Extra Axial Cerebrospinal Fluid Volume and a Diagnosis of Alzheimer’s

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Biomarkers from MRI scans

- The most widely used biomarkers for Alzheimer's disease are beta-amyloid 42, tau, and phospho-tau, which are all detectable in CSF.

Hypothetical model of biomarker changes in Alzheimer’s Disease

Extra-Axial Cerebrospinal Fluid

- Shen et al, 2013: cerebrospinal fluid is a circulatory and regulatory system
- Da Mesquita et al, 2018: Regulation of waste clearance in the brain
Previous EACSF Findings

- Shen et al, 2013 and Shen et al, 2017: 24% more EACSF in infants at 6 months who develop the most severe Autism Spectrum Disorder (ASD) symptoms at 24 months.

[Graph showing changes in extra-axial CSF over time for different risk groups.]

Low-Risk Infant with Normal MRI; **ASD-negative**

High-Risk Infant with Increased Extra-Axial CSF; **Diagnosed with ASD**
Cerebrospinal Fluid Overlooked

- Major neuroimaging software does not retain CSF space during skull-stripping step

FreeSurfer segmentation

Novel process to retain CSF spaces
Shen et al, 2017
AutoEACSF Processing

- CSF above the AC-PC line is considered extra-axial cerebrospinal fluid

**The AutoEACSF pipeline**

**Inputs:**
- T1* (and optionally T2*) MRI image(s) of the brain
- Optional masks

**First step:** Reference alignment: putting all images and optional masks in the same reference space

**Second step:** Skull stripping: removing the skull from the input T1 (and T2 if provided) image(s)

**Third step:** Segmentation: labelling the different regions of the brain (GM*, WM*, CSF*)

**Fourth step:** Ventricle masking: removing the CSF located in the ventricles from the segmentation

**Outputs:**
- Segmentation of the extra-axial CSF
- Scalar value of the volume of EACSF*

**Notes:**
- WM: white matter
- GM: gray matter
- (EA)CSF: (extra-axial) cerebrospinal fluid
- T1: T1 weighted image, a type of MRI in which CSF appears dark, WM appears light and GM appears gray
- T2: T2 weighted image, a type of MRI in which CSF appears bright, WM appears dark gray and GM light gray
Data for this study

- Only T1-weighted images were available for each subject

- This study utilized the MRI and demographic data available from ADNI
Processing Issues

- First round using automatic FreeSurfer brain mask processing was insufficient, so second multi-atlas round was run.

Brain Mask ratings
- 2% rejected

EACSF Segmentation ratings
- 15% rejected
Diagnosis Groups

<table>
<thead>
<tr>
<th>Normal Development Control (CN)</th>
<th>Subjective Cognitive Decline (SMC)</th>
<th>Early Mild Cognitive Impairment (EMCI)</th>
<th>Late Mild Cognitive Impairment (LMCI)</th>
<th>Alzheimer’s Disease (AD)</th>
</tr>
</thead>
</table>

- Nonaccelerated 6-month:
  - Tissue loss: -3%, -2%, -1%, 0%, 1%, 2%, >3%
  - Ventricle expansion

- CN
- SMC
- EMCI
- LMCI
- AD

## Sample Statistics

<table>
<thead>
<tr>
<th>Diagnosis Group</th>
<th>Age (Years)</th>
<th>Male</th>
<th>Normalized EACSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CN</td>
<td>41</td>
<td>73.1</td>
<td>5.2</td>
</tr>
<tr>
<td>MCI</td>
<td>47</td>
<td>72.9</td>
<td>7.6</td>
</tr>
<tr>
<td>AD</td>
<td>23</td>
<td>76.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Change</td>
<td>17</td>
<td>73.7</td>
<td>7.0</td>
</tr>
</tbody>
</table>

![Diagnosis Categorization](image1.png)

![Proportion](image2.png)
No significant differences found between diagnosis groups at either time point.

<table>
<thead>
<tr>
<th>Diagnosis Group</th>
<th>Mean Initial</th>
<th>Mean Final</th>
<th>Change in Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>11.7%</td>
<td>12.7%</td>
<td>+1.0%</td>
</tr>
<tr>
<td>MCI</td>
<td>11.3%</td>
<td>12.9%</td>
<td>+1.6%</td>
</tr>
<tr>
<td>AD</td>
<td>12.1%</td>
<td>12.6%</td>
<td>+0.5%</td>
</tr>
<tr>
<td>Change</td>
<td>11.1%</td>
<td>12.4%</td>
<td>+1.3%</td>
</tr>
</tbody>
</table>

*% EACSF of ICV
Other Volumes Associated with EACSF

- EACSF significantly correlated with ventricle volume
- In a general linear model predicting EACSF, entorhinal and ventricle volumes were significant variables

*normalized by dividing by ICV
>The differences in ventricle volume across diagnosis groups were all significant or near-significant.
The differences in ventricle/EACSF proportion across diagnosis groups were all significant or near-significant. The comparison between CN and MCI was more significant than either EACSF or ventricles alone.
Longitudinal Population

- Longitudinal subjects
- Cross-sectional subjects
EACSF by Days

- Four longitudinal models - one for each diagnosis group - with days, ICV, age, and sex as variables.
Comprehensive Model

- Comprehensive models using the data from all four diagnosis groups were made. The variables and their significance levels are shown.

*because of matrix deficiency, the intercept term was taken to reflect the AD diagnosis variable and associated higher order interaction terms*
Two Group Comparison

- Six models compared two diagnosis groups at a time. Only the MCI-Change model had a statistically significant diagnosis variable.

Fixed effects:

|            | Estimate | Std. Error | df  | t value | Pr(>|t|) |
|------------|----------|------------|-----|---------|----------|
| (Intercept)| 129588.027 | 37797.531  | 33.719 | 3.428  | 0.00162 ** |
| Days       | 1.558    | 2.113      | 138.502 | 0.737  | 0.46231  |
| PTGENDERMale | 3359.584 | 7295.705   | 34.014 | 0.460  | 0.64810  |
| DXMCI      | -15237.933 | 7698.308  | 33.951 | -1.979 | 0.05593 . |
| AGE        | 697.487  | 492.494    | 33.687 | 1.416  | 0.16589  |

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Conclusion

- No association between EACSF and Alzheimer’s Disease
- Increased support for T1-only data with AutoEACSF
- Potentially interesting EACSF-ventricle relationship
- Additional investigation needed for those who changed diagnosis
Thank you for listening!

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