Effect of denoising on brain atrophy measurements based on MRI for Alzheimer's disease

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Dataset from two Phase I studies

Clinical Trials

Axon CO 18700 – A 3-months randomized, placebo-controlled, parallel group, double-blinded, multi-centre, phase I study to assess tolerability and safety of AADvac1 applied to patients with mild to moderate Alzheimer's disease with a 3-months open label extension period.
AC-AD-002 "FUNDAMANT" – An 18-months open label phase I follow-up study on patients with Alzheimer's disease who have completed the AADvac1 phase I study "AXON CO 18700".

Key people

Clinical Project Leader: Prof. Michal Novak (AXON Neuroscience CRM Services SE, Bratislava, Slovakia)
Senior Medical Analyst: Petr Novak, MD (AXON Neuroscience CRM Services SE, Bratislava, Slovakia)
Brain Imaging Analyst: Miroslav Smisek, MD (AXON Neuroscience CRM Services SE)

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Univ. Prof. Dr. Peter Dal-Bianco (Medizinische Universität Wien, Wien, Austria)
Dr. Susanne Grinzinger (Universitätsklinik für Neurologie, Christian-Doppler-Klinik, Salzburg, Austria)

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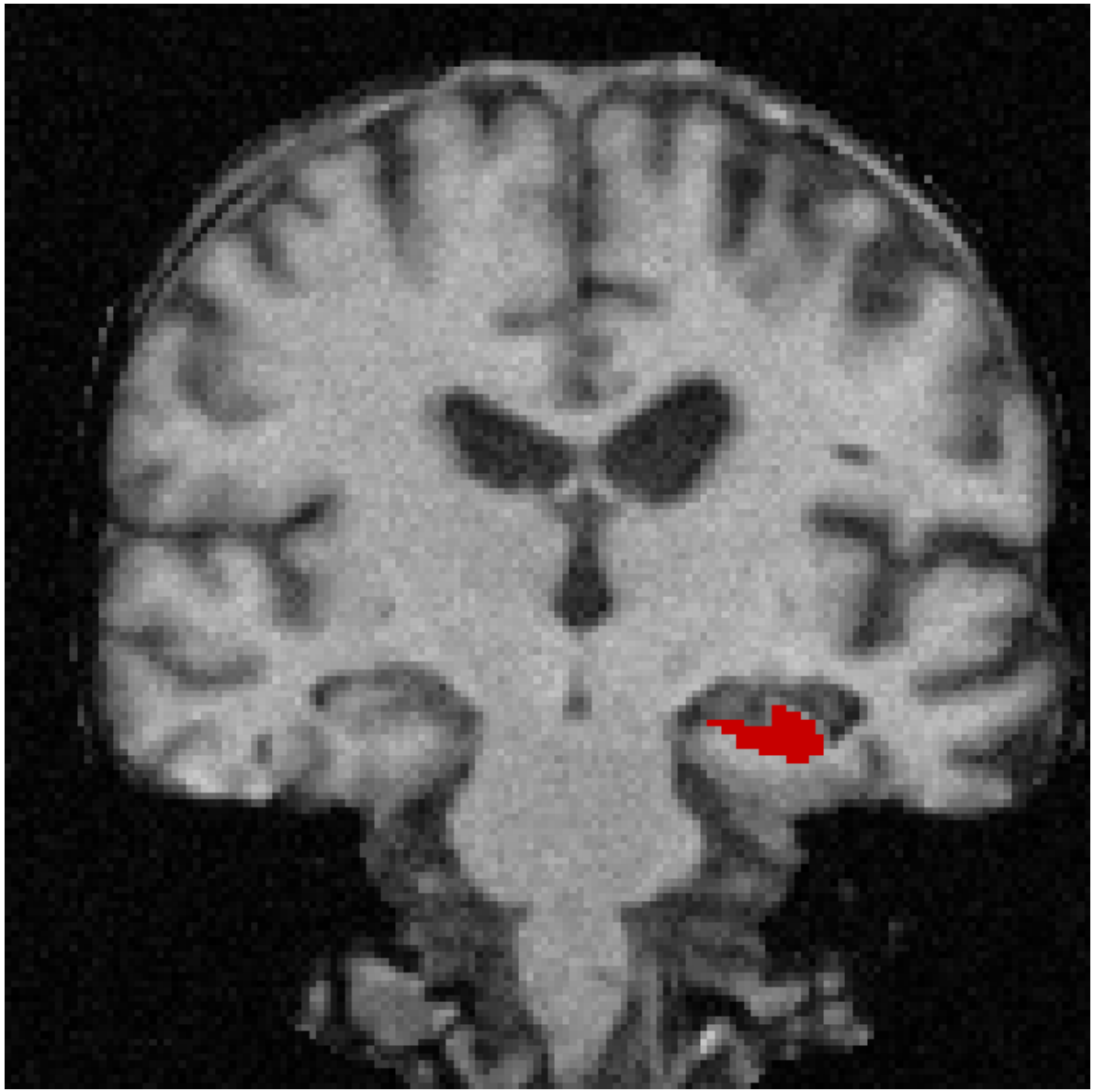
The Brain



Introduction

Goals

Goal I

Reduce variance in volumetric measurements with denoising across multiple scans of single patient.

Goal II

Measure atrophy of brain and other ROIs (hippocampus) and assert its difference between placebo and verum (treated) groups.

Dataset Characteristics

	Verum (n=22)	Placebo (n=6)
Age	67.3 ± 6.7 [53-77]	68.5 ± 12.4 [55-82]
Sex, male	10 (45%)	6 (100%)
Scans	5 ± 0	$5^{1} \pm 0$
MRI	1.5T (80%), 3T (20%)	1.5T (100%), 3T (0%)

Other details

- First phase out of three phases
- 5 MRI scans for each patient within 180 days
- Repeated scans when poor quality scan was observed
- 3 measuring sites, different quality of MRI scans (1.5T, 3T)

[1] Patients were given vaccination at their third visit

Denoising

MRI Denoising

Why denoising MRI?

- Registration / segmentation methods are often sensitive to noise in data
- Many available softwares do not use denoising or use less effective methods (such as gaussian smoothing) which can lead to sub-par results

What's hard about denoising MRI?

- Noise has Rician distribution which is similar to Gaussian in high intensity areas, but non-Gaussian in the background
- Computationally much more demanding than denoising 2D images - a lot of papers deal with optimizing existing methods for 3D

Methods in MRI Denoising

Gaussian smoothing

Non-local means

Currently state of the art in terms of performance and visual quality

Anisotropic diffusion

Image is diffused according to given PDE, similar to gaussian smoothing, but preserves edges

Fourier / Wavelet based methods

Transform to frequency domain, remove noise there and then transform back

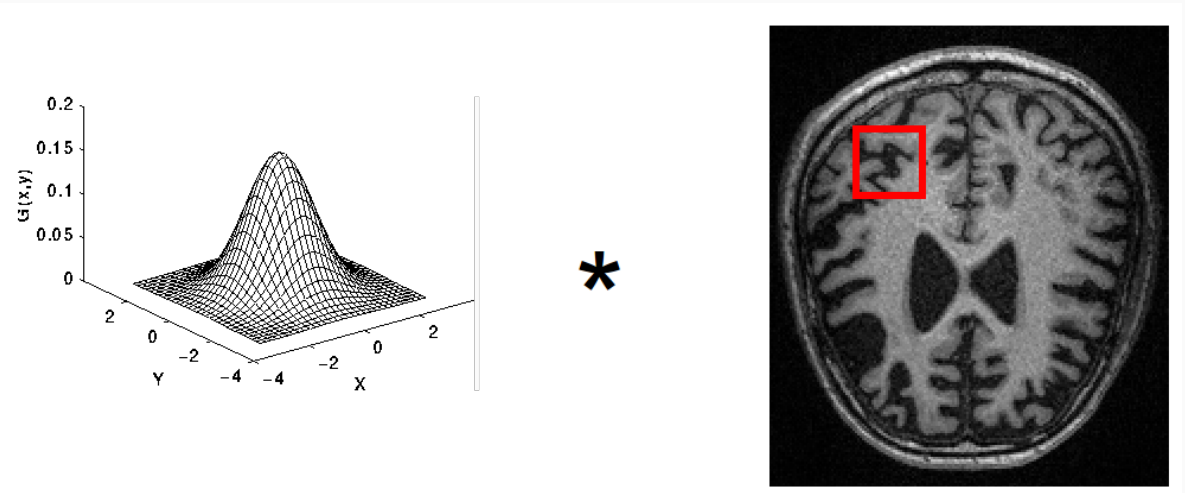
Gaussian Smoothing

- Convolution with the Gaussian kernel
- “Blurs” the image including edges
- Super-fast computation and super-easy implementation

$$\mathcal{GS}(x) = \frac{\int_{N(x)} w(x,y)u(y)dy}{\int_{N(x)} w(x,y)dy},$$

where w(x, y) is a standard Gaussian kernel

$$w(x,y) = \frac{1}{\sqrt{2\pi h^2}} e^{-\frac{|x-y|^2}{2h^2}}.$$



Non-local Means

Let $u : \Omega \to \mathbb{R}$ represent image intensity, then

$$\mathcal{NL}(x) = \frac{\int_\Omega w(x,y)u(y)dy}{\int_\Omega w(x,y)dy},$$

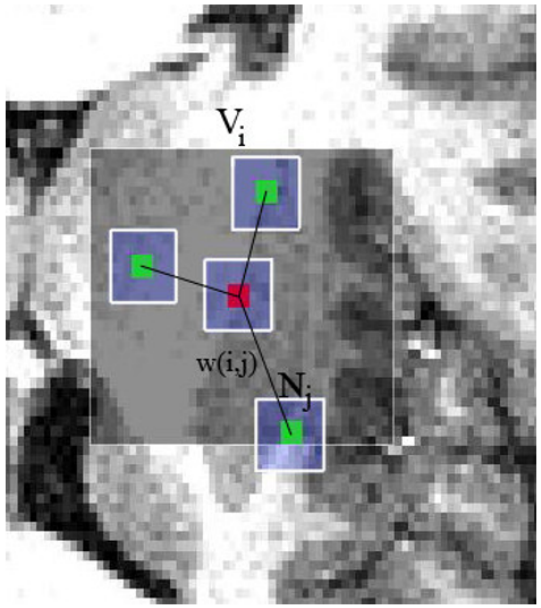
where

$$w(x,y) = e^{-\frac{|N(x)-N(y)|^2}{h^2}}$$

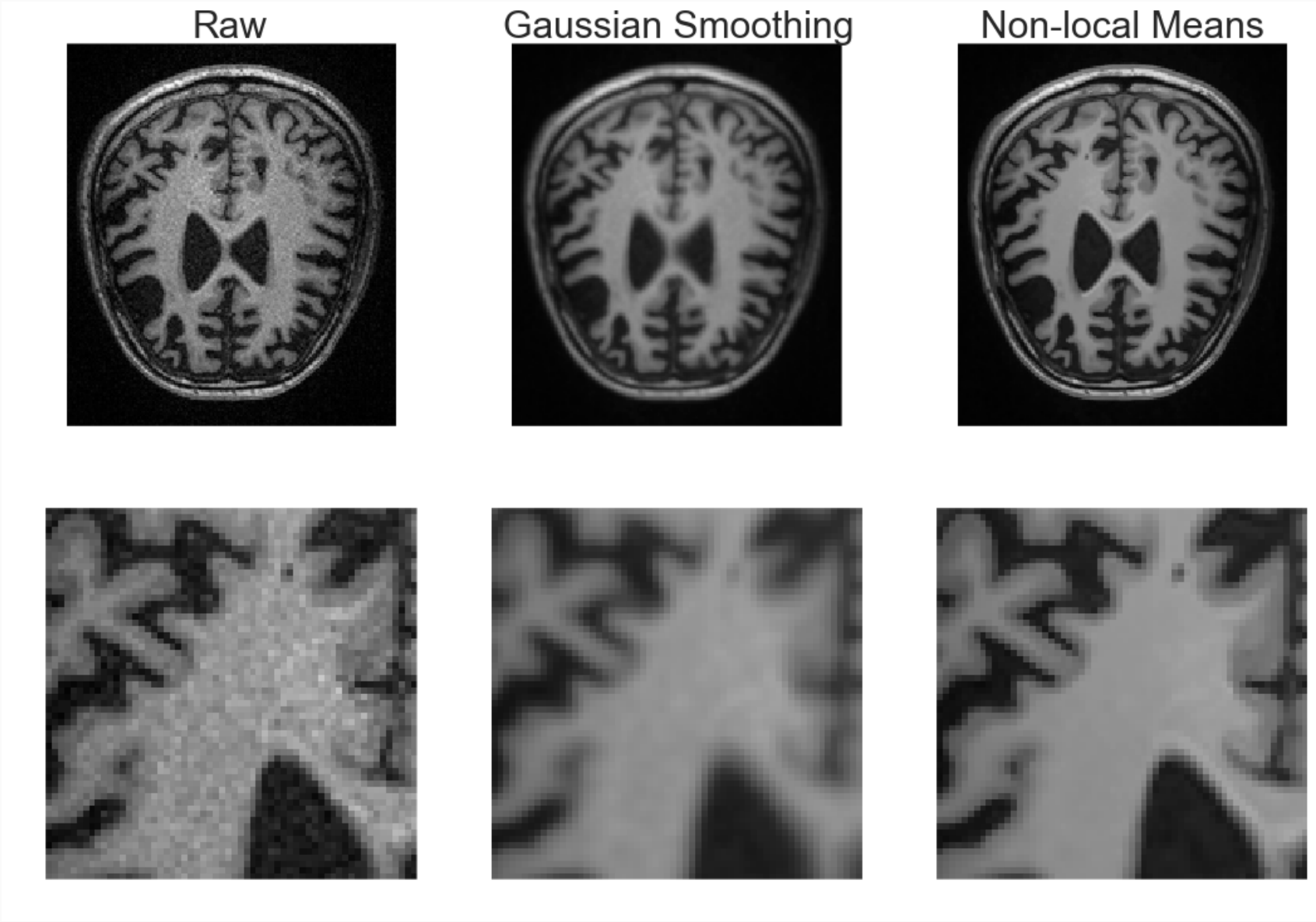
with N being a neighborhood and h acting as a smoothing parameter.

= *Find the most similar neighborhoods to neighborhood of a processed voxel and average their intensities.*

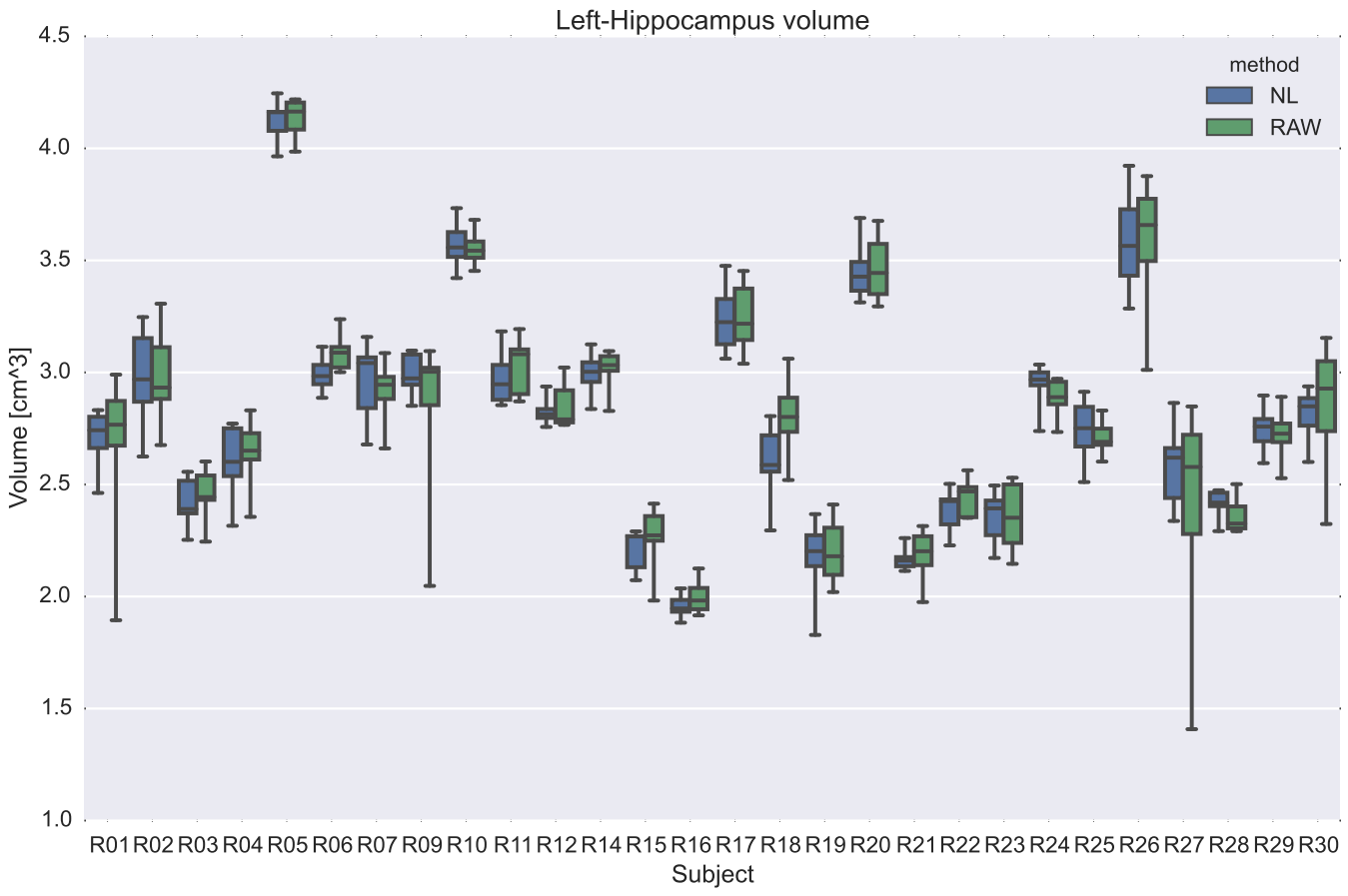
Needs some optimizations to finish computation in a reasonable time



Methods side-by-side



Effect of Smoothing on Volume Measurements

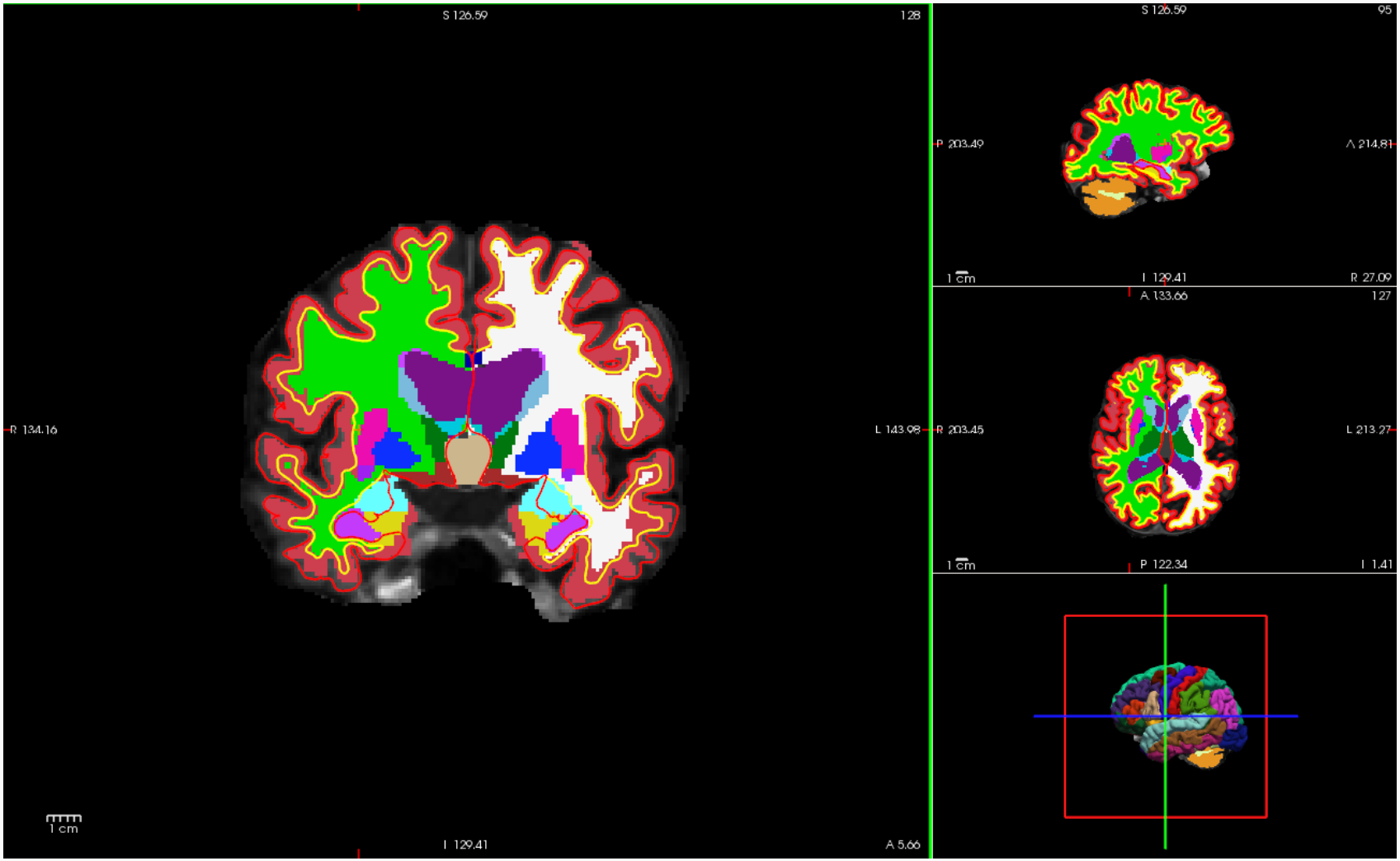


Error reduction from 6.79% to 3.54%

Detailed view https://multi-armed-bandit.shinyapps.io/mriapp/

Segmentation

Segmented Brain



How to achieve best segmentation

Voxels intensity

Voxel brightness indicates tissue type (normalization is not easy though). Typically **Gaussian Mixture Model** is used.

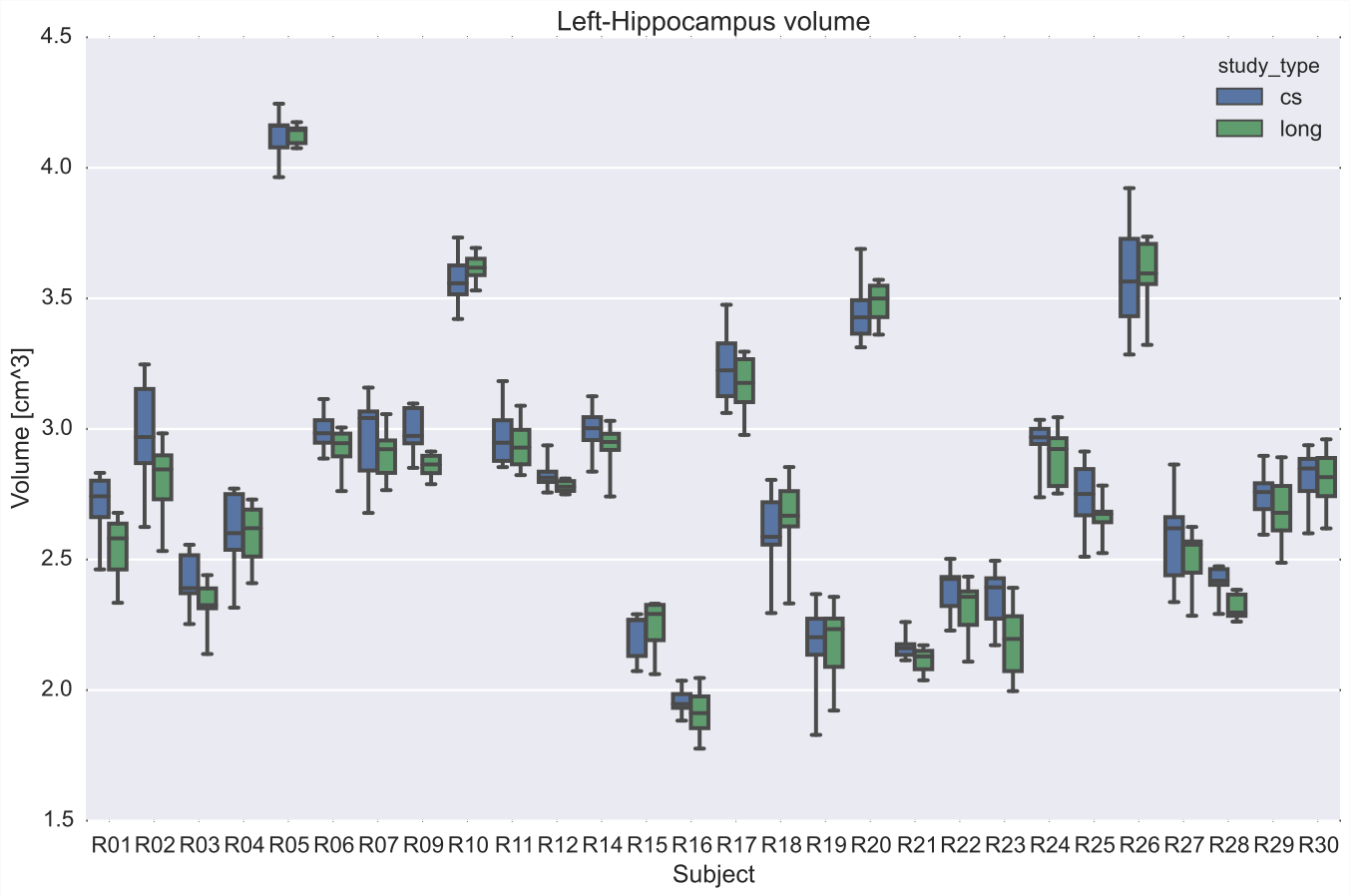
Spatial coherence

Voxels belonging to the same tissue will be likely next to each other. **Markov Random Fields** could be used to force coherence.

Apriori information

We approximately know where to look for hippocampus (and other ROIs). Take brains that have been already labeled, deform our brain onto them and construct **probabilistic map** that is used as an apriori probability (in a Bayesian sense). Even better is to use other scans of the same person from the longitudinal study $\rightarrow$ **longitudinal segmentation**.

Effect of Longitudinal Segmentation on Volume Measurements



Error reduction from 3.54% to 2.50%

Detailed view https://multi-armed-bandit.shinyapps.io/mriapp/

Atrophy Measurements

Atrophy Measurements

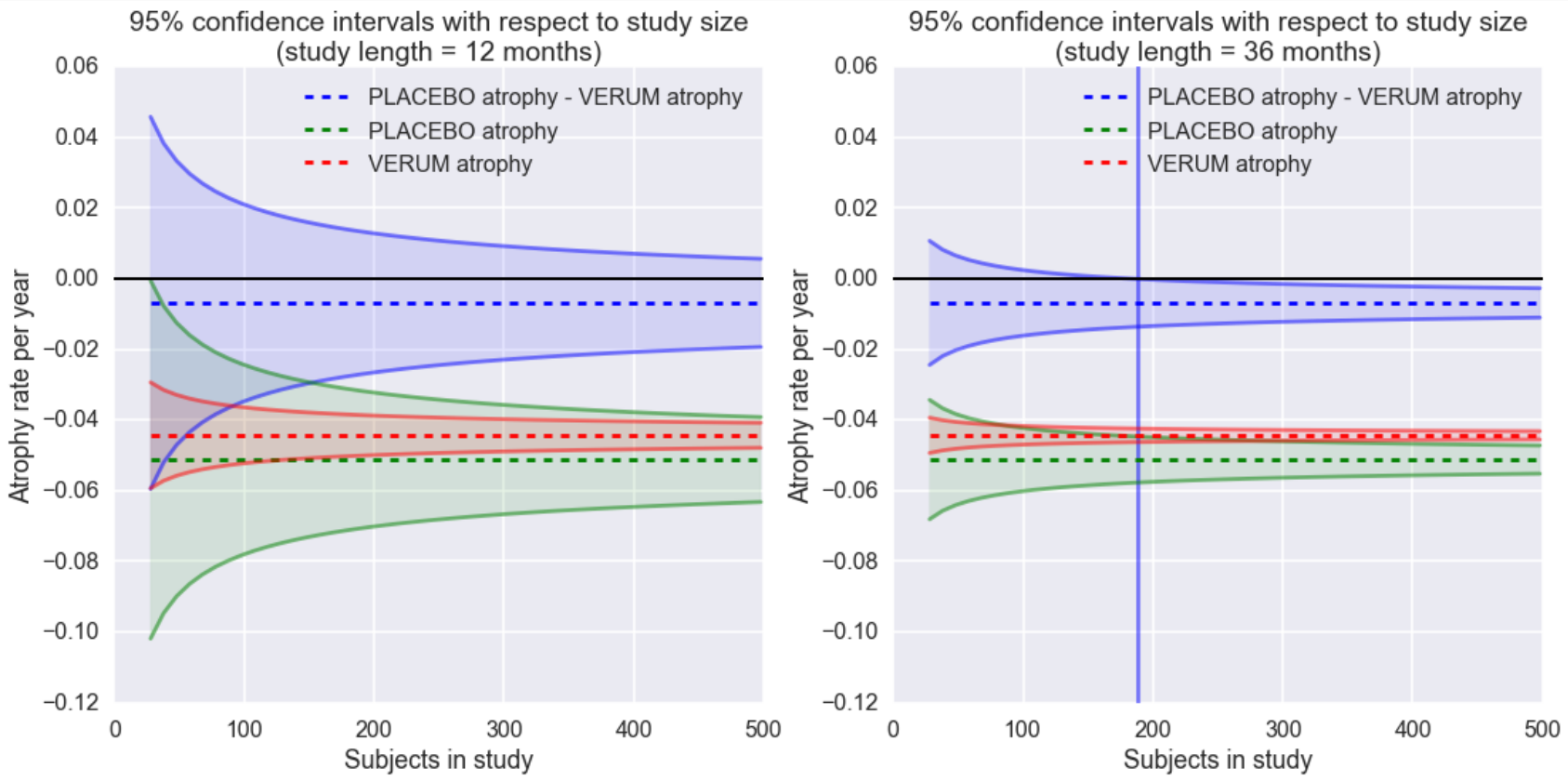
Atrophy Measurements

$$log(volume) \sim time : Treatement + (1 + time|subject)$$

	Coef. FE Intercept	time:Tr[PLACEBO]	time:Tr[VERUM]	Std.Err. FE Intercept	time:Tr[PLACEBO]	time:Tr[VERUM]	loglike
Left-Hippocampus	7.952	-0.051	-0.047	0.033	0.010	0.006	314.213
Right-Hippocampus	8.005	-0.049	-0.048	0.039	0.012	0.007	310.510
Left-Cerebellum-White-Matter	9.544	-0.039	0.004	0.036	0.019	0.012	167.157
Right-Cerebellum-White-Matter	9.530	-0.032	-0.012	0.027	0.017	0.011	189.978
Left-Amygdala	6.946	-0.041	-0.060	0.050	0.022	0.013	155.173
Right-Amygdala	6.994	-0.052	-0.048	0.047	0.030	0.017	165.088
Left-Lateral-Ventricle	10.006	0.107	0.073	0.059	0.045	0.025	197.936
Right-Lateral-Ventricle	9.891	0.104	0.076	0.061	0.039	0.022	215.307
lhCortexVol	12.033	-0.052	-0.047	0.023	0.012	0.007	316.225
rhCortexVol	12.057	-0.048	-0.035	0.026	0.013	0.008	326.390
CortexVol	12.739	-0.051	-0.041	0.024	0.012	0.007	328.307
CorticalWhiteMatterVol	13.027	0.014	0.010	0.025	0.012	0.007	322.764
TotalGrayVol	13.086	-0.037	-0.032	0.018	0.009	0.005	358.729

Sample size estimation

Length of study in longitudinal studies is more important[2] to significance than number of subjects.



[1] Assuming linearity of atrophy

Preliminary Results

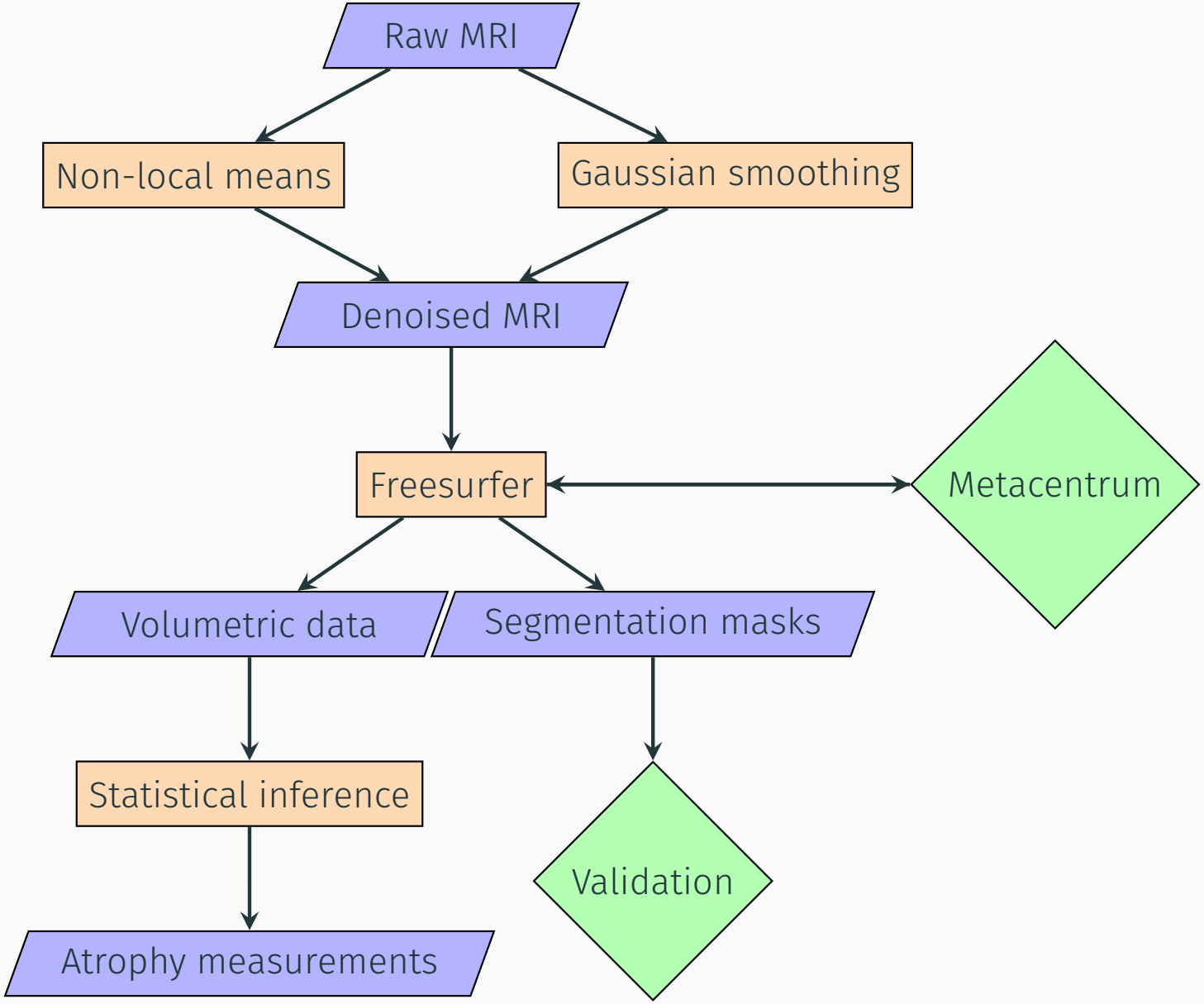
- Not enough samples to make any statistically valid conclusions
- Need to wait for more patients from Phase II and Phase III or additional scans from current patients
- Our primary aim right now is to reduce measurement error and set up infrastructure for data processing

Practical Considerations

Computation

- 28 patients x 5 scans x 3 methods x 6 hours = 105 days of processing time
- We utilized MetaCentrum clusters
  - Access to almost infinite computational resources
  - Easy to get started, setup scripts were really simple
  - Reduced processing time to 6 hours due to parallelization
- Other software claim to be faster than Freesurfer, but had other issues
  - Not an end-to-end analysis like Freesurfer
  - Need for parameter tuning
  - Closed-source
  - Lack of command line interface or API (only application was available)

Processing Pipeline



Future Work

Future Work

1. Upcoming Freesurfer 6.0 release implements hippocampal subfields segmentation that combines T1 and T2 scans to improve segmentation accuracy.
2. Phase II of clinical trial
3. Using neural networks for denoising (work in progress, not very promising so far)

Thank you for your attention!

Questions?

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