Arg-ADNI

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and Arg-ADNI group.

Memory and Aging Center
Institute for Neurological Research (FLENI)
Buenos Aires, Argentina

WW-ADNI update: Copenhagen, July 11, 2014

*speaker
1. Background
2. Work-Plan
3. Results
4. AAIC and other meetings
5. Publications
6. New Projects
Worldwide Life Expectancy

Argentina

Buenos Aires

Font: CIA World Factbook / INDEC
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Arg-ADNI

1st Arg-ADNI: FLENI Cohort (2011-2014)
Single-Center, Pilot Study-60pts

Main Project

2nd Arg-ADNI: Multicenter Cohort (2015-2018)
Arg-ADNI
1st Cohort (FLENI)
Study Timelines

1. Recruitment: 24 months
2. Follow-up: 24 months
Arg-ADNI
1st Cohort (FLENI)
Patients’ Flowchart

Patients Invited to ADNI Nº= 73

Patients Screened at FLENI Nº= 60

Screening Failure Nº= 7
- 2 Claustrophobia
- 1 Psychiatric Disease
- 1 Cancer
- 1 Adult ADHD
- 2 without informant

Dropout Nº= 3
- 2 removed inform.cons
- 1 by distance/caregiver

Patients Followed (1st year) Nº= 50

Healthy Controls Nº= 10

Early MCI Nº= 15

Late MCI Nº= 16

Dementia AD Nº= 9
### Table 1: Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Early MCI</th>
<th>Late MCI</th>
<th>Dementia AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>68</td>
<td>70</td>
<td>75</td>
<td>75</td>
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<tr>
<td><strong>Education (years)</strong></td>
<td>14</td>
<td>12.9</td>
<td>13.6</td>
<td>12.1</td>
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<tr>
<td><strong>Sex (%fem)</strong></td>
<td>70%</td>
<td>40%</td>
<td>68.8%</td>
<td>44.4%</td>
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<tr>
<td><strong>MMSE</strong></td>
<td>30</td>
<td>28.9</td>
<td>27.1</td>
<td>21.4</td>
</tr>
</tbody>
</table>
Arg-ADNI
1st Cohort (FLENI)
Methods: ADNI

1. Demographic and Neurological Exams
2. Neuropsychological Assessment
3. Cognitive Reserve Inventory
4. Blood sampling including DNA banking
5. Cerebro Spinal Fluid (AB42, tau and f-tau)
6. MRI (3.0T)
7. FDG PET-CT scan
8. $^{11}$C-PiB PET-CT scan
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## Arg-ADNI

### 1st Cohort (FLENI) Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Total N°</th>
<th>NPS Ass</th>
<th>MRI</th>
<th>CSF Aβ-tau</th>
<th>PET FDG</th>
<th>PET PiB</th>
<th>Follow-up 1 year</th>
<th>Follow-up 2 year</th>
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</thead>
<tbody>
<tr>
<td>Healthy Controls</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Early MCI</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>15</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Late MCI</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>11</td>
<td>15</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Dementia AD</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td><strong>38 (76%)</strong></td>
<td><strong>49 (98%)</strong></td>
<td><strong>43 (86%)</strong></td>
<td><strong>23</strong></td>
<td></td>
</tr>
</tbody>
</table>
Brain $^{18}$FDG PET scan

Uptake Map

AD

Hypometabolism Map

Brain $^{11}$C-PiB PET scan

Indivduo A
Frontal s.b. Der.
PiB: 0.219±0.001
(FDG: 0.261±0.001)

Frontal s.g. Izq.
$\text{F.s.g.Izq.} = 0.944$

Frontal s.b. Der.
$\text{F.s.b.Der.} = 0.981$

Indivduo B
Frontal s.b. Der.
PiB: 0.276±0.001
(FDG: 0.267±0.001)

Frontal s.g. Izq.
$\text{F.s.g.Izq.} = 1.362$

Frontal s.b. Der.
$\text{F.s.b.Der.} = 1.446$

Healthy

AD
Table 3: PET Scanning as of June 2014

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET Normal</th>
<th>FDG-PET Pathol</th>
<th>PiB-PET Negative</th>
<th>PiB-PET Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Controls</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>0</td>
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<tr>
<td>Early MCI</td>
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<td>5</td>
<td>3</td>
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<tr>
<td>Late MCI</td>
<td>3</td>
<td>11</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Dementia AD</td>
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<td>9</td>
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<tr>
<td>Total</td>
<td>10</td>
<td>34</td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>
Brain Bank.
FLENI houses the only brain bank in Argentina. ADNI participants are being asked to consent brain donation at the time of death.

Brain banking: opportunities, challenges and meaning for the future
Hans Kretzschmar
Nature Reviews Neuroscience 10, 70-78 (January 2009)
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Importancia de la Volumetría Hipocampal como Biomarcador en el Deterioro Cognitivo Leve (ADNI-Arg)

Introducción y Objetivos

La volumetría hipocampal se ha utilizado como biomarcador en el deterioro cognitivo leve (DCL). El objetivo de este estudio es evaluar la relación entre la volumetría del hipocampo y el deterioro cognitivo en pacientes con DCL.

Métodos

Se incluyeron 50 pacientes con DCL y 50 controles. Se realizó una volumetría del hipocampo utilizando la técnica de resonancia magnética. Se compararon las medidas entre ambos grupos y se evaluó la sensibilidad y especificidad del biomarcador.

Resultados

Se observó una reducción significativa en el volumen del hipocampo en pacientes con DCL en comparación con los controles. La volumetría del hipocampo mostró una sensibilidad y especificidad del 80% para el diagnóstico de DCL.

Conclusiones

La volumetría del hipocampo puede ser un útil biomarcador para el diagnóstico de DCL.
MRI Volumetric Analysis, Cognitive profiles and biomarkers in a sample of Argentina - ADNI patients

Objectives
Our goal was to evaluate MRI volumetric analysis and its correlation to clinical impairment. We aimed to determine if the hippocampus showed significant differences in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to controls in order to determine deposition of clinical cognitive cut-off points.

Background
According to the clinicopathological criteria by Braak and Braak 1991, hippocampus volume change (HV) has been used as a measure of hippocampal atrophy and has been used as a diagnostic tool in AD. HV has been quantified in patients with MCI and AD using MRI volumetric analysis. Previous studies have shown a significant correlation between HV and clinical impairment and cognitive decline in MCI and AD patients. However, the use of hippocampus volume as a biomarker for clinical diagnosis is limited due to the small sample size of the studies.

Methods/Methods
Patients were included in the study if they had a diagnosis of MCI or AD based on the NINCDS-ADRDA criteria. MRI scans were acquired using a 3T MRI scanner. The hippocampus was manually traced using the FreeSurfer software. The hippocampal volume was automatically calculated using the software. The volume was compared to the healthy controls to determine if there were significant differences in HV.

Results
No significant differences were observed in the hippocampus volumes of MCI and AD patients compared to the healthy controls. The results were consistent with previous studies that have used MRI volumetric analysis to evaluate hippocampus volume and cognitive impairment.

Conclusions
A simple clinical tool to measure hippocampus volume could be determined using MRI. The results show that hippocampus volume is a useful biomarker for clinical diagnosis and prediction of AD.

“Utility of Amyloid Neuroimaging in Clinical Practice”

Patricio Chrem Méndez, Gabriela Cohen, Julieta Russo, Marcos Fernández Suarez, Jorge Campos, Griselda Russo, Janus Kremer, Alejandra Amengual, Silvia Vázquez, Ramón Leiguarda, Gustavo Sevlever and Ricardo F. Allegri

Aging and Memory Center, (FLENI)
Buenos Aires, Argentina
POSTER in AAIC>14
Alzheimer’s Imaging Consortium (AIC) pre-conference

1. Discrepancy between PiB amyloid imaging in typical and atypical clinical diagnosis. *(nº: IC-P-005)*

Argentine – ADNI
2011-2014

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Creation of the Argentina-Alzheimer’s Disease Neuroimaging Initiative

María Julieta Russo\textsuperscript{a,b,c}, Deborah Gustafson\textsuperscript{b,c}, Silvia Vázquez\textsuperscript{a}, Ezequiel Surace\textsuperscript{a}, Salvador Guinjoan\textsuperscript{a}, Ricardo F. Allegrì\textsuperscript{a}, Gustavo Sevlever\textsuperscript{a}, members of the Argentina-Alzheimer’s Disease Neuroimaging Initiative\textsuperscript{a}

\textsuperscript{a}Aging and Memory Center, Instituto de Investigaciones Neurológicas Rafael Carrera (FLENI), Buenos Aires, Argentina
\textsuperscript{b}Department of Neurology, State University of New York Downstate Medical Center, Brooklyn, NY, USA, Neuropsychiatric Epidemiology Unit
\textsuperscript{c}Institute for Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

Table 1
Neurocognitive assessments for the Argentina-Alzheimer’s Disease Neuroimaging Initiative

<table>
<thead>
<tr>
<th>Screening visit</th>
<th>Baseline visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Hachinski Score \textsuperscript{[7]}</td>
<td>Alzheimer’s Disease Assessment Scale Cognitive Subscale \textsuperscript{[12]}</td>
</tr>
<tr>
<td>Mini-Mental State Examination Test \textsuperscript{[8]}</td>
<td>Boston Naming Test \textsuperscript{[13]}</td>
</tr>
<tr>
<td>Logical Memory I and II (Delayed Paragraph Recall) \textsuperscript{[9]}</td>
<td>Categorical and Phonological Fluency Test \textsuperscript{[14]}</td>
</tr>
<tr>
<td>Spanish Geriatric Depression Scale \textsuperscript{[10]}</td>
<td>Clock Drawing Test \textsuperscript{[16]}</td>
</tr>
<tr>
<td>Clinical Dementia Rating \textsuperscript{[11]}</td>
<td>Digit Span Test \textsuperscript{[16]}</td>
</tr>
</tbody>
</table>

Table 2
Demographic, neuropsychological, and CSF characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control, mean $\pm$ SD</th>
<th>EMCI, mean $\pm$ SD</th>
<th>LMCI, mean $\pm$ SD</th>
<th>AD, dementia, mean $\pm$ SD</th>
<th>ANOVA</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.38 $\pm$ 4.1</td>
<td>67.09 $\pm$ 6.4</td>
<td>73.13 $\pm$ 7.2</td>
<td>77.00 $\pm$ 4.7</td>
<td>8.275</td>
<td>.000</td>
</tr>
<tr>
<td>Female, $%$</td>
<td>60</td>
<td>40</td>
<td>58.3</td>
<td>50</td>
<td>21.78 $\pm$ 2.9</td>
<td>21.576</td>
</tr>
<tr>
<td>MMSE score, pt</td>
<td>29.90 $\pm$ 0.316</td>
<td>28.87 $\pm$ 1.9</td>
<td>27.64 $\pm$ 1.7</td>
<td>21.78 $\pm$ 2.9</td>
<td>21.576</td>
<td>.000</td>
</tr>
<tr>
<td>GDS</td>
<td>1.70 $\pm$ 1.7</td>
<td>2.07 $\pm$ 1.9</td>
<td>2.13 $\pm$ 1.8</td>
<td>2.10 $\pm$ 1.0</td>
<td>0.00 $\pm$ 0.00</td>
<td>12.145</td>
</tr>
<tr>
<td>WMST-III Delay</td>
<td>8.00 $\pm$ 1.9</td>
<td>6.0 $\pm$ 1.9</td>
<td>2.09 $\pm$ 2.5</td>
<td>2.00 $\pm$ 0.00</td>
<td>12.145</td>
<td>.000</td>
</tr>
<tr>
<td>Boston Test</td>
<td>28.11 $\pm$ 3.3</td>
<td>26.29 $\pm$ 2.9</td>
<td>24.00 $\pm$ 3.6</td>
<td>22.17 $\pm$ 4.8</td>
<td>2.381</td>
<td>.093</td>
</tr>
<tr>
<td>Categorical VFT</td>
<td>22.50 $\pm$ 3.3</td>
<td>18.85 $\pm$ 2.9</td>
<td>17.30 $\pm$ 3.6</td>
<td>11.83 $\pm$ 4.8</td>
<td>11.615</td>
<td>.000</td>
</tr>
<tr>
<td>Letter VFT</td>
<td>18.80 $\pm$ 3.3</td>
<td>15.75 $\pm$ 6.6</td>
<td>15.40 $\pm$ 5.4</td>
<td>13.40 $\pm$ 5.4</td>
<td>1.309</td>
<td>.208</td>
</tr>
<tr>
<td>RAVLT-Delay</td>
<td>8.60 $\pm$ 2.5</td>
<td>4.62 $\pm$ 2.9</td>
<td>2.56 $\pm$ 2.0</td>
<td>1.00 $\pm$ 2.4</td>
<td>14.078</td>
<td>.000</td>
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<tr>
<td>RAVLT-Reocg</td>
<td>7.70 $\pm$ 6.6</td>
<td>7.62 $\pm$ 5.0</td>
<td>4.67 $\pm$ 4.7</td>
<td>5.50 $\pm$ 4.9</td>
<td>0.746</td>
<td>.532</td>
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<tr>
<td>CSI Biomarkers, n</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>48.95 $\pm$ 48.8</td>
<td>2.323</td>
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<tr>
<td>p-Tau</td>
<td>75.89 $\pm$ 210</td>
<td>94.72 $\pm$ 352</td>
<td>457.3 $\pm$ 488</td>
<td>678.9 $\pm$ 483</td>
<td>2.323</td>
<td>.130</td>
</tr>
<tr>
<td>ADCS-CIR profile</td>
<td>1.5 $\pm$ 0.3</td>
<td>2.09 $\pm$ 1.09</td>
<td>0.48 $\pm$ 0.08</td>
<td>1.7 $\pm$ 1.4</td>
<td>3.242</td>
<td>.054</td>
</tr>
</tbody>
</table>

Abbreviations: CSI, cerebrospinal fluid; SD, standard deviation; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer’s disease; ANOVA, analysis of variance; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; WMST, Wechsler Memory Scale III delayed; VFT, Verbal Fluency Test; RAVLT, Rey Auditory Verbal Learning Test delay recall trial; RAVLT-Reocg, RAVLT recognition trial; TAU, phosphorylated tau.
Table 1. Results

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mild Cognitive Impairment</th>
<th></th>
<th>Frontotemporal Dementia, n = 3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Progressed to AD, n = 5</td>
<td>Did Not Progress to AD, n = 5</td>
<td>AD, n = 7</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>P-Value</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Amyloid-beta 42, pg/mL</td>
<td>275 ± 88</td>
<td>.65</td>
<td>443.6 ± 65.8</td>
</tr>
<tr>
<td>Total tau, pg/mL</td>
<td>304 ± 242</td>
<td>.21</td>
<td>358.6 ± 218</td>
</tr>
<tr>
<td>Hyperphosphorylated tau, pg/mL</td>
<td>66.2 ± 52.1</td>
<td>.30</td>
<td>42.8 ± 18.3</td>
</tr>
<tr>
<td>Amyloid-beta 42/hyperphosphorylated tau</td>
<td>12.7 ± 12.8</td>
<td>.11</td>
<td>11.8 ± 5.7</td>
</tr>
<tr>
<td>Cerebrospinal fluid biomarkers for AD profile</td>
<td>0.68 ± 0.41</td>
<td>.02</td>
<td>0.75 ± 0.32</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; SD = standard deviation.

points for the group with AD, and 22 for the group with FTD. CDR was 0.5 for the group with MCI and 1 for the other groups. RAVLT mean results were 31 points for the group with MCI, 20 for the group with AD, and 15 for the group with FTD.

Aβ42, t-tau, and p-tau were quantified in CSF using an enzyme-linked immunosorbent assay. Ratios of Aβ42 to p-tau and CSF AD profile (Aβ42/(240 + [1.18 × t-tau])) were calculated. (A CSF ratio <1.3 was considered suggestive of AD pathology.) The Mann-Whitney one-tailed test was used to determine the difference between groups.

Mean clinical follow-up was 4.7 years (range 1–8 years). As expected, functional status and overall cognitive tests deteriorated over time for individuals with AD and FTD. CDR was 2 for the groups with AD and FTD. For the group with MCI, participants were classified based on clinical and cognitive evolution into a group that progressed to AD (n = 5), with a mean MMSE score of 24 and CDR of 1, and a group that did not (n = 5), with MMSE and CDR scores that did not change from baseline.

The mean value of biomarkers and the ratios were not significantly different in the three main groups (AD, MCI, FTD) because of the high dispersion observed in the MCI group. There were significant differences between the conclusions of this study should be taken cautiously because of the small sample size and lack of confirmatory pathological examination, but active patient recruitment is underway to strengthen these observations. Overall, this first AD biomarker study in Latin America supports that combined analysis of all three core AD biomarkers represent a powerful tool in clinical setting.

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Elisa Smyth, PhD
Griselda Russo, MD
Alejandra Amengual, MD
Ricardo Allegri, MD
Ramón Leiguarda, MD
Gustavo Sevlever, MD
Jorge Campos, MD

Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Instituto de Investigaciones Neurológicas Raúl Carrea, Buenos Aires, Argentina
Utilidad de la neuroimagen amiloidea en Neurología asistencial


Hasta la fecha, en el Instituto FLENI se han realizado 100 estudios con $^{11}$C-PiB-PET, en colaboración con el Instituto Kremer de Córdoba y una parte de ellos en el marco de estudio de Alzheimer Disease Neuroimaging Initiative Argentina (ADNI Arg).

<table>
<thead>
<tr>
<th>Tabla 2 – Características demográficas basales de la muestra de estudio</th>
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<tbody>
<tr>
<td>Categoría diagnóstica</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Controles</td>
</tr>
<tr>
<td>DCL amnésico</td>
</tr>
<tr>
<td>DCL amnésico plus</td>
</tr>
<tr>
<td>DCL no amnésico</td>
</tr>
<tr>
<td>DTA</td>
</tr>
<tr>
<td>DPT</td>
</tr>
<tr>
<td>APP</td>
</tr>
<tr>
<td>ACP</td>
</tr>
<tr>
<td>DCB</td>
</tr>
<tr>
<td>Angiopatía amiloide</td>
</tr>
<tr>
<td>Demencia mixta</td>
</tr>
</tbody>
</table>

ACP: atrofia cortical posterior; APP: ataxia primaria progresiva; DCB: degeneración cortico basal; DCL: deterioro cognitivo leve; DFT: demencia frontotemporal; DTA: demencia tipo Alzheimer.

Figura 1 – Comparación de participantes con marcación con $^{11}$C-PiB-PET según probabilidad diagnóstica pretest de patología de enfermedad de Alzheimer.
Familial Dementia With Frontotemporal Features Associated With M146V Presenilin-1 Mutation

Miguel A. Riudavets¹; Leonardo Bartoloni³; Juan C. Troncoso⁴; Olga Pletnikova⁴; Peter St. George-Hyslop⁵; Marcelo Schultz¹; Gustavo Sevlever¹; Ricardo F. Allegri²

¹ Department of Neuropathology, FLENI. Buenos Aires, Argentina.
² Department of Neurology, FLENI. Buenos Aires, Argentina.
³ Department of Neuropathology, University of Buenos Aires. Buenos Aires, Argentina.
⁴ Neuropathology, FLENI. Buenos Aires, Argentina.
⁵ Tanz Center for Research, University of Chicago, Chicago, IL, USA.
Papers submitted

1. Concordance between C\textsuperscript{11}-PiB amyloid imaging and clinical diagnosis in a memory clinic. *American Journal of Alzheimer’s Disease and other Dementias.*


3. Hippocampal atrophy. Automated volumetry vs visual examination: an ARG ADNI cohort analysis
Argentine – ADNI
2011-2014

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Future Tasks

Arg-DIAN (Dominantly Inherited Alzheimer Network)

- National grant application (CONICET) June 2014
- to study an Argentine DIAN cohort of 40 participants.

- Start-up October 2014
Future Tasks

**Arg-ADNI 2\textsuperscript{nd} Cohort (Argentine Multicenter Study)**

- National grant application (2015-2018)
- to study larger Argentina ADNI 2 cohort of 180pts
- involving at least 8 new sites (AD Centers).

**Buenos Aires**
- 1.- FLENI
- 2.- Hospital Zubizarreta (GCBA)
- 3.- INEBA
- 4.- Hospital Fernandez (GCBA)
- 5.- Hospital Borda (GCBA)

**La Plata**
- 6.- Instituto Neuropsiquiátrico Luria

**Córdoba**
- 7.- CEMA

**Mar del Plata**
- 8.- Instituto Neuropsiquiátrico Kremer

**Mendoza**
- 9.- Univ. Mendoza
Thank you
ADNI Argentina