IL CERVELLO CHE CAMBIA 7
Sabato 11 novembre 2017
Genova, Aula Magna Clinica Neurologica

Quest'anno ho letto un articolo che mi ha aperto gli occhi su…

La Risonanza magnetica: tecniche avanzate

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INFN

◆ Human Brain Mapping 00:00–00 (2017)

Your Algorithm Might Think the Hippocampus Grows in Alzheimer's Disease: Caveats of Longitudinal Automated Hippocampal Volumetry

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Integrating longitudinal information in hippocampal volume measurements for the early detection of Alzheimer's disease

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Longitudinal analysis

Your Algorithm Might Think the Hippocampus Grows in Alzheimer's Disease: Caveats of Longitudinal Automated Hippocampal Volumetry

Abstract: Hippocampal atrophy rate—measured using automated techniques applied to structural MRI scans—is considered a sensitive marker of disease progression in Alzheimer's disease, frequently used as an outcome measure in clinical trials. Using publicly accessible data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we examined 1-year hippocampal atrophy rates generated by each of five automated or semiautomated hippocampal segmentation algorithms in patients with Alzheimer's disease, subjects with mild cognitive impairment, or elderly controls. We analyzed MRI data from 398 and 62 subjects available at baseline and at 1 year at MRI field strengths of 1.5 T and 3 T, respectively. We observed a high rate of hippocampal segmentation failures across all algorithms and diagnostic categories, with only 50.8% of subjects at 1.5 T and 58.1% of subjects at 3 T passing stringent segmentation quality control. We also found that all algorithms identified several subjects (between 2.94% and 48.68%) across all diagnostic categories showing increase in hippocampal volume over 1 year. For any given algorithm, hippocampal "growth" could not entirely be explained by excluding patients with flawed hippocampal segmentations, scan–rescan variability, or MRI field strength. Furthermore, different algorithms did not uniformly identify the same subjects as hippocampal "growers," and showed very poor concordance in estimates of magnitude of hippocampal volume change over time (intraclass correlation coefficient 0.319 at 1.5 T and 0.149 at 3 T). This precluded a meaningful analysis of whether hippocampal "growth" represents a true biological phenomenon. Taken together, our findings suggest that longitudinal hippocampal volume change should be interpreted with considerable caution as a biomarker. *Hum Brain Mapp 00:000–000, 2017.*

5 independent segmentation algorithms

poor concordance among methods?

scattered and inconsistent hippocampal "growth"?

how is it possible? there is a large body of literature on hippocampal segmentation and its impact on clinics & research…

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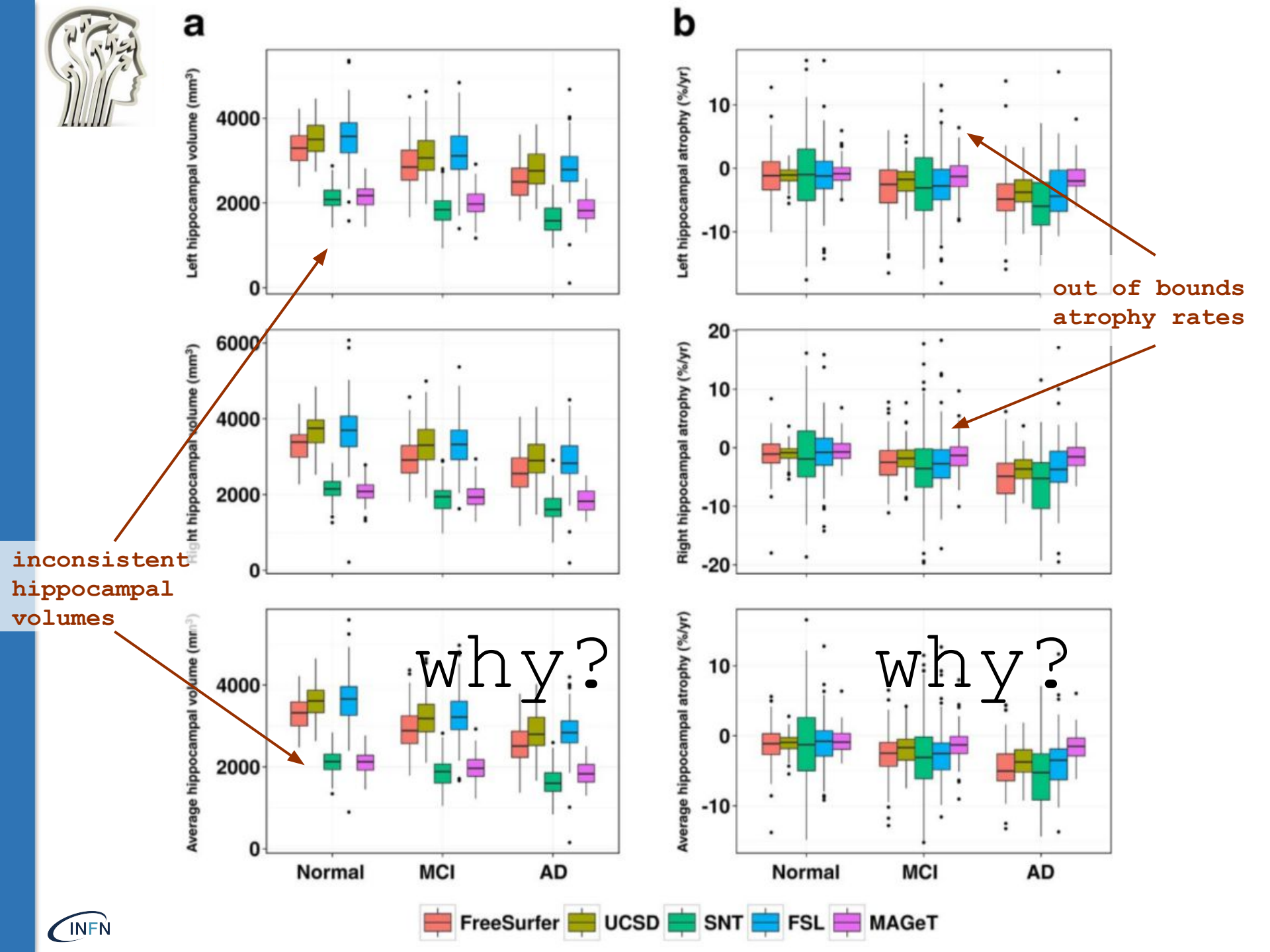
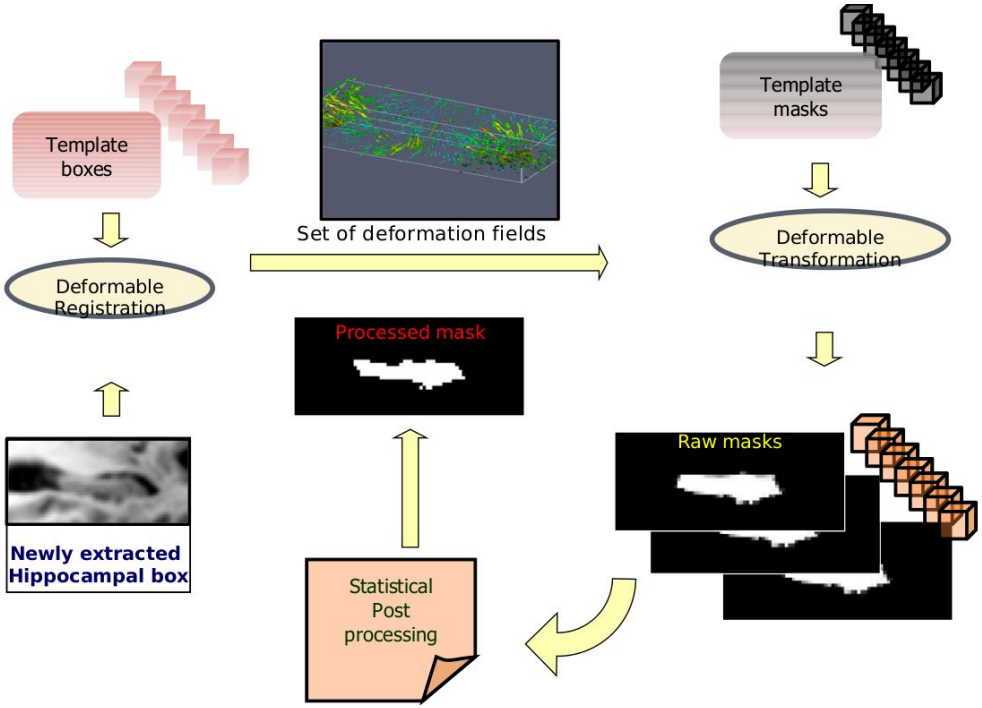
~400 subj (ADNI), 1y follow-up, 1.5T & 3.0T

TABLE I. Selected demographic and clinical features of subjects by diagnostic category and field strength

	AD	MCI	Normal	*P* value
1.5 T				
N	90	179	129	-
Mean age (range)	74.7 (56–89)	74.9 (55–89)	76.2 (62–90)	0.16
#Females	41	60	60	0.050
MMSE (SD)	23.4 (1.90)	27.1 (1.75)	29.1 (1.03)	<0.001
3 T				
N	15	24	23	-
Mean age (range)	72.1 (57–88)	74.2 (56–88)	75.6 (70–85)	0.35
#Females	9	9	15	0.39
MMSE (SD)	23.1 (2.12)	26.92 (2.00)	29.43 (0.73)	<0.001

P values are reported for one-way ANOVA for age and MMSE, and for chi-square test (1.5 T) or Fisher's exact test (3 T) for proportion of females. MMSE was significantly different between groups.


a
b
Left hippocampal volume (mm³)
Right hippocampal volume (mm³)
Average hippocampal volume (mm³)
Left hippocampal atrophy (%/yr)
Right hippocampal atrophy (%/yr)
Average hippocampal atrophy (%/yr)
Normal
MCI
AD
FreeSurfer
UCSD
SNT
FSL
MAGeT
inconsistent hippocampal volumes
out of bounds atrophy rates
why?
why?



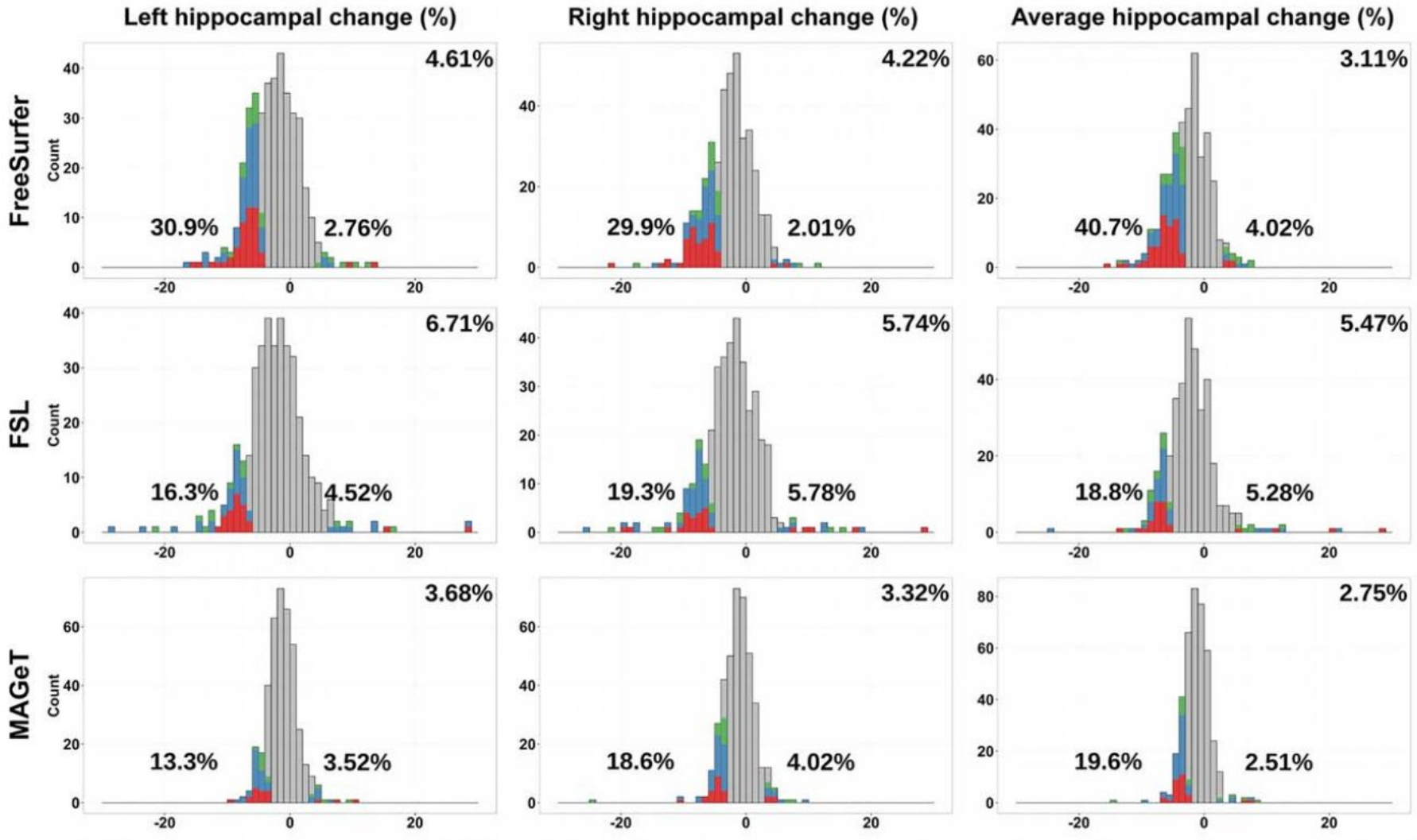
typical segmentation algorithm:

templates are mapped onto the new structure by some deformable registration process

huge weight of the training templates

different ground truth (gold standard) = different output

by the way: this is also why a huge effort on hippocampal harmonization was undertaken ... see http://www.hippocampal-protocol.net



ADNI 1-year hippocampal atrophy distributions thresholded at the 90th percentile of the OASIS absolute test–retest distributions, for both positive and negative atrophy rates. Within each graph, top right percentage indicates the 90 th percentile threshold used, while percentages on either side of the distributions indicate the percentage of subjects exhibiting potential growth atrophy after thresholding.

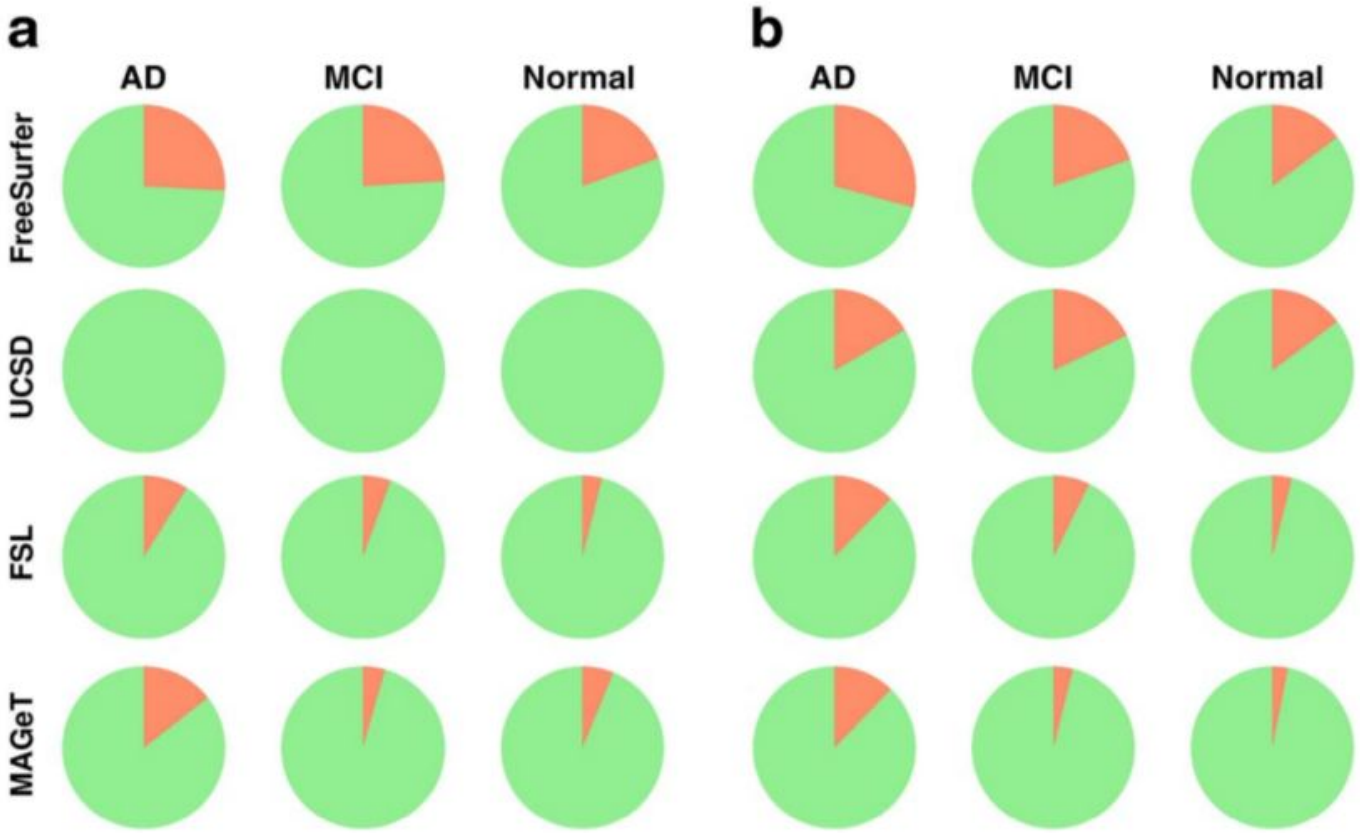


Figure 2.
Graphical summary of the proportion of hippocampal segmentation failures at 1.5 T by algorithm, diagnostic category, and time point: (A) baseline and (B) 1-year follow-up.

segmentation failure = 15 coronal slices randomly sampled. visual assessment (different between human & software > 10 voxels in >=3 slices)

growing the hippocampus: a real biological event?

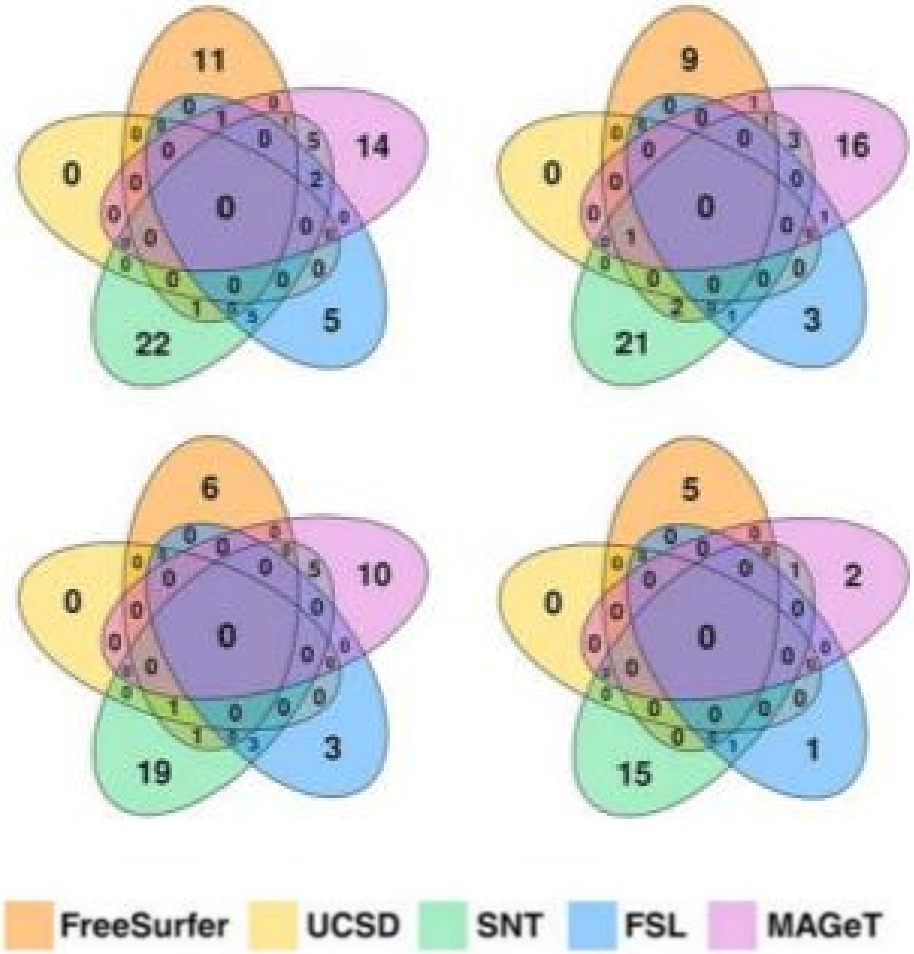


Figure 3.

Venn diagrams demonstrating overlap of subjects identified as hippocampal "growers" at 1.5 T across all 5 segmentation algorithms
Clockwise from upper left, individual Venn diagrams represent overlap for left, right, bilateral, and average hippocampal growth respectively.

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CONCLUSION

In an assessment of five different automated or semi-automated segmentation algorithms designed to measure hippocampal volume from structural MRI data, we found an unexpectedly high incidence of subjects in the ADNI database who demonstrated hippocampal growth over time. For no individual algorithm could this counterintuitive finding be entirely explained by gross segmentation errors, scan–rescan variability, or field strength of MRI acquisition. Furthermore, algorithms did not consistently identify the same subjects as hippocampal growers, and more generally our analysis revealed poor concordance between algorithms in their estimates of the magnitude and direction of hippocampal volume change over time, which precluded a meaningful analysis of whether hippocampal growth could be a true biological phenomenon. These findings suggest that, in patients with either AD or MCI, or age-matched elderly controls, longitudinal hippocampal volume change should be interpreted with considerable caution as a biomarker at the individual subject level, and may have important limitations at a group-wide level as well.

conclusions… what is missing?

key concept:

differential measures are more accurate than cross-sectional ones

estimation of physiological noise and acquisition noises

insight to pathology models

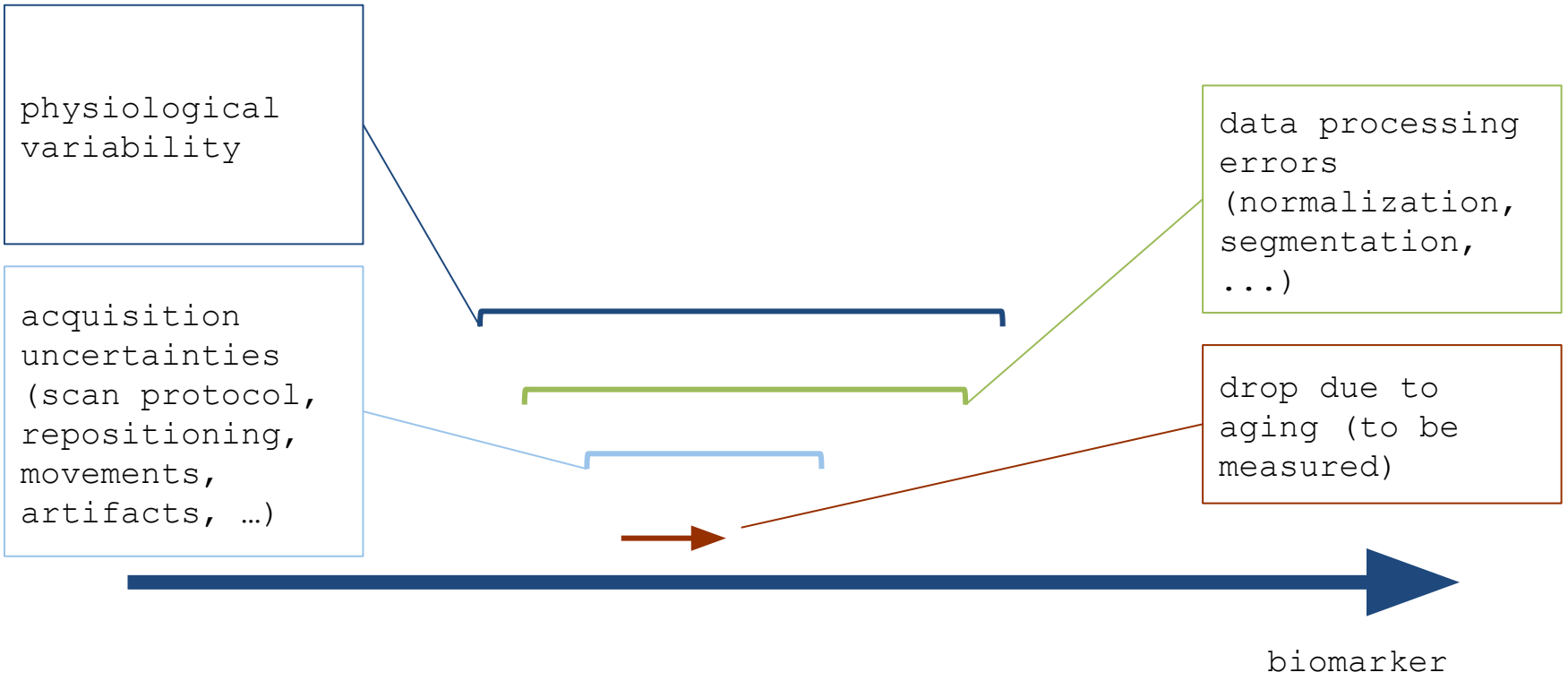
key point:

$$\tau_{path} >> (<<) \ \tau_{nuisances}$$

for instance, in hippocampal volumetry

$$(\tau_{atrophy} \sim \text{years}) >> (\tau_{physiological} \sim \text{days})$$

physiological variability can be: hydration, hormonal, vascular, comorbidities ...


physiological variability
acquisition uncertainties (scan protocol, repositioning, movements, artifacts, …)
data processing errors (normalization, segmentation, ...)
drop due to aging (to be measured)
biomarker

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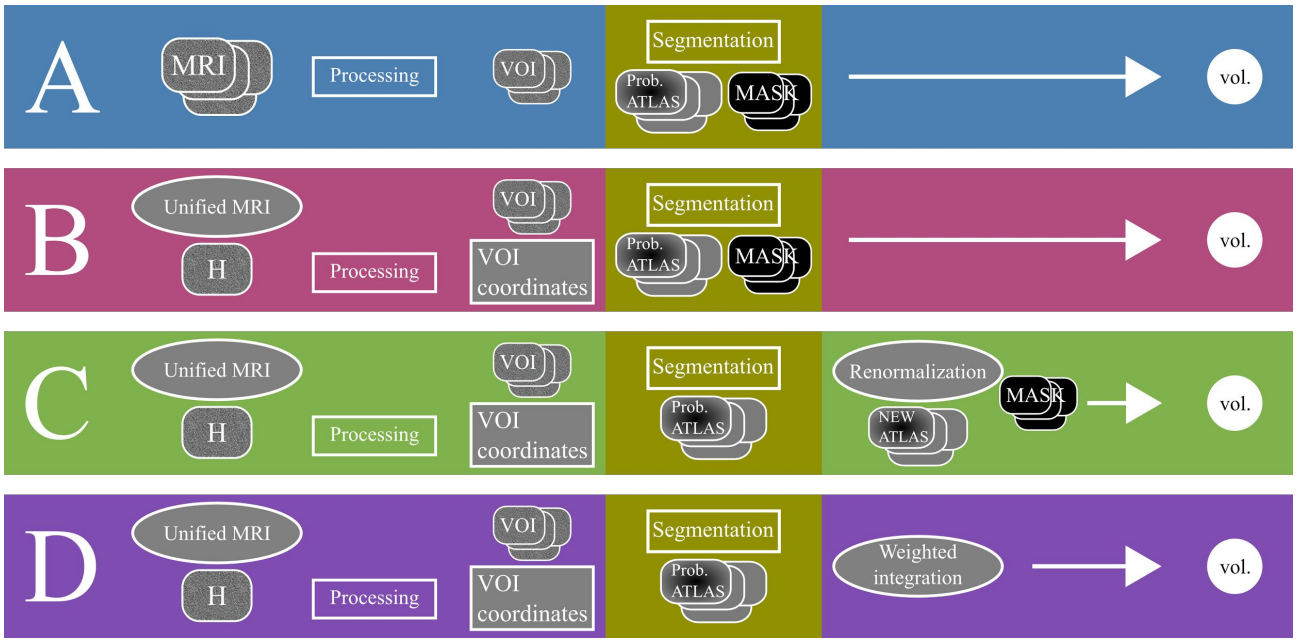
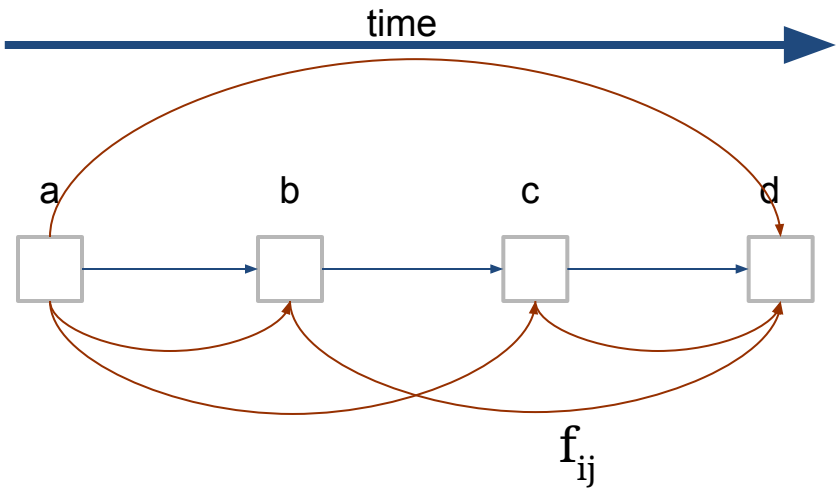
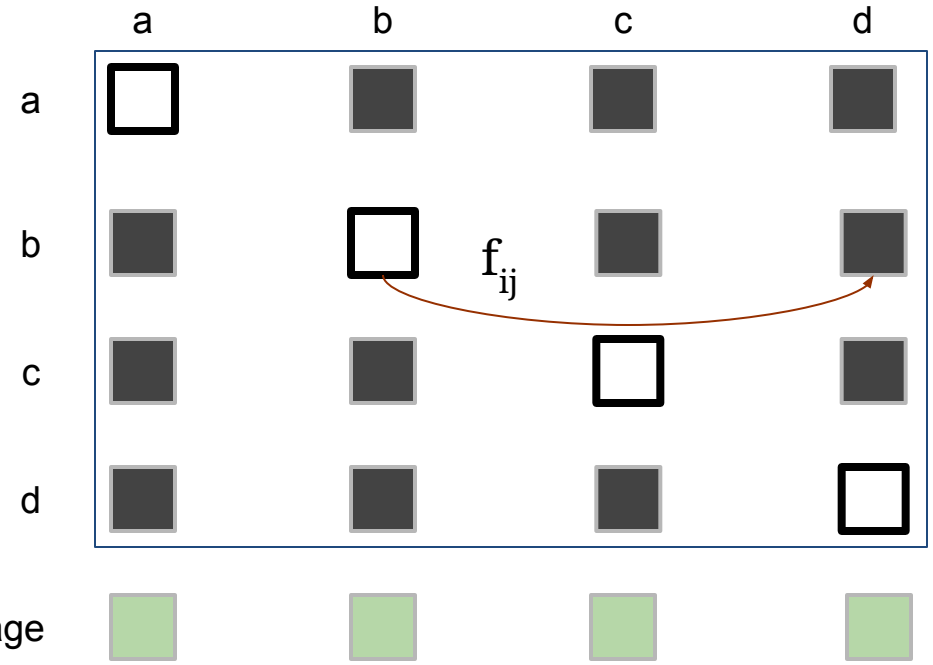




MRI

all paths a → d

deformation field



segmentation matrix

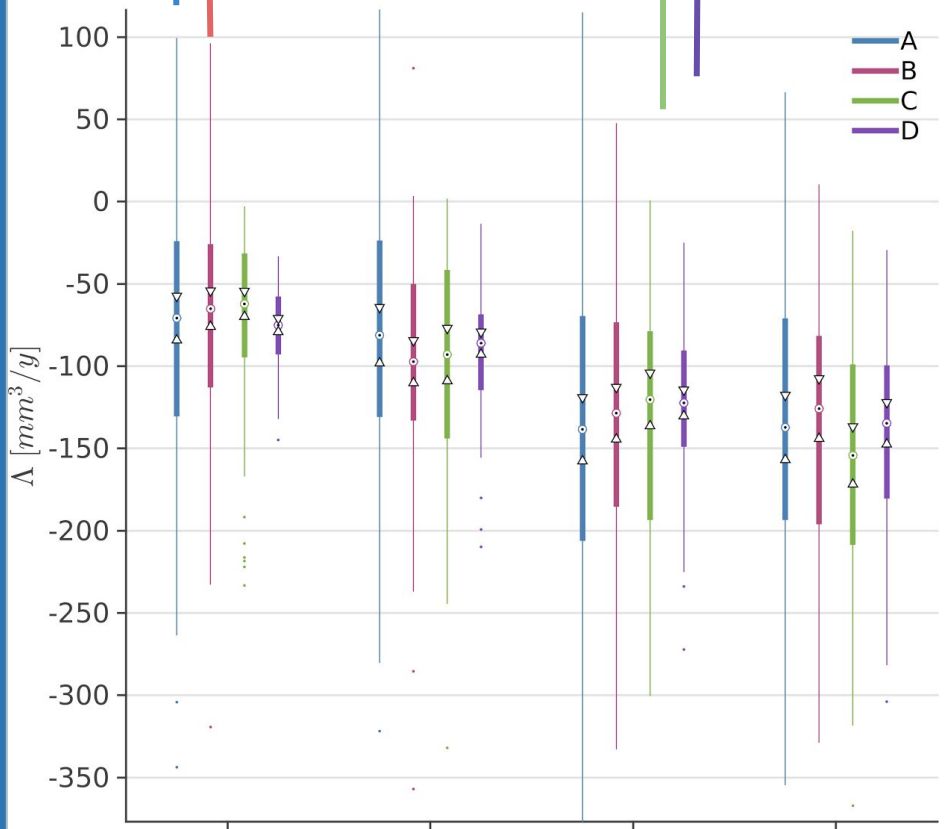
renormalized averages

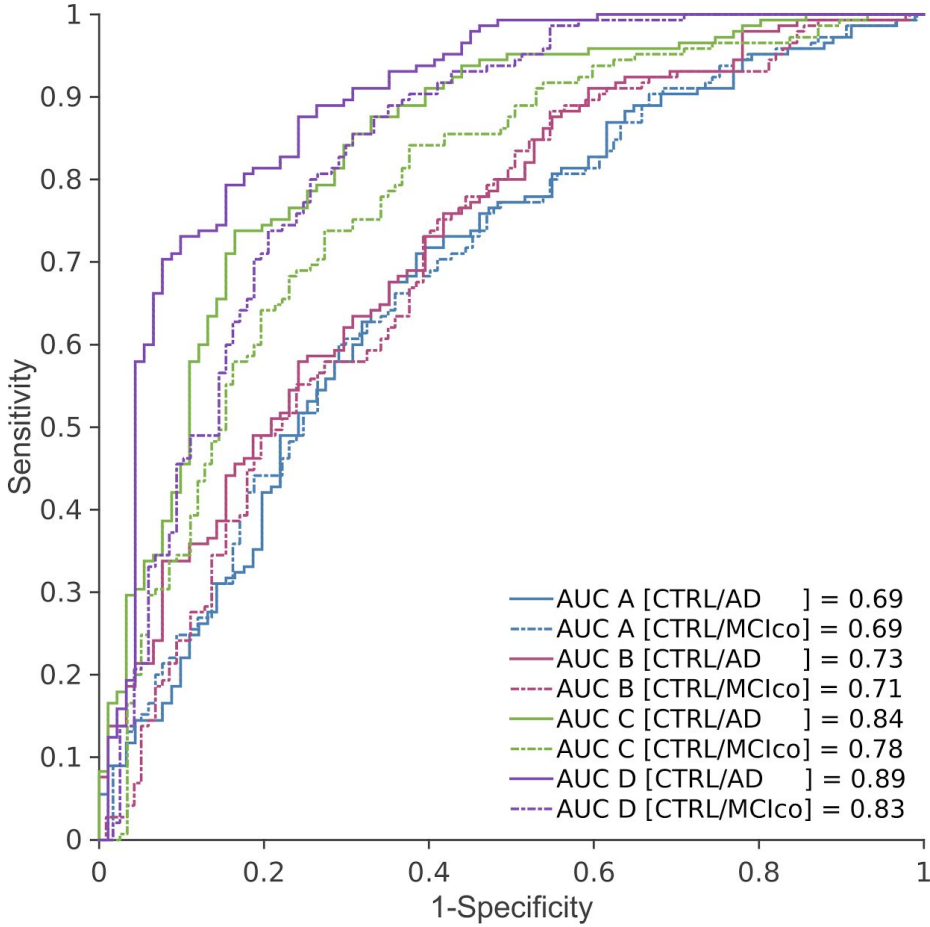
time-dependent normalization
time-dependent metric

independent normalization
independent metric

integrated, time-dependent normalization & metric

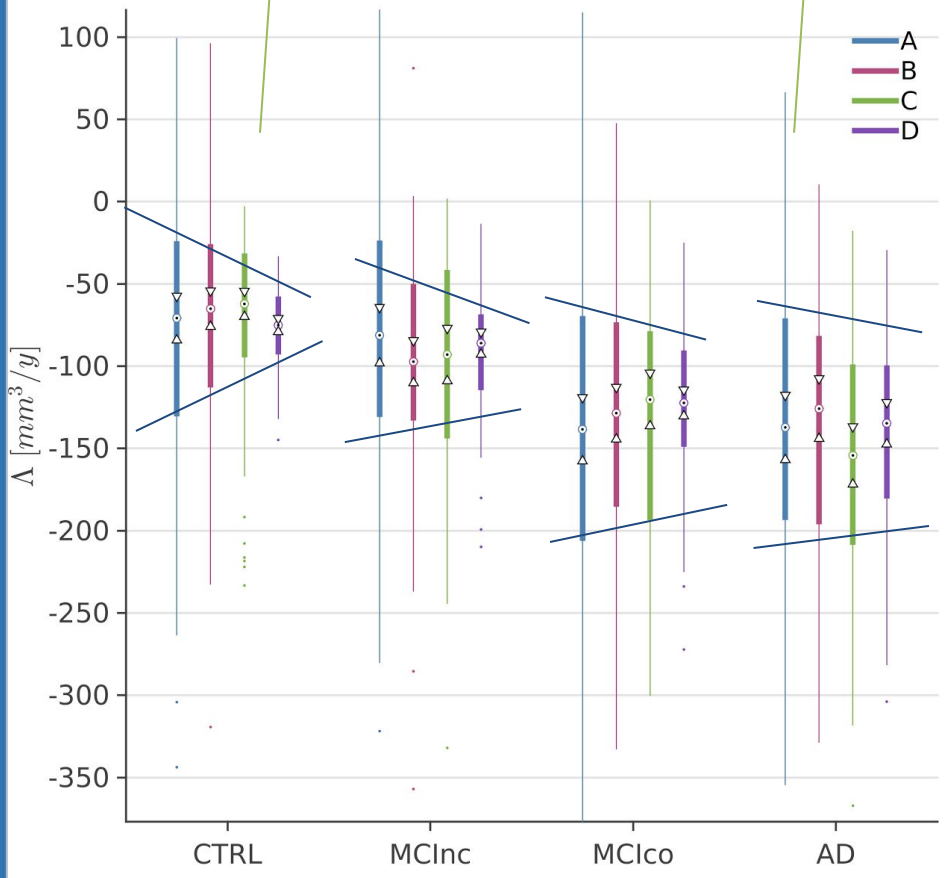
time-dependent normalization
independent metric





big variability reduction in CTRL

small variability reduction in AD



intrinsic (cohort) variability surrogate

=

most time-integrated measure

⇒

the processing error is greatly reduced

surrogate increases from CTRL -> MCI -> AD

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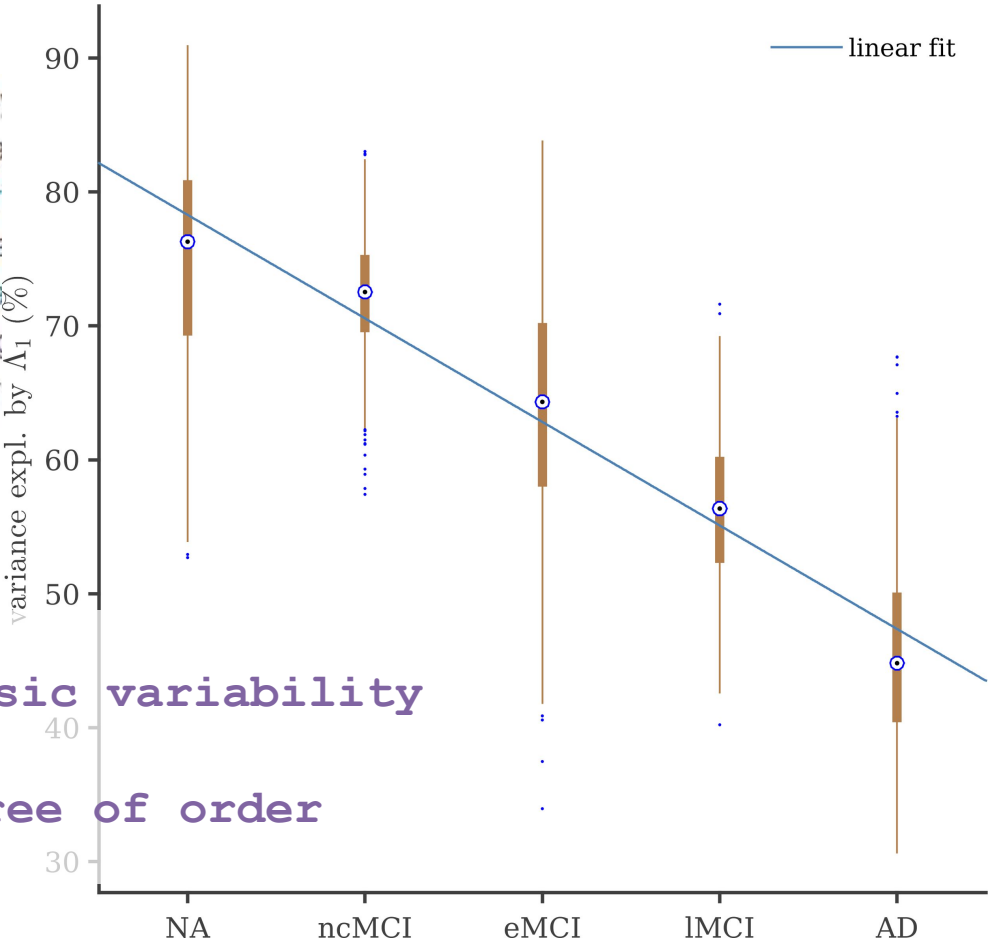
Predicting the transition from normal aging to Alzheimer's disease: A statistical mechanistic evaluation of FDG-PET data

Marco Pagani [a, b], Alessandro Giuliani [c], Johanna Öberg [d], Andrea Chincarini [e], Silvia Morbelli [f], Andrea Brugnolo [g], Dario Arnaldi [g], Agnese Picco [g], Matteo Bauckneht [f], Ambra Buschiazzo [f], Gianmario Sambuceti [f], Flavio Nobili [g]

The assessment of the degree of order of brain metabolism b
mechanistic approach applied to FDG-PET, allowed us to cha
well as patients with mild cognitive impairment and Alzheimer
signals from 24 volumes of interest were submitted to principa
giving rise to a major first principal component whose eigenva
index of order. This index linearly decreased from 77 to 44% g
patients with intermediate conditions between these values (r
analysis confirmed the statistical significance of the results.

closing the circle...



small [big] intrinsic variability

=

high [low] degree of order

Longitudinal investigations can provide very interesting insights but...

- all measures (automatic or manual) are inherently noisy
- there are many ways to perform a longitudinal measure: the difference between independent probes at two time-points is not the best one

mitigation strategies on poor longitudinal protocols:

- you should consider having a few subjects on which you can acquire multiple time points
- you should consider having a separate dataset to disentangle the various noises: physiological, acquisition, data processing, ...

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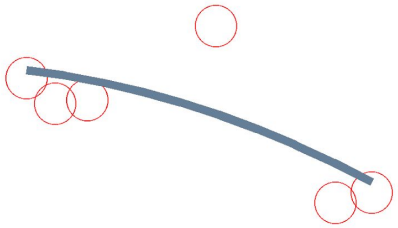
fit based on clinical model



uncertainties:

physiological
variability
acquisition nuisance
data analysis
comorbidity

longitudinal protocol is important too!
remember the time-scale τ of the process