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

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### 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)

### Principal Investigators

**Univ. Prof. Dr. Reinhold Schmidt** (Medizinische Universität Graz, Graz, Austria)

**Univ. Prof. Dr. Peter Dal-Bianco** (Medizinische Universität Wien, Wien, Austria)

**Dr. Susanne Grinzinger** (Universitätsklinik für Neurologie, Christian-Doppler-Klinik, Salzburg, Austria)
1. Introduction
2. Denoising
3. Segmentation
4. Atrophy Measurements
5. Practical Considerations
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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

<table>
<thead>
<tr>
<th></th>
<th>Verum (n=22)</th>
<th>Placebo (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.3 ± 6.7 [53-77]</td>
<td>68.5 ± 12.4 [55-82]</td>
</tr>
<tr>
<td>Sex, male</td>
<td>10 (45%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Scans</td>
<td>5 ± 0</td>
<td>5¹ ± 0</td>
</tr>
<tr>
<td>MRI</td>
<td>1.5T (80%), 3T (20%)</td>
<td>1.5T (100%), 3T (0%)</td>
</tr>
</tbody>
</table>

### 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)

¹Patients 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
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

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

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

Raw          Gaussian Smoothing          Non-local Means
Effect of Smoothing on Volume Measurements

Error reduction from 6.79% to 3.54%
Segmentation
Segmented Brain
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 → **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

Volume of Left-Hippocampus across time

- **verum** (green)
- **placebo** (red)

**X-axis:** Months

**Y-axis:** Volume \([\text{cm}^3]\)

The graph shows the volume of the left hippocampus over time for both verum and placebo groups. The green lines represent the verum group, while the red lines represent the placebo group. The data points are marked with circles, with red circles indicating the placebo group and green circles indicating the verum group.
### Atrophy Measurements

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

<table>
<thead>
<tr>
<th></th>
<th>Coef. FE</th>
<th>Std.Err. FE</th>
<th>loglike</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-Hippocampus</td>
<td>7.952</td>
<td>-0.051</td>
<td>-0.047</td>
</tr>
<tr>
<td>Right-Hippocampus</td>
<td>8.005</td>
<td>-0.049</td>
<td>-0.048</td>
</tr>
<tr>
<td>Left-Cerebellum-White-Matter</td>
<td>9.544</td>
<td>-0.039</td>
<td>0.004</td>
</tr>
<tr>
<td>Right-Cerebellum-White-Matter</td>
<td>9.530</td>
<td>-0.032</td>
<td>-0.012</td>
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<tr>
<td>Left-Amygdala</td>
<td>6.946</td>
<td>-0.041</td>
<td>-0.060</td>
</tr>
<tr>
<td>Right-Amygdala</td>
<td>6.994</td>
<td>-0.052</td>
<td>-0.048</td>
</tr>
<tr>
<td>Left-Lateral-Ventricle</td>
<td>10.006</td>
<td>0.107</td>
<td>0.073</td>
</tr>
<tr>
<td>Right-Lateral-Ventricle</td>
<td>9.891</td>
<td>0.104</td>
<td>0.076</td>
</tr>
<tr>
<td>lhCortexVol</td>
<td>12.033</td>
<td>-0.052</td>
<td>-0.047</td>
</tr>
<tr>
<td>rhCortexVol</td>
<td>12.057</td>
<td>-0.048</td>
<td>-0.035</td>
</tr>
<tr>
<td>CortexVol</td>
<td>12.739</td>
<td>-0.051</td>
<td>-0.041</td>
</tr>
<tr>
<td>CorticalWhiteMatterVol</td>
<td>13.027</td>
<td>0.014</td>
<td>0.010</td>
</tr>
<tr>
<td>TotalGrayVol</td>
<td>13.086</td>
<td>-0.037</td>
<td>-0.032</td>
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</table>
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

Raw MRI

Non-local means

Gaussian smoothing

Denoised MRI

Freesurfer

Freesurfer

Volumetric data

Segmentation masks

Statistical inference

Validation

Atrophy measurements

Metacentrum
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?

Within-subject template estimation for unbiased longitudinal image analysis. 