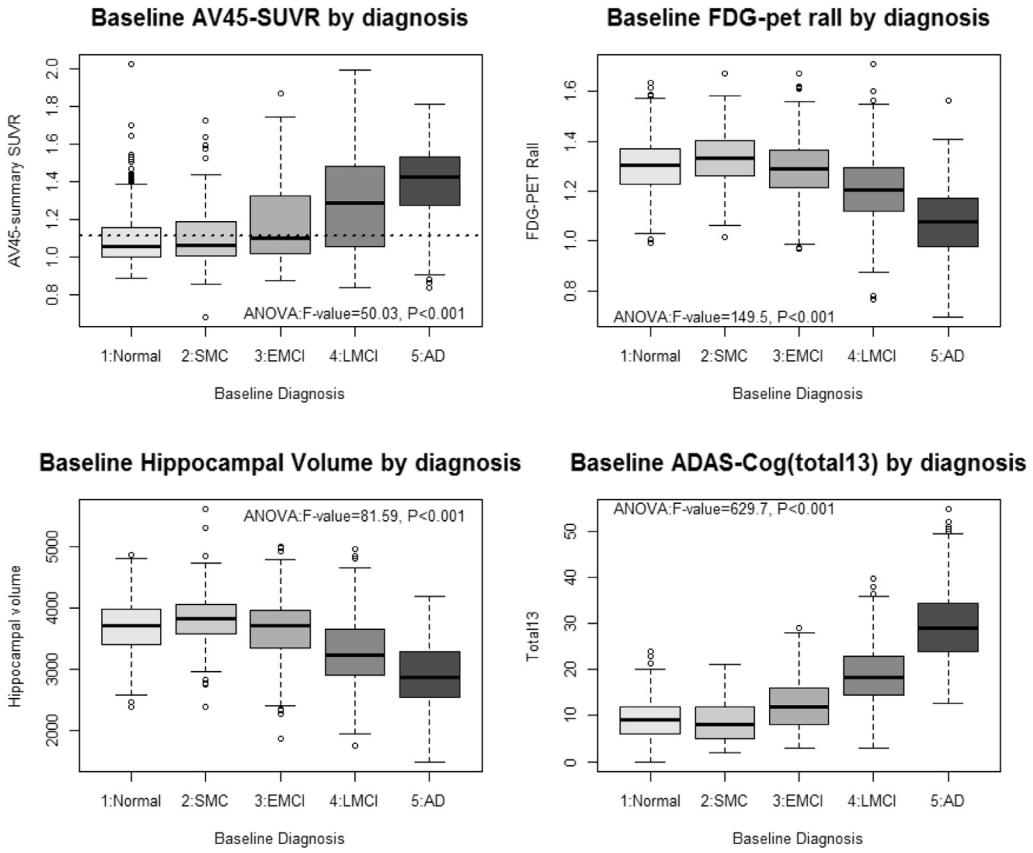

Fig. 3. Box plot of representative imaging and cognitive summary measures. Multiple comparison results from analysis of variance (ANOVA): normal control (NC) do not differ from subjective memory complaint (SMC) in any measure, and both are worse than late mild cognitive impairment (LMCI), which is worse than Alzheimer's disease (AD), in all measures. Early mild cognitive impairment (EMCI) is between and different from SMC and LMCI for [18F] fluorodeoxyglucose uptake, measured by positron emission tomography (FDG-PET) and Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), but does not differ from SMC for AV45 or from NC for hippocampal volume.

Significant Difference (HSD) multiple comparison test. In particular, NC do not differ from SMC in these four measures. NC and eMCI also do not differ in hippocampal volume or FDG PET and SMC and eMCI are similar in AV45. All other group comparisons are significantly different in these four measures.

We examined the ADNI-2 SMC and NC groups in more detail, to see whether neuroimaging and fluid biomarkers could distinguish more homogeneous subgroups, as previously found in ADNI-1 for NC [23] and MCI [24]. Unsupervised cluster analysis identified three distinct subgroups in both the NC and the SMC groups, very similar to those in the ADNI-1 NC (Fig. 4). One subgroup in both NC and SMC (groups labeled 2 in the figure) displayed normal levels of all measurements, comparable to the best levels observed across the ADNI cohorts. A second subgroup in each diagnostic group (groups labeled 3 in the figure) corresponded well to the Jack sequence for early signs of AD, with elevated brain amyloid, decreased CSF Aβ, and somewhat decreased hippocampal volume compared with the healthy subgroup 2 participants. The third subgroup (labeled groups 1 in the figure) was similar to the subgroup 2 participants in brain amyloid and CSF Aβ, but had substantially reduced hippocampal volume. Interestingly, *APOE* genotype, which was not used in determining clusters, was markedly different across the three subgroups, with group 3 showing much higher frequency of 4 alleles.

3.3. Added measures, as predictors of progression

We found a highly significant difference in progression from SMC/NC to LMCI between those with versus without elevated amyloid at baseline ($P < .001$; Fig. 5). The amyloid effect was confirmed (hazard ratio 3.43, 95% CI 1.34 to 8.81, $P = .010$) with a multivariate Cox model controlling for age ($P = .826$), PACC ($P = .004$), and hippocampal volume ($P < .001$) at baseline.

In the EMCI group (n = 292), entorhinal cortical thickness ($\beta = -0.05$, SE = 0.02, $P = .01$), FDG-PET composite ($\beta = -0.07$, SE = 0.02, $P = .001$), and the AV45 composite ($\beta = 0.09$, SE = 0.02, $P < .001$) were significantly associated with change in the number of errors on the MMSE (Fig. 6). Hippocampal volume ($\beta = -0.01$, SE = 0.02, $P = .53$), total brain ($\beta = 0.02$, SE = 0.02, $P = .42$), and ventricular volume ($\beta = 0.01$, SE = 0.02, $P = .45$) were not significantly associated with change. When restricted to

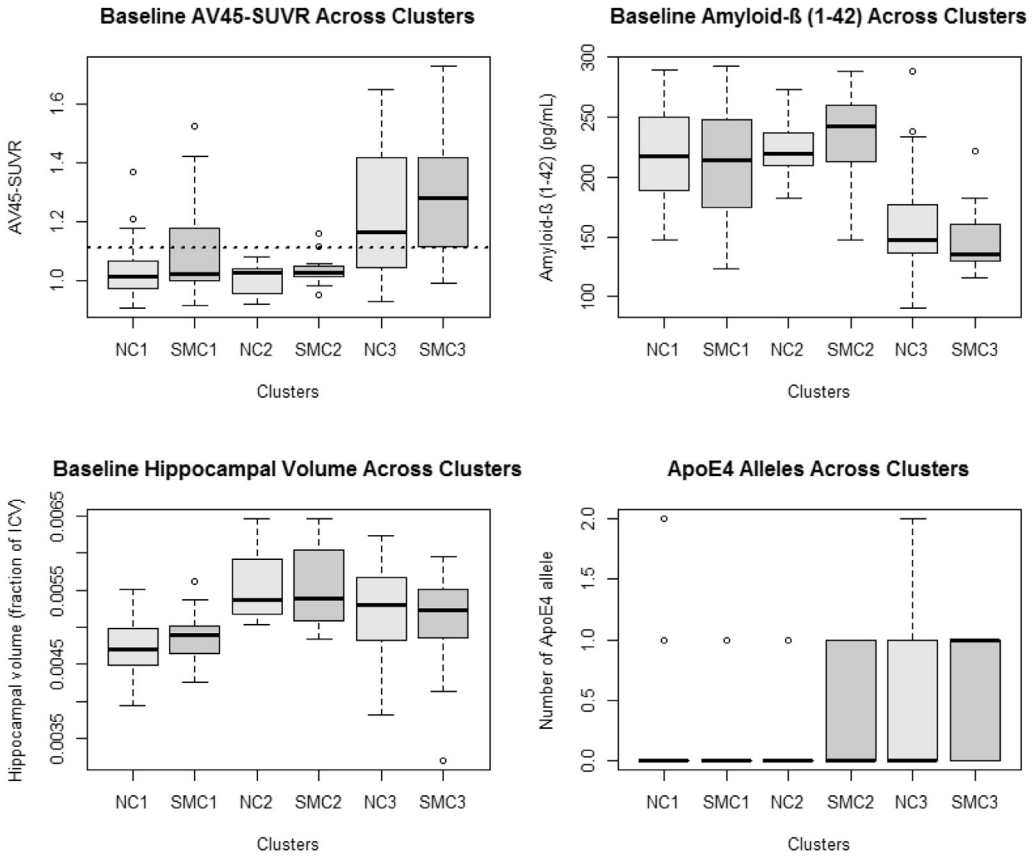

Fig. 4. Subjective memory complaint (SMC) is heterogeneous, in a very similar way to normal control (NC), and similar to previous work in NC and mild cognitive impairment (MCI).

amyloid-positive individuals (n = 138), the FDG-PET composite (β = −0.07, SE = 0.03, P = .01) and the AV45 composite (β = 0.09, SE = 0.03, P = .002) remained significantly associated with change in the number of errors. Thickness of the entorhinal cortex was not quite significant (β = −0.06, SE = 0.03, P = .06). A similar pattern was observed in the LMCI group, except that the FDG-PET composite was not quite significant (results not shown).

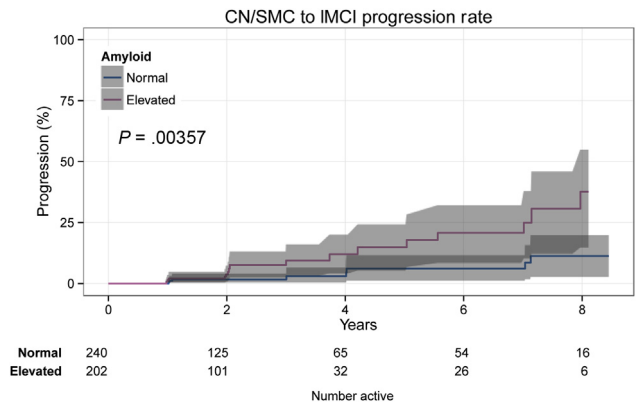

Fig. 5. Amyloid positivity predicts conversion from subjective memory complaint/normal control (SMC/NC) to late mild cognitive impairment (LMCI). The Kaplan-Meier plot depicts the proportion diagnosed as LMCI at least once over time by baseline amyloid status (log-rank P = .00357). The amyloid effect was confirmed (hazard ratio 3.43, 95% confidence interval [CI] 1.34 to 8.81, P = .010) in multivariate Cox model controlling for age, Preclinical Alzheimer's Cognitive Composite (PACC), and hippocampal volume at baseline.

4. Discussion

ADNI-2 has made possible new insights into the longer-term trajectory of the earliest signs and gradual progression of AD and its biological correlates. The Biostatistics Core has developed and applied new methods to characterize the entire spectrum from age 50 to age 90 years, and our results support both the Jack model for the progression of classic AD, and the likelihood of considerable heterogeneity in the aging process.

This heterogeneity is further illustrated by differences within the NC and SMC groups. Both groups appear to be comprised of at least three somewhat dissimilar subgroups, with one group looking more like the earliest stages of classic AD, one group looking normal in all regards, and one having signs of brain atrophy without amyloid pathology. These results are consistent with our earlier work with ADNI-1 NC, where we found three subgroups [23],

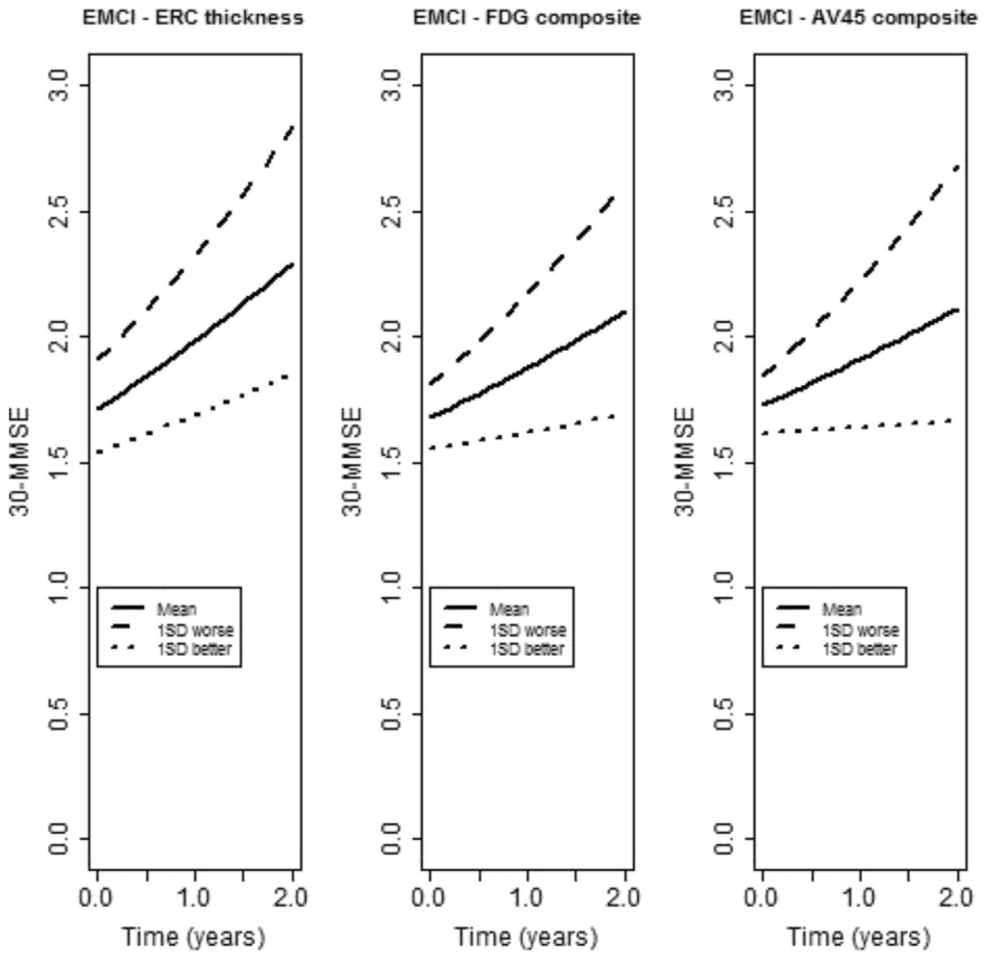

Fig. 6. Predicted trajectories of number of errors on Mini-Mental State Examination (MMSE) for early mild cognitive impairment (eMCI) patients with baseline levels average, 1 standard deviation (SD) worse, or 1 SD better than average for cortical atrophy (entorhinal cortex [ERC] thickness), [18F]fluorodeoxyglucose uptake (FDG, composite across regions of interest), or amyloid uptake (AV45 composite across regions of interest).

one of which later was determined to have many characteristics consistent with vascular pathology rather than amyloid-based abnormalities [28]. Further follow-up will help to establish whether the distinct subgroups identified in both SMC and NC as possible early AD do indeed convert to MCI, and whether the SMC group converts more rapidly than the NC group. In addition, further data collection for the two groups which show signs of cortical atrophy without amyloid pathology should help to assess whether they have vascular damage, as found in our ADNI-1 NC [28], or other pathology.

The early MCI group fits nicely between the NC and the later MCI group initially defined by ADNI-1. Thus a relatively straightforward expansion of the MCI inclusion standards can yield a group that covers much of the range between cognitive normality and dementia diagnosis. Long-term follow-up will help to establish whether indeed most of this early group will progress to increased cognitive impairment comparable with the late MCI group, and later to dementia, or whether the group is even more heterogeneous than we found with the late MCI group [24].

New imaging measures clearly show, even with the limited follow-up available so far in ADNI-2, that amyloid pathology in the brain is an ominous prodromal sign for progression, whether defined as conversion to MCI, or deteriorating cognitive and functional measurements. This holds true even after taking into account other correlates and predictors.

A major accomplishment of ADNI has been data sharing [8]. The richness and complexity of the database, although, poses challenges for researchers getting started using data. The Biostatistics Core has played a substantial role in making the database more widely accessible, via our support: teleconference workshops, online slide decks from workshops, R and SAS code for accessing and merging and setting up data; online help resources (http://adni.loni.usc.edu/support/, and https://groups.google.com/forum/#!forum/adni-data).

In summary, ADNI provides a rich data set of imaging and fluid markers and clinical information for individuals across the full spectrum of cognitive abilities. The Biostatistics Core aims to analyze data generated by the other ADNI Cores to provide a comprehensive picture of what can

be learned by ADNI. Indirectly, the Biostatistics Core further supports the study of AD progression by assisting non-ADNI investigators in understanding the complexities of the ADNI data.

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RESEARCH IN CONTEXT

1. Systematic review: A review of the relevant literature using PubMed was conducted.
2. Interpretation: Our findings illustrate the heterogeneity in aging and Alzheimer's disease pathology. Components of the amyloid cascade hypothesis are supported, but there is evidence of earlier occurrence of cognitive impairment. Subgroups of cognitively normal individuals with and without subjective memory complaints exhibit biomarker patterns similar to Alzheimer's disease patients, normal aging, and other pathologies. Amyloid leads to clinical progression and cognitive decline.
3. Future directions: Additional follow-up of Alzheimer's Disease Neuroimaging Initiative subjects will help to further evaluate the amyloid cascade hypothesis and whether different patterns of pathology correspond to the observed heterogeneity in the aging process. The addition of newer measures, including tau-imaging, may provide insight into some of this heterogeneity.

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