Analysis of ADNI data: statistical considerations

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Outline

ADNI-1 data
- Description
- Challenges

Analysis examples
- Cross-sectional
- Longitudinal change
- Conversion
- Correlating changes

ADNI-1 plan: 800 participants, seen every 6-12 m

- 229 normal control (NC)
- 398 mild cognitive impairment (MCI)
- 192 mild to moderate AD

- Clinical diagnosis, cognitive tests, function
- Structural MRI (1.5T, and 3T on subset)
- PET scan on subset (FDG-PET, PiB)
- CSF on subset
- Serum biomarkers, genetics

Baseline means: some key variables

Variable	NC	MCI	AD
% ApoE4+	27	53	66
ADAS-cog total	6.2	11.5	18.6
CSF Abeta	206	163	143
Avg HippoVol	2133	1848	1612
Avg FDG PET (ROI)	1.28	1.20	1.08

Mean annual change: some key variables

Variable	NC	MCI	AD
ADAS-cog total	-0.5	1.1	4.4
CSF Abeta	-0.9	-1.4	-0.1
Avg HippoVol	-40	-80	-116
Avg FDG PET (ROI)	-0.006	-0.015	-0.055

First impressions of ADNI findings

At baseline, compared to NC:

- AD have higher prevalence of E4 carriers.
- AD have worse ADAS-COG total scores.
- AD have more atrophy, less metabolic activity, and less CSF Abeta.
- MCI are intermediate.

Over 2 years of follow-up:

- NC improve a bit in ADAS-COG; MCI, AD get worse.
- CSF Abeta decreases more in MCI than NC, both more than AD.
- Hippocampal atrophy in all 3 groups, AD > MCI > NC.
- FDG PET similar to hippocampal volume.

Next steps: Analysis of this very rich database

General kinds of analyses that we can do:

- Baseline descriptions, comparisons, and correlations (key first steps).
- Characterizing change in key measures and progression.
- Predictors and correlates of change and progression.
- Relationships between changes: sequence, correlations.
- Assessing, decomposing and summarizing high-dimensional measures.

Challenges for statistical analysis of ADNI data: The design

- Not a community or population study!
- Three very sharply defined groups
- Selected to have limited overlap, minimal comorbidity
- Thus we cannot infer diagnostic accuracy in community setting.
- Designed to help move clinical research forward in 3 groups.

More challenges of ADNI data: sheer magnitude!

- Data were initially very slow to come in.
- .

More challenges of ADNI data: sheer magnitude!

- Data were initially very slow to come in.
- This is no longer a problem.

ADNI data: measured in terabytes

A high-dimensional database:

- Each person has MRI (200K voxels).
- Each person has a lot of cognitive and clinical measures.
- Cognitive measures have many sub-items.
- Half the people have CSF measures.
- Different half have FDG-PET.
- Some have amyloid imaging.
- Genetics data now available (next talk).
- Other high-throughput assays (proteomics, etc.)
- Many of these are measured every 6-12 months.

More challenges: missing data

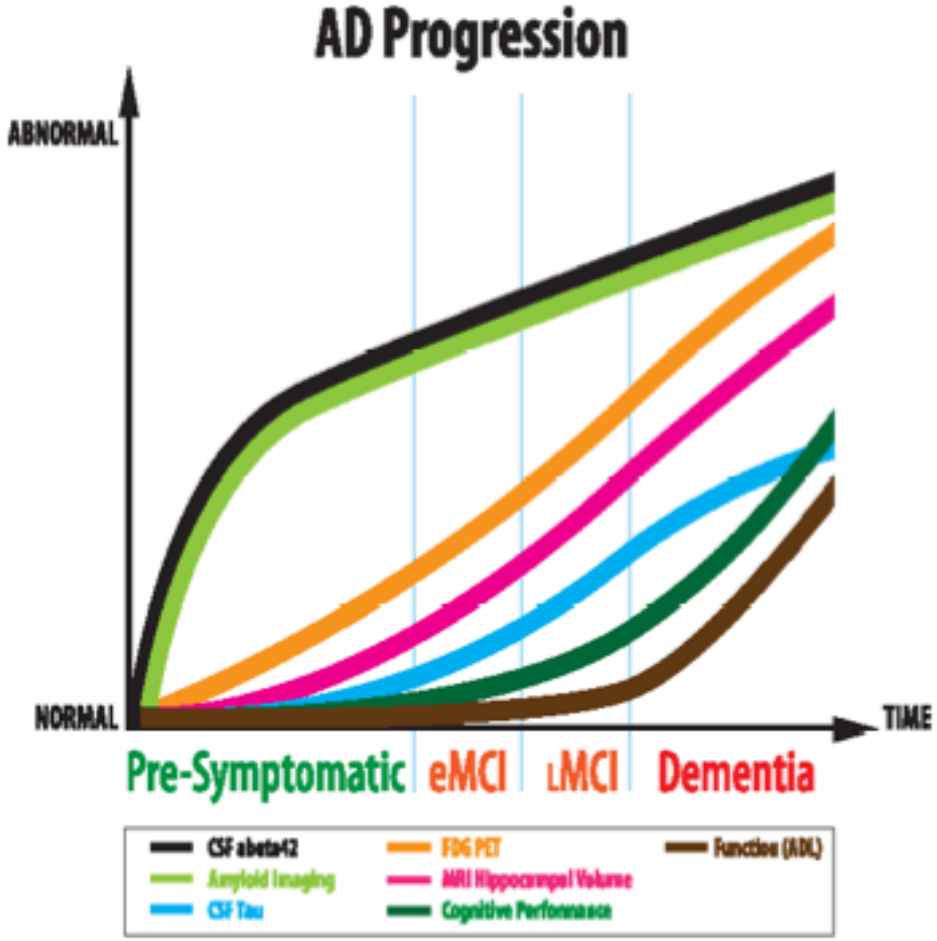
- Loss to follow-up, death.
- Structural missingness: only half have FDG-PET (balanced design).
- Only half have CSF (those who consented). Not the same half.
- Some measures missing because of poor image quality.
- **Check the image quality variables!**

More challenges: specific to different analyses

In the rest of the talk, I'll go over some kinds of analyses we have done and show how we have addressed some challenges. A few examples:

- Cross-sectional description and association
- Describing longitudinal change
- Conversion from MCI to AD
- Relationships between change

Hypothesized model for development and progression of AD (Jack)

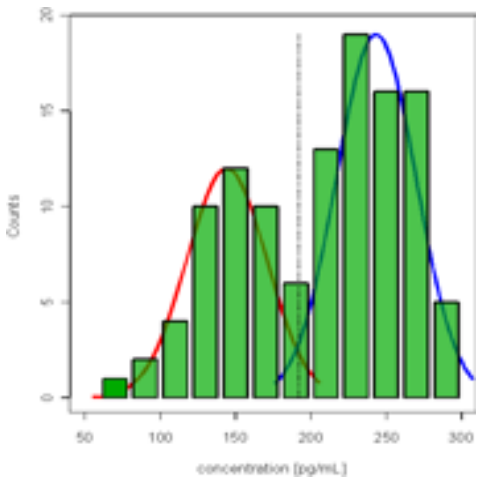


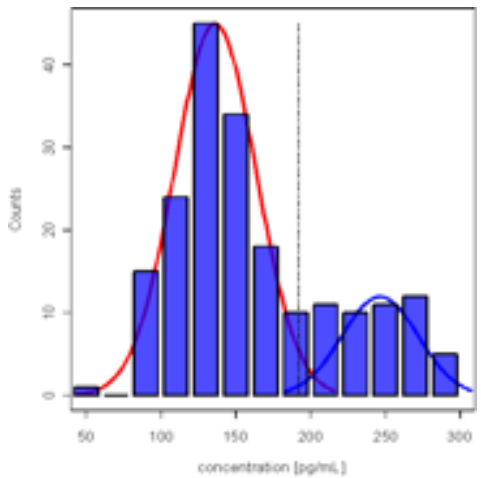
Sequence

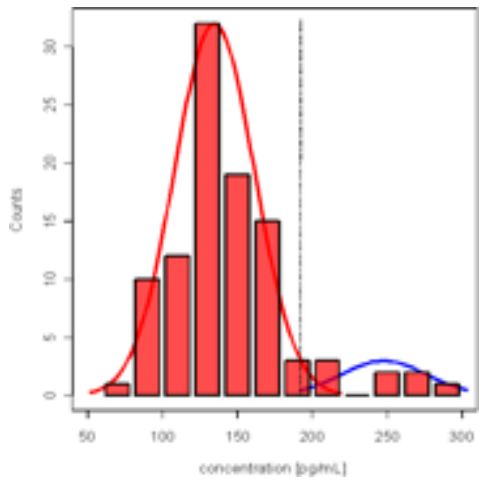
- CSF Aβ $\Downarrow$
- Amyloid image $\Uparrow$
- CSF tau $\Uparrow$
- FDG activity $\Downarrow$
- Cortical volume $\Downarrow$
- Cognitive tests $\Downarrow$
- ADL's $\Downarrow$

Cross-sectional analyses: Looking at early biomarkers

Changes in cerebrospinal fluid amyloid β appear to show up very early. Green=normal, blue =MCI, red=AD. Simple descriptive summaries.







Cautions on cross-sectional comparison of groups

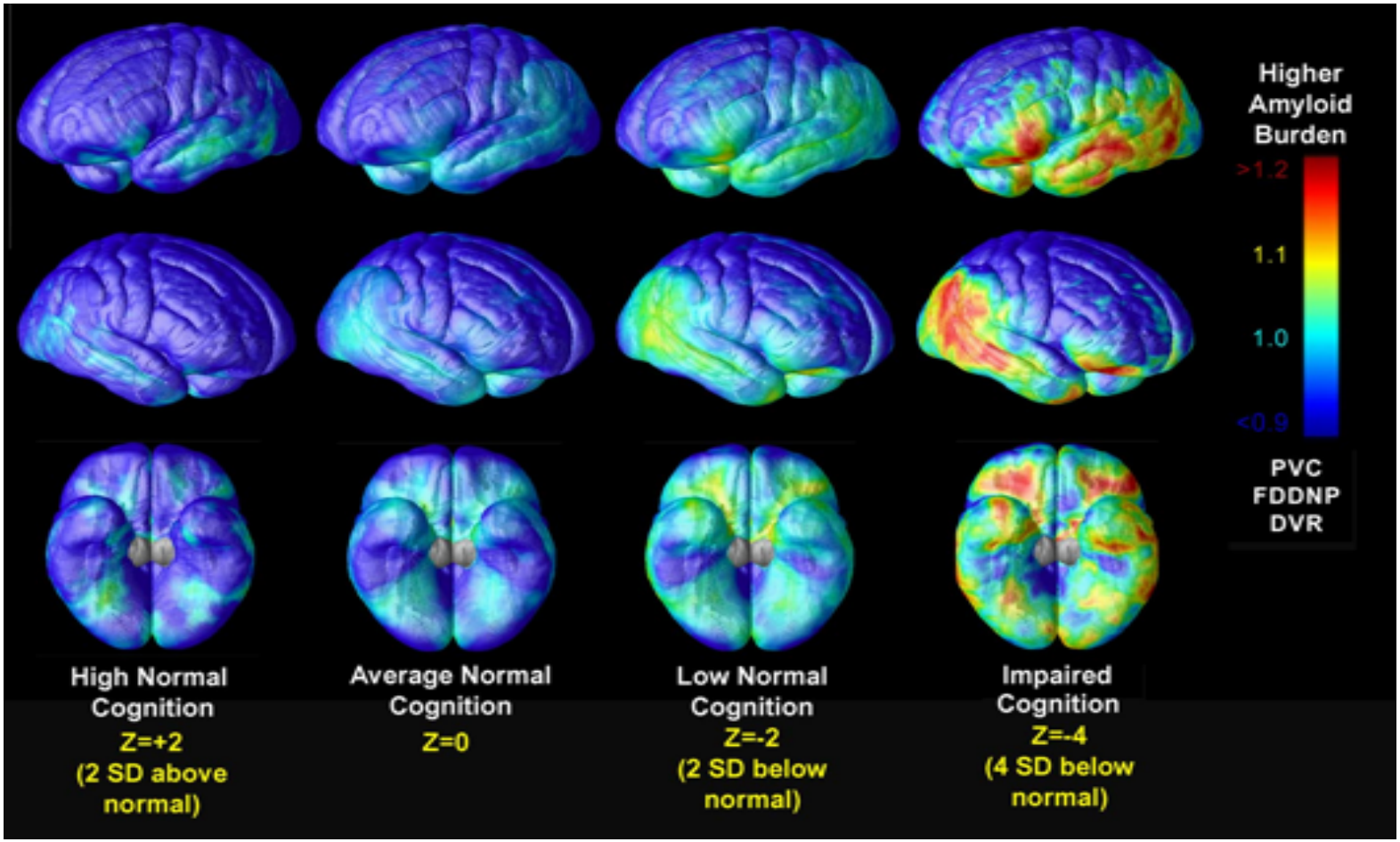
- Not a community study: limits the generalizability of discrimination studies.
- Cross-validation design: at time of enrollment, people split
  - 40% training sample
  - 60% validation sample
  - Also 10% groups for 10-fold cross-validation
- Note: cut-point shown for CSf Aβ was from prior studies.

Results: loss of CSF Aβ consistent with theory

The CSF Aβ is much lower in AD patients, and in most MCI patients. And some NC also have decreased CSF Aβ.

Another way to look at Aβ: amyloid imaging (only available in a few subjects so far). The next pictures will show a voxel-based approach to analysis.

PET summaries showing amyloid in brain (Thompson)

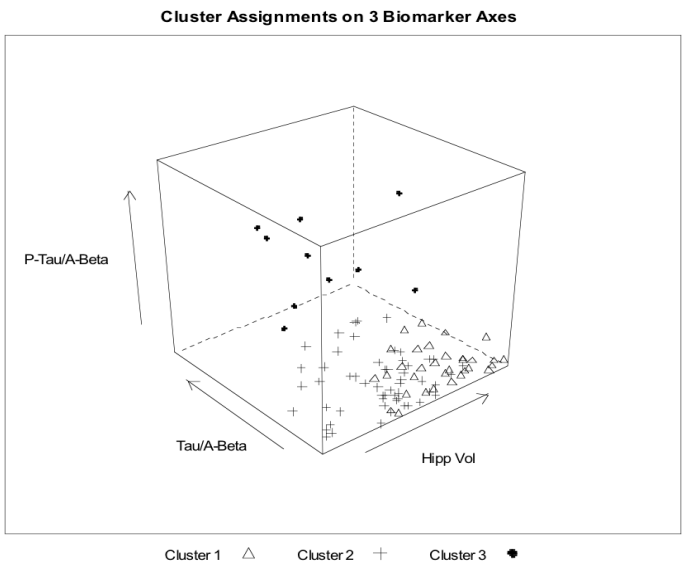


Another cross-sectional look: Normal Controls

- NC have very good cognitive function and very few conversions to MCI or AD.
- But there is considerable heterogeneity in MRI and CSF markers.
- We wanted to explore for patterns in this group.
- We used “unsupervised cluster analysis" of CSF and imaging measures.
- That is, we did not look at possible outcomes (longitudinal change, conversion) to form clusters.
- Analysis note: we tried a number of clustering algorithms in R.

Cluster analysis results in the Normal Controls

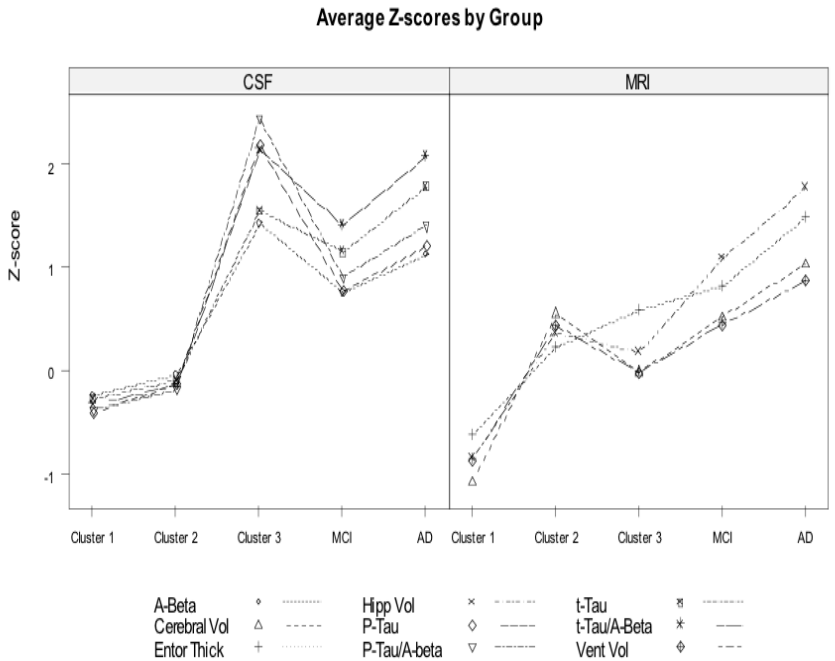
We found three clusters. One looked quite odd.



Small group 3: bad CSF levels.
Turned out to be declining in ADAS-COG.
Nettiksimmons Neurobiol Aging 2010.

Comparing the 3 NC groups, MCI, and AD

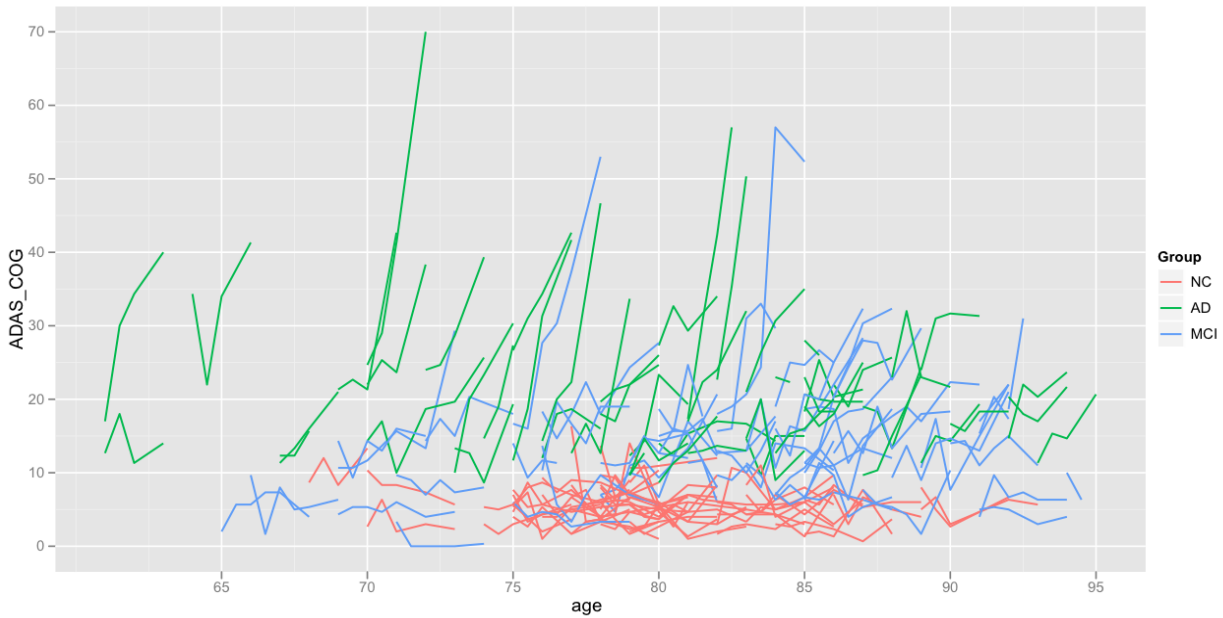
The picture shows average levels of CSF (left panel) and brain size (right panel) measures. Note that the shapes of curves parallel our hypotheses about what happens first!



Damage may be present already in some NC.

Analyzing change: trajectories, and how they differ

Spaghetti plot of ADAS-COG trajectories for random samples of NC (red), MCI (blue) and AD (green). Note the variation in starting level, slope, and within-person value (noise!).



Hippocampal volume plots: somewhat less noisy

Spaghetti plot of hippocampal volumes over time for random samples of NC (red), MCI (blue) and AD (green). Note there is no natural ceiling here.

Longitudinal models for trajectories of AD measures

Often we use repeated measures models with mixed effects (Laird and Ware, 1984).

$$Y_i = X_i\beta + Z_iA_i + e_i$$

- Y is the vector representing person i's trajectory
- X and Z are covariates for that person
- β are the coefficients for predictors (fixed effects)
- A represent person-specific random features of trajectory
- e represents within-person noise.

Cautions for longitudinal modeling

We need to be quite careful in fitting these models for ADNI data. Challenges:

- Floor effects, for example in ADAS-COG.
- “Practice effects" for cognitive tests in NC, maybe MCI.
- Helpful to standardize measures for comparison.
- If within-person noise big, hard to detect between-person slopes (models won’t converge).
- Careful hypothesis specification of predictors is important.
- For some measures, we use generalized linear models, GEE approach.

One example of results of longitudinal model (Beckett *et al* 2010)

Predictors of ADAS-COG trajectories in MCI (coefficients for change, standardized measures, multivariate model)

Predictor	Coefficient	P-value
Apo4+	0.57	0.24
Yrs of educ	-0.004	0.96
CSF Aβ	0.06	0.83
CSF tau	0.20	0.16
FDG-PET avg ROI	-0.40	0.040
Hippocampal Vol	-0.014	0.94
Ventricular Vol	0.38	0.070

Conversion from MCI to AD

Analysis of time to conversion has challenges, also.

- About 40% have converted from MCI to AD.
- Very few NC have converted to MCI, and only one to AD.
- Some people revert: what to do with those?
- Data are interval censored.

Accelerated failure time models for conversion

We usually handle the interval censoring by using accelerated failure time (AFT) models rather than the more widely known proportional hazards models.
The model assumes that the time to conversion is described by:

$$P[T > t] = S_0(t \exp[-\beta X])$$

- T is event time,
- X is vector of predictors,
- β is coefficient vector for effects; big ones “stretch" time to event.
- S_0 is a baseline survival function (we have used Weibull).

Results of a survival model (Beckett 2010)

Here are results of a survival model using AFT, with ridge regression to handle correlation among the predictors (standardized), using people who had MRI and FDG PET.

Predictor	Coefficient	P-value
Baseline FAQ	-0.073	0.043
Baseline ADAS-COG	-0.074	0.059
Baseline hippocampus	0.070	0.070
Baseline FDG-PET ROI	0.071	0.091

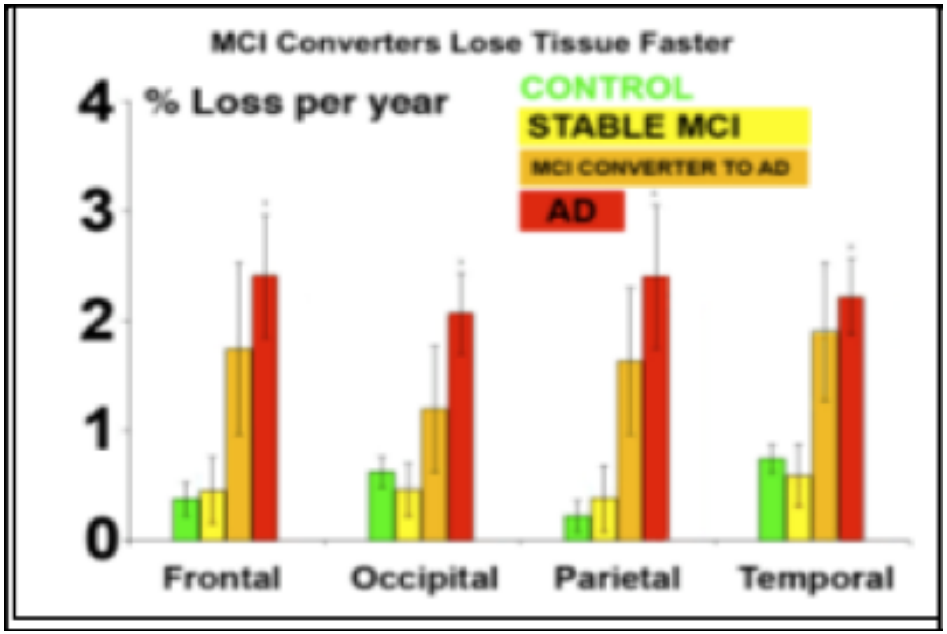
Correlating change in two or more outcomes

Typical questions we might want to answer:

- Are those who showed greatest brain atrophy during the follow-up the most likely to convert from NC to MCI, or from MCI to AD?
- Is greater decrease in FEG PET metabolism linked to faster decline in cognitive testing?
- Is more rapid decrease in CSF Aβ associated with faster accumulation of amyloid as shown by imaging?

Simple analysis linking conversion to atrophy

People with AD when ADNI started had brains that shrank faster. So did people with MCI who converted to AD.



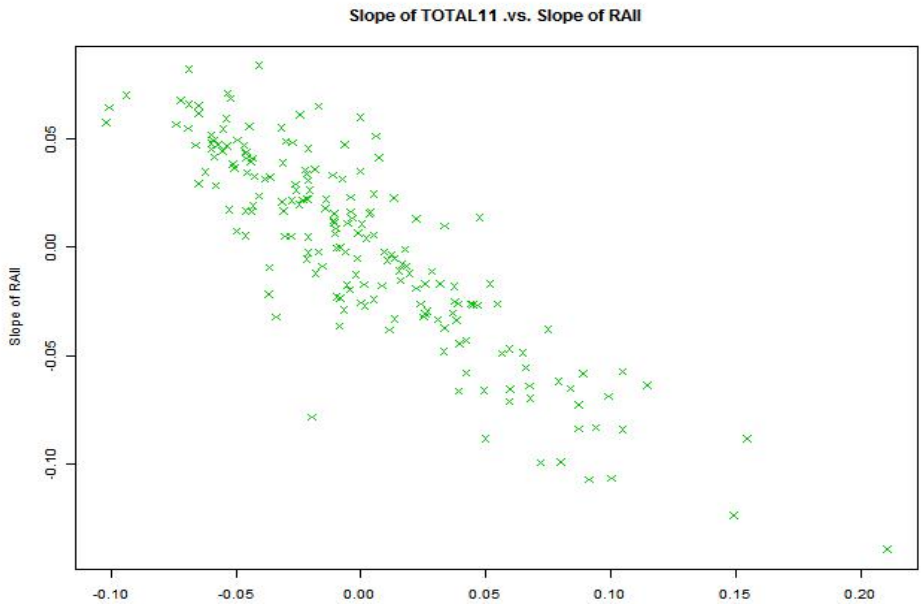
Red (AD) shrank fastest (tallest bar).
Gold (MCI who converted to AD) almost as fast.

Linking trajectories is trickier!

- Simple idea: calculate slopes for each person, correlate using linear regression.
- Our work (Beckett, Tancredi, WIlson 2004) has shown this greatly underestimates association because of noise.
- A better approach uses latent variables (see paper for details).
- Note: some ADNI measures are still too noisy in short term for this approach.

Results: Brain metabolism and errors on cognitive tests

Decline in brain metabolism (PET image) is linked to increasing number of errors on cognitive test (ADAS-COG).



Farther left: fast declines in brain metabolism. Farther up: faster increases in errors on test.

Tomorrow: Workshops will begin to look at ADNI data

Some cautions!

- Complicated data: read the documentation carefully!
- Many choices: outcomes, predictors, models.
- Remember the limitations of the ADNI design.
- Strengths: very thorough characterization of change.
- Also: inter-related measures give insight into process.

Open for questions now!

Thank You!

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