Arg-ADNI

Gustavo E. Sevlever, Silvia Vázquez, Deborah R. Gustafson,
Salvador M. Guinjoan, Ricardo F. Allegri(*)
and Arg-ADNI group.

Memory and Aging Center

Institute for Neurological Research (FLENI)

Buenos Aires, Argentina

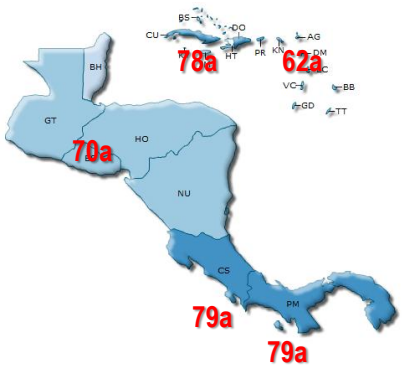
WW-ADNI update: Copenhagen, July 11, 2014

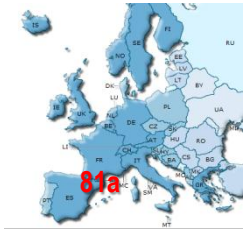
*speaker

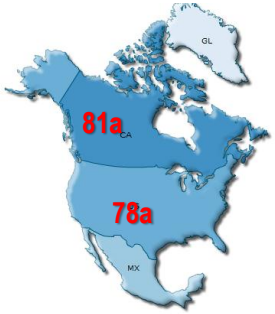
Argentine – ADNI
2011-2014

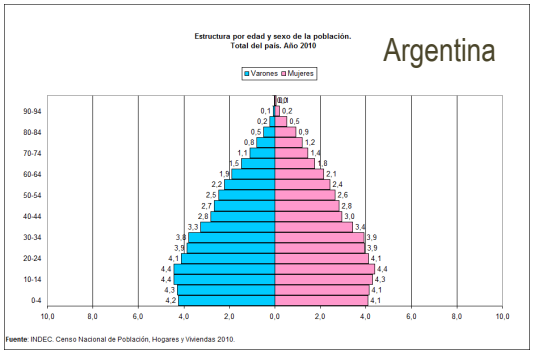
1. Background
2. Work-Plan
3. Results
4. AAIC and other meetings
5. Publications
6. New Projects

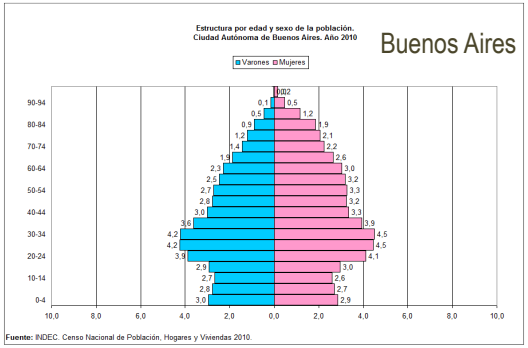
Worldwide Life Expectancy











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World Wide Alzheimer's Disease Neuroimaging Initiative

About WW-ADNI

North American ADNI

European ADNI

Japan ADNI

Australian ADNI

Taiwan ADNI

Korea ADNI

China ADNI

Argentina ADNI

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

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Argentine – ADNI
2011-2014

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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

Management Committee

Sevlever G, Allegri RF, Guinjoan S, Gustafson D, Vazquez S.

Clinical Stream

Neurologists

Ricardo Allegri (*)
Jorge Campos
Alejandra Amengual
Gabriela Cohen
Marcos Fernández Suárez
Patricio Chrem
Julieta Russo

Psychiatrists

Salvador Guinjoan
Griselda Russo
Pablo Bagnati
Lucas Drucaroff

Neuropsychologists

Liliana Sabe
María Eugenia Martín
Florencia Clarens
Lucía Crivelli
Paula Harris

Neuroimaging Stream

Silvia Vazquez S (*)
Esteban Obenaus
German Falasco
Leandro Urrutia
Fernando Ventrice

Laboratory Stream

Gustavo Sevlever (*)
Horacio Martinetto
Ezequiel Surace
Miguel Riudavetz

Epidemiological Stream

Deb Gustafson (*)

(*) Stream Chair

Arg-ADNI

1st Cohort (FLENI)

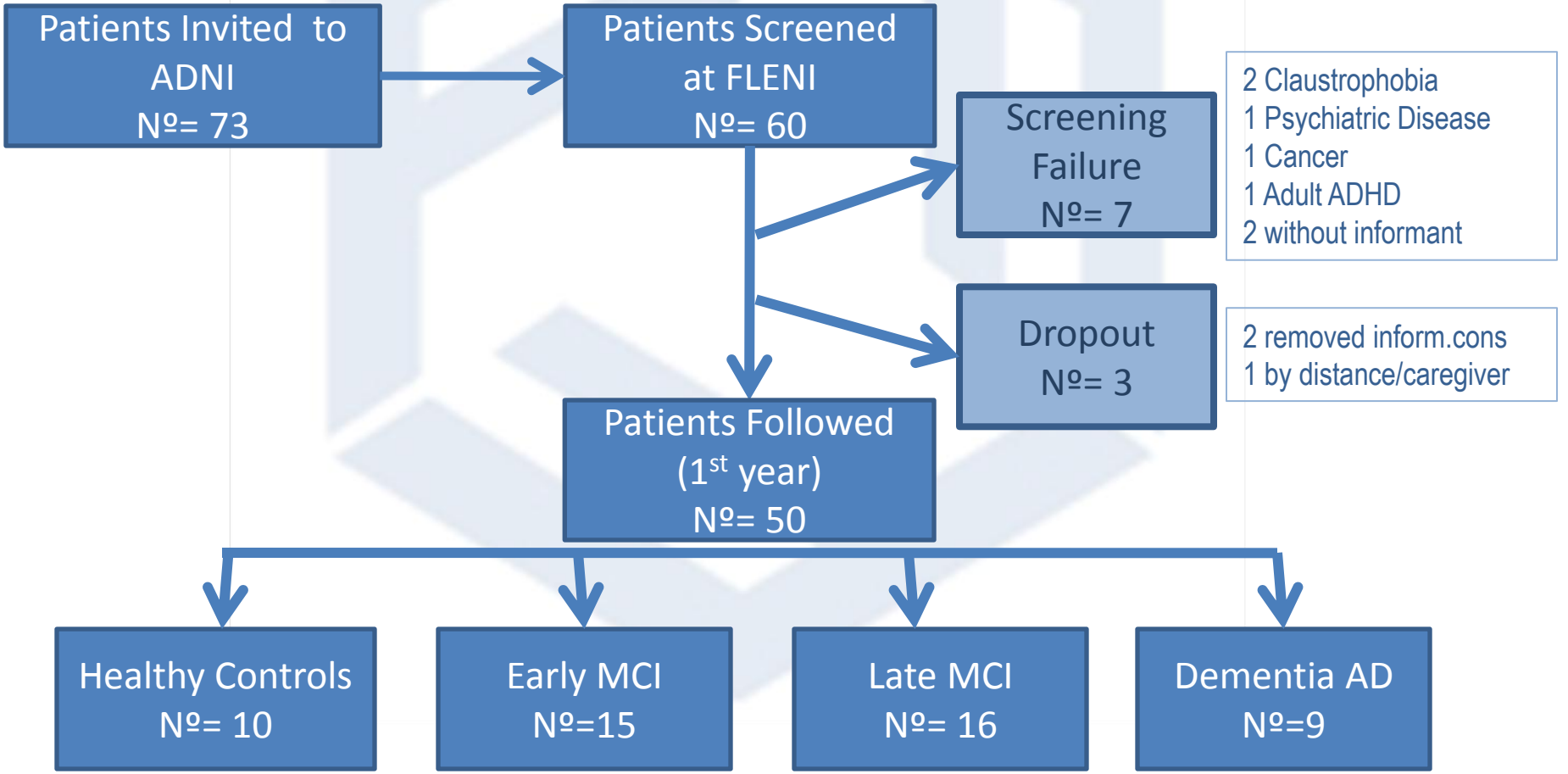
Study Timelines

1. **Recruitment: 24 months**
2. **Follow-up: 24 months**

Arg-ADNI

1st Cohort (FLENI)

Patients' Flowchart



Arg-ADNI

1st Cohort (FLENI)

Table 1: Demographic Data

	Healthy Controls	Early MCI	Late MCI	Dementia AD
	10	**15**	**16**	**9**
Age (years)	68	70	75	75
Education (years)	14	12.9	13.6	12.1
Sex (%fem)	70%	40%	68.8%	44.4%
MMSE	30	28.9	27.1	21.4

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

Argentine – ADNI
2011-2014

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Arg-ADNI

1st Cohort (FLENI)

Results

Baseline → Follow-up

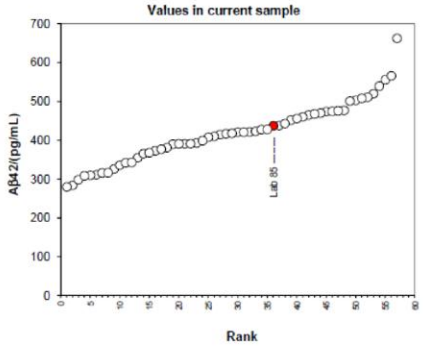
	Total Nº	NPS Ass	MRI	CSF Aβ-tau	PET FDG	PET PiB	Follow-up 1 year	Follow-up 2 year
Healthy Controls	10	10	10	7	10	9	6	
Early MCI	15	15	15	12	15	12	8	
Late MCI	16	16	16	11	15	13	7	
Dementia AD	9	9	9	8	9	9	2	
TOTAL	**50**	**50**	**50**	**38 (76%)**	**49 (98%)**	**43 (86%)**	**23**	

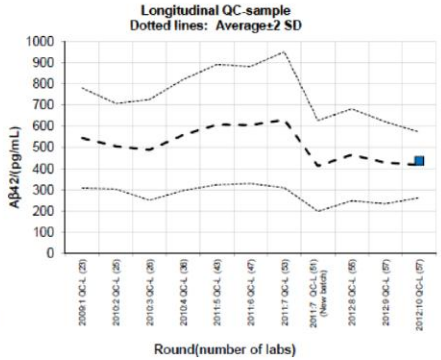
Alzheimer's Association QC program for CSF

Aβ42

Longitudinal evaluations

	Buenos Aires (Lab 85)		All 57 labs in this round
Round:	2012:10QC-L	Mean:	418 pg/mL
Result:	437 pg/mL	SD:	77 pg/mL
Method:	INNOTEST	CV:	18,5%



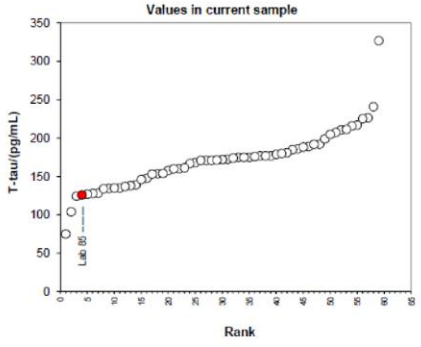


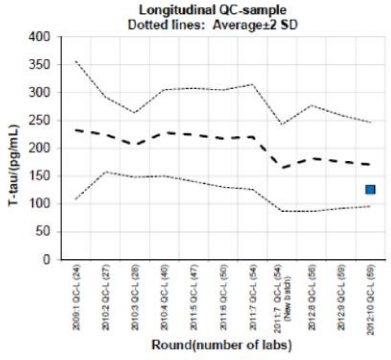
Alzheimer's Association QC program for CSF

T-tau

Longitudinal evaluations

	Buenos Aires (Lab 85)		All 59 labs in this round
Round:	2012:10QC-L	Mean:	171 pg/mL
Result:	126 pg/mL	SD:	38 pg/mL
Method:	INNOTEST	CV:	22,1%



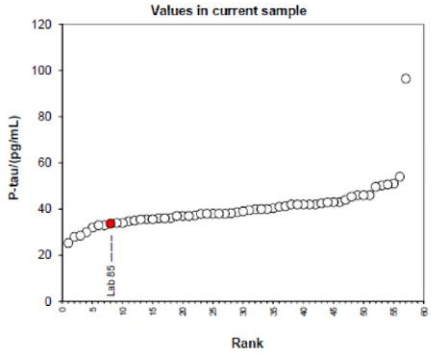


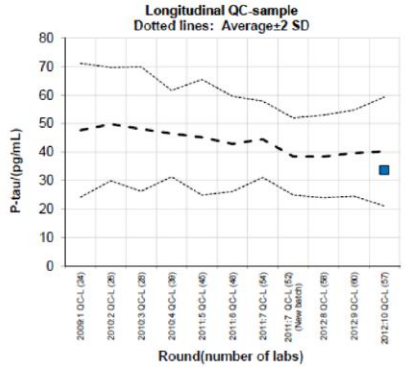
Alzheimer's Association QC program for CSF

P-tau

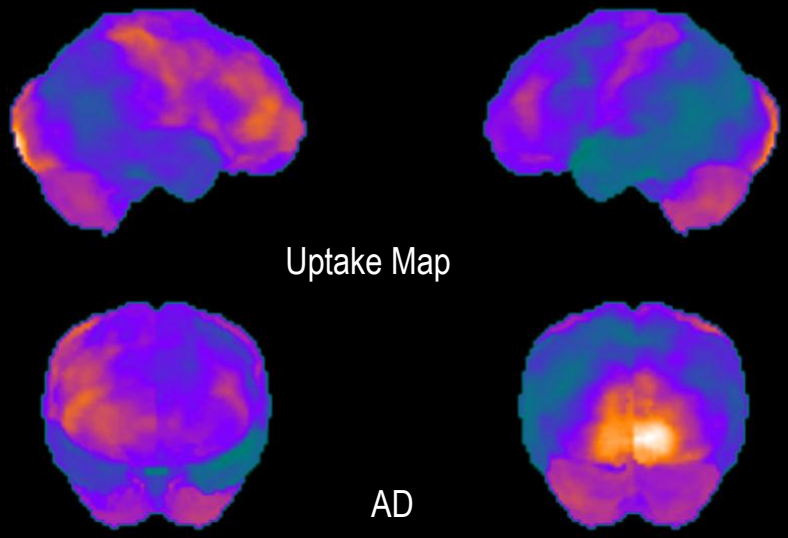
Longitudinal evaluations

	Buenos Aires (Lab 85)		All 57 labs in this round
Round:	2012:10QC-L	Mean:	40 pg/mL
Result:	34 pg/mL	SD:	10 pg/mL
Method:	INNOTEST	CV:	23,7%



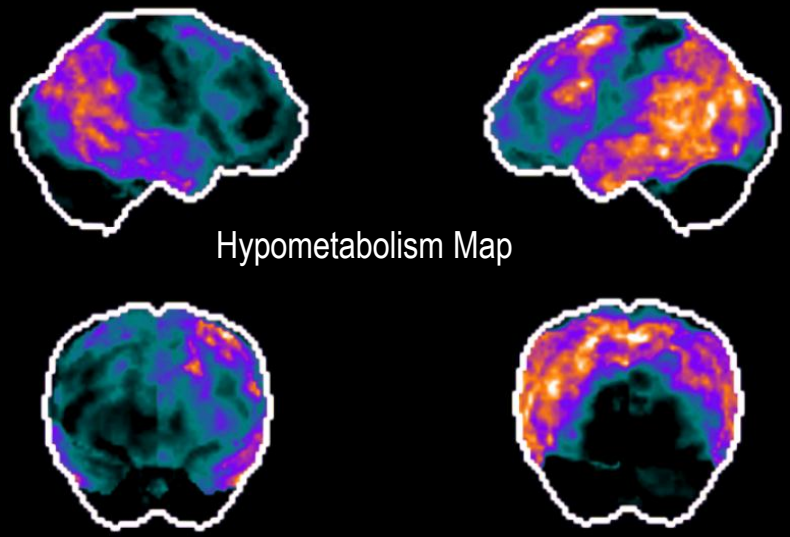


Brain ^{18}FDG PET scan



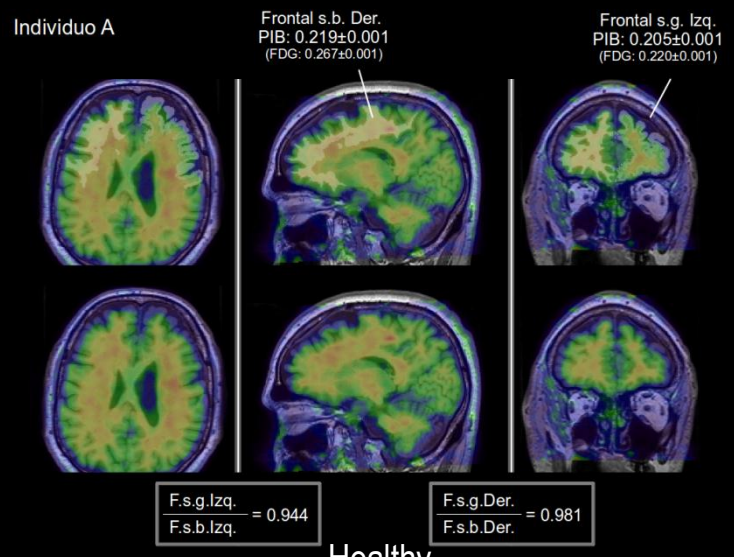
Uptake Map

AD

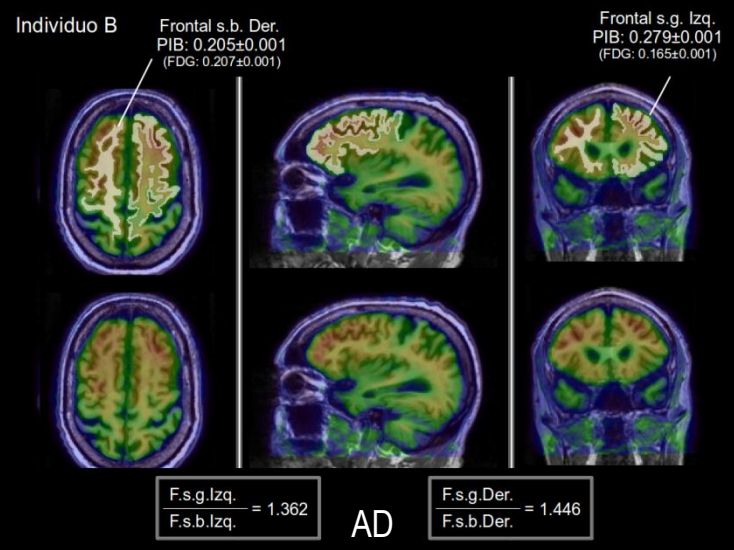


Hypometabolism Map

Brain ^{11}C-PiB PET scan



Healthy



AD

Arg-ADNI

1st Cohort (FLENI)

Results

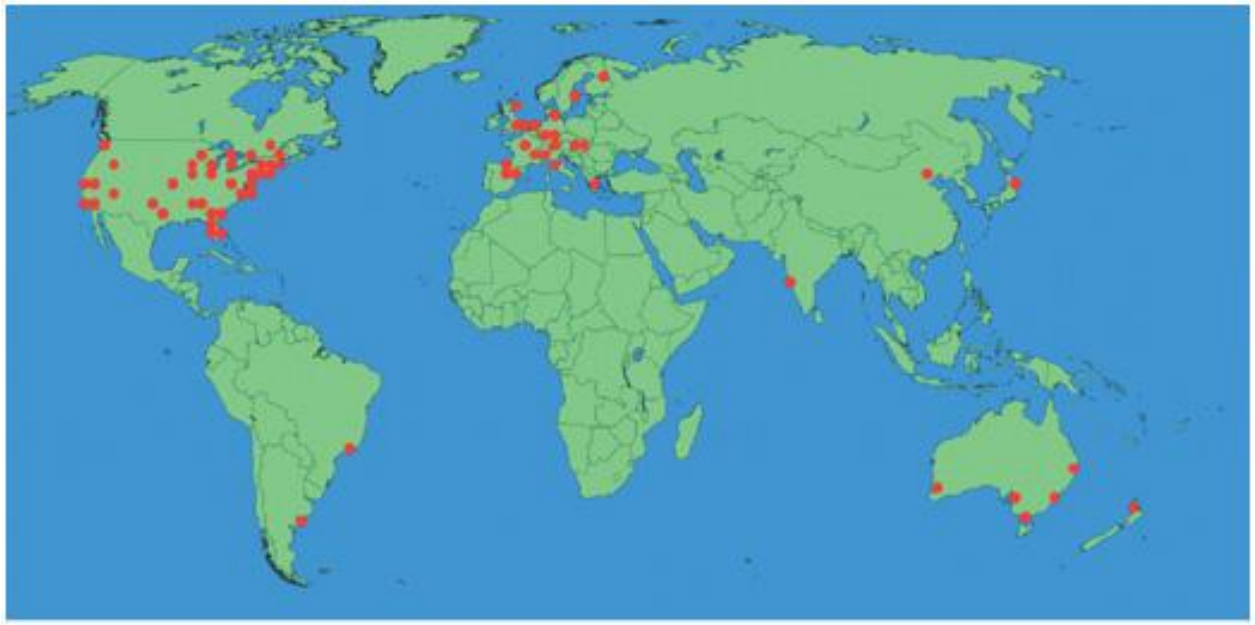
Table 3: PET Scanning as of June 2014

	FDG-PET Normal	FDG-PET Pathol	PiB-PET Negative	PiB-PET Possitive
Healthy Control s	5	5	10	0
Early MCI	2	9	5	3
Late MCI	3	11	4	8
Dementia AD	0	9	1	8
Total	10	34	20	19

Brain Bank.

FLENI houses the only brain bank in Argentina.

ADNI participants are being asked to consent brain donation at the time of death.



Nature Reviews | Neuroscience

BACE

Banco de Cerebros

Brain banking: opportunities, challenges and meaning for the future

Kretzschmar

Nature Reviews Neuroscience 10, 70-78 (January 2009)

Argentine – ADNI
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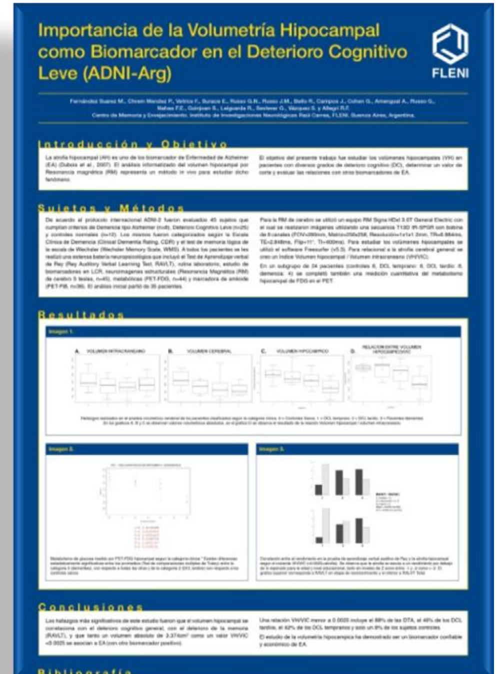
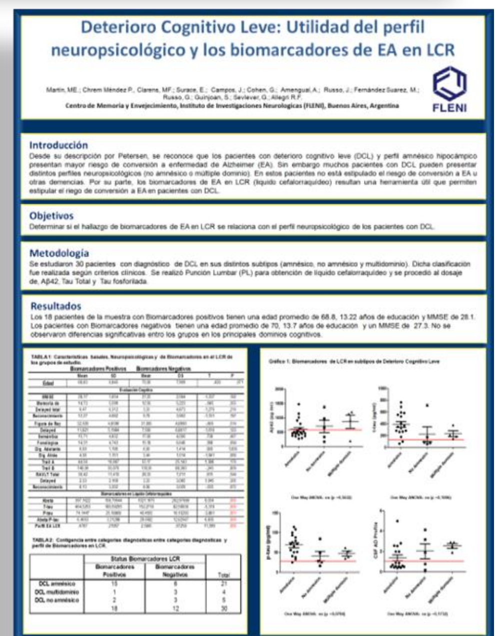
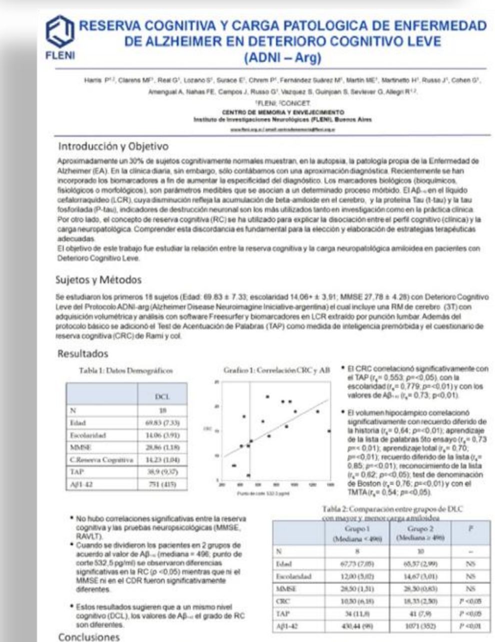
AÑOS
Congreso Argentino
de Neurología
20 al 23 de Noviembre de 2013
Mar del Plata • Hotel Sheraton


Importancia de la Volumetría Hipocampal como Biomarcador en el Deterioro Cognitivo Leve (ADNI-Arg)
FLENI
Introducción y Objetivo
Sujetos y Métodos
Resultados
Conclusiones
Bibliografía


Índice de Discriminabilidad en Memoria de Reconocimiento en pacientes con Deterioro Cognitivo Leve tipo amnésico (World Wide-ADNI)
FLENI

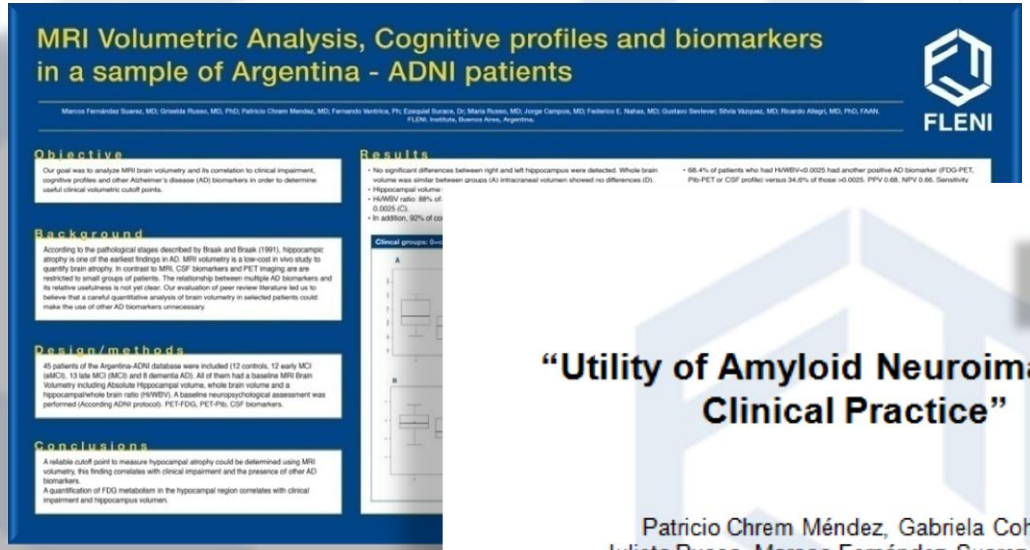

Iniciativa de Neuroimágenes en Enfermedad de Alzheimer en Argentina (ADNI-Arg): Experiencia y hallazgos iniciales
FLENI
Introducción
Métodos
Resultados
Conclusiones


Deterioro Cognitivo Leve: Utilidad del perfil neuropsicológico y los biomarcadores de EA en LCR
FLENI
Introducción
Objetivos
Metodología
Resultados


RESERVA COGNITIVA Y CARGA PATOLOGICA DE ENFERMEDAD DE ALZHEIMER EN DETERIORO COGNITIVO LEVE (ADNI – Arg)
FLENI
Introducción y Objetivo
Sujetos y Métodos
Resultados
Conclusiones

April 2014

AMERICAN ACADEMY OF NEUROLOGY



MRI Volumetric Analysis, Cognitive profiles and biomarkers in a sample of Argentina - ADNI patients

FLENI

Objective

Background

Design/methods

Conclusions

Results

AMERICAN ACADEMY OF NEUROLOGY

"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

FLENI

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)***

2. Hippocampal atrophy. Automated volumetry vs visual examination: Arg-ADNI cohort analysis ***(nº: IC-P-006)***

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ELSEVIER

Alzheimer's & Dementia 10 (2014) S84–S87

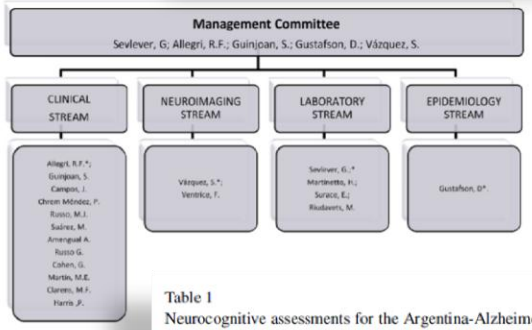
Alzheimer's & Dementia

Research News

Creation of the Argentina-Alzheimer's Disease Neuroimaging Initiative

María Julieta Russo[a,*], Deborah Gustafson[b,c], Silvia Vázquez[a], Ezequiel Surace[a], Salvador Guinjoan[a], Ricardo F. Allegri[a], Gustavo Sevlever[a], members of the Argentina-Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Aging and Memory Center, Instituto de Investigaciones Neurológicas Raúl Carrea (FLENI), Buenos Aires, Argentina*
[b]*Department of Neurology, State University of New York-Downstate Medical Center, Brooklyn, NY, USA. Neuropsychiatric Epidemiology Unit*
[c]*Institute for Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden*



* Stream Chair.

Argentina-ADNI, Argentina-

Fig. 1. Structural organization of

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

Screening visit
Modified Hachinski Score [7]
Mini-Mental State Examination Test [8]
Logical Memory I and II (Delayed Paragraph Recall) [9]
Spanish Geriatric Depression Scale [10]
Clinical Dementia Rating [11]
Baseline visit
Alzheimer's Disease Assessment Scale Cognitive Subscale [12]
Boston Naming Test [13]
Categorical and Phonological Fluency Test [14]
Clock Drawing Test [16]
Digit Span Test [16]
Rey Auditory Verbal Learning Test [17]
Trail Making Test, parts A and B [18]
Digit Symbol Substitution Test [16]
Functional Activities Questionnaire [19]
Neuropsychiatric Inventory Q [20]
Scale of Cognitive Reserve [21]

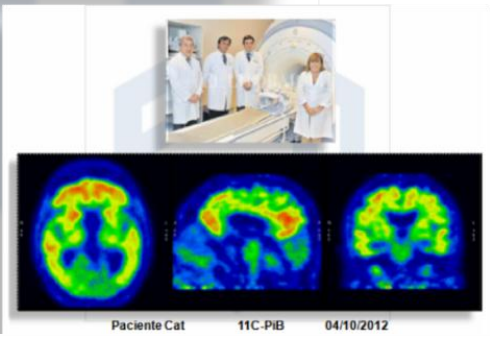


Table 2
Demographic, neuropsychological, and CSF characteristics at baseline

Characteristic	Control, mean ± SD	EMCI, mean ± SD	LMCI, mean ± SD	AD dementia, mean ± SD	ANOVA	*P* value
Age, y	62.38 ± 4.1	67.09 ± 6.1	73.13 ± 7.2	77.00 ± 4.7	8.275	.000
Female, %	60	40	58.3	50		
MMSE score, pt	29.90 ± 0.316	28.87 ± 1.9	27.64 ± 1.7	21.75 ± 2.9	21.576	.000
GDS	1.70 ± 1.7	2.07 ± 1.9	1.73 ± 1.8	1.20 ± 1.0	0.309	.819
WMS III-Delay	8.00 ± 1.9	6.0 ± 1.9	2.09 ± 2.5	0.00 ± 0.00	12.145	.000
Boston Test	28.11 ± 3.3	26.29 ± 2.9	23.40 ± 3.6	22.17 ± 4.8	2.311	.093
Categorical VFT	22.50 ± 3.3	18.85 ± 2.9	17.30 ± 3.6	11.83 ± 4.8	11.615	.000
Letter VFT	18.80 ± 3.8	15.75 ± 6.6	15.40 ± 5.0	13.40 ± 5.4	1.309	.288
RAVLT-Delay	8.60 ± 2.5	4.62 ± 2.9	2.56 ± 2.0	1.00 ± 2.4	14.078	.000
RAVLT-Recog	7.70 ± 6.6	7.62 ± 5.0	4.67 ± 4.7	5.50 ± 4.9	0.746	.532
CSF biomarkers, n	4	8	4	2		
Aβ1–42	758.9 ± 210	943.7 ± 375.2	457.3 ± 48.8	678.9 ± 482.3	2.232	.130
p-Tau	40.3 ± 7.9	45.3 ± 15.1	95 ± 17.5	26.6 ± 2.3	16.420	.000
Tau	213.2 ± 44	205.1 ± 116.9	597.9 ± 67.7	137 ± 52.3	20.036	.000
AD CSF profile	1.5 ± 0.5	2.09 ± 1.09	0.48 ± 0.08	1.7 ± 1.4	3.242	.054

Abbreviations: CSF, 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 [9]; GDS, Geriatric Depression Scale [11]; WMS III-Delay, Wechsler Memory Scale III delayed [10]; VFT, Verbal Fluency Test [15]; RAVLT-Delay, Rey Auditory Verbal Learning Test delay recall trial; RAVLT-Recog, RAVLT recognition trial (trial VIII) [18]; Aβ, amyloid-β; p-Tau, phosphorylated tau.

Table 1. Results

	Mild Cognitive Impairment			AD, n = 7	Frontotemporal Dementia, n = 3
	Progressed to AD, n = 5	Did Not Progress to AD, n = 5			
Marker	Mean ± SD		*P*-Value	Mean ± SD	
Amyloid-beta 42, pg/mL	355 ± 88	800 ± 345	.02	443.6 ± 65.8	855 ± 270
Total tau, pg/mL	304 ± 242	189.6 ± 113	.21	358.6 ± 218	108.3 ± 45
Hyperphosphorylated tau, pg/mL	66.2 ± 52.1	35.8 ± 18.5	.30	42.8	18.3
Amyloid- beta 42/hyperphosphorylated tau	12.7 ± 12.8	30.6 ± 22.1	.11	11.8 ± 5.7	48.5 ± 6.9
Cerebrospinal fluid biomarkers for AD profile	0.68 ± 0.41	1.9 ± 1.17	.02	0.75 ± 0.32	2.3 ± 0.50

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.

$A\beta_{42}$, t-tau, and p-tau were quantified in CSF using an enzyme-linked immunosorbent assay. Ratios of Aβ-42 to p-tau and CSF AD profile $(A\beta42/(240 + [1.18 \times \text{t-tau}]))$[10] 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 clusions 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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Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Instituto de Investigaciones Neurológicas Raúl Carrea, Buenos Aires, Argentina

NEUROL ARG. 2014;6(2):68–76

Neurología Argentina

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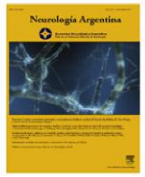
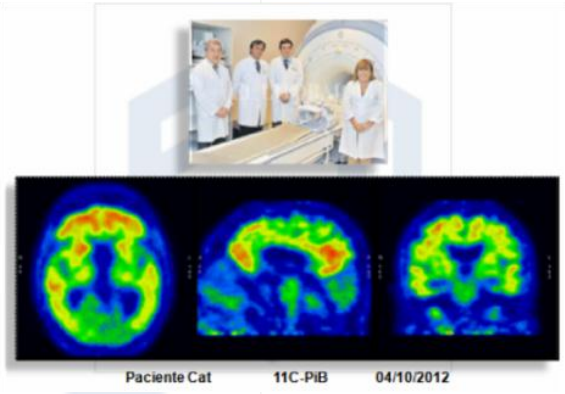


Artículo original

Utilidad de la neuroimagen amiloidea en Neurología asistencial

Patricio Chrem Méndez[a,*], *Gabriela Cohen*[b], *María Julieta Russo*[a], *Marcos Fernandez Suarez*[a], *Federico Nahas*[c], *Griselda Russo*[d], *Claudio R. Wierszylo*[e], *Santiago Paz*[f], *Leonardo Tabaschi*[f], *Jorge Campos*[g], *Alejandra Amengual*[g], *Janus Kremer*[h], *Salvador Guinjoan*[d], *Ramón Leiguarda*[i], *Gustavo Sevlever*[j], *Silvia Vázquez*[k] y *Ricardo Allegri*[l]



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 Iniciative* Argentina (ADNI Arg).

Tabla 2 – Características demográficas basales de la muestra de estudio

Categoría diagnóstica	n	Mujeres (n)	Edad, media ± DE	MMSE, media ± DE
Controles	12	7	63,9 ±8,7	29,9±0,3
DCL amnésico	29	13	70,0 ±7,3	27,8±2,1
DCL amnésico plus	7	6	71,0 ±8,4	27,5±2,1
DCL no amnésico	10	3	68,3 ±4,9	28,2±1,9
DTA	11	10	70,9 ±7,3	21,7±2,5
DFT	3	1	68,0±1,7	20,0±11,3
APP	9	8	65,8±10,4	24,5±2,5
ACP	3	0	62,6±14,8	22,5±12,7
DCB	1	1	70	24
Angiopatía amiloide	1	1	61	26
Demencia mixta	3	1	68,3 ±8,7	23

ACP: atrofia cortical posterior; APP: afasia primaria progresiva; DCB, degeneración corticobasal; DCL: deterioro cognitivo leve; DFT: demencia frontotemporal; DTA: demencia tipo Alzheimer.

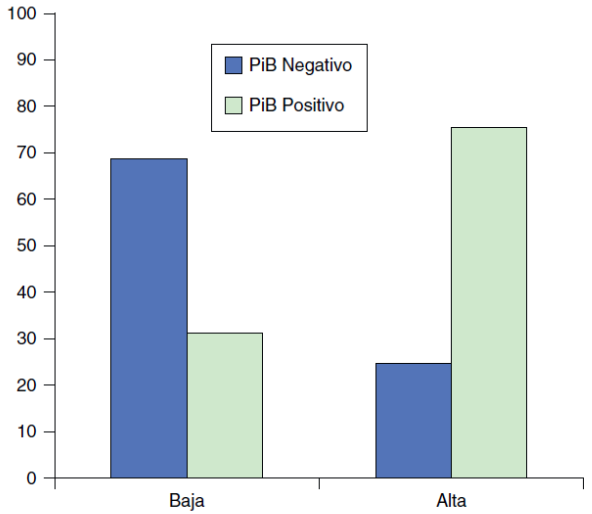


Figura 1 – Comparación de participantes con marcación con ^{11}C-PiB-PET según probabilidad diagnóstica pretest de patología de enfermedad de Alzheimer.

Brain Pathology ISSN 1015-6305

RESEARCH ARTICLE

Familial Dementia With Frontotemporal Features Associated With M146V Presenilin-1 Mutation

Miguel A. Riudavets[1*]; Leonardo Bartoloni[3*]; Juan C. Troncoso[4]; Olga Pletnikova[4]; Peter St. George-Hyslop[5]; Marcelo Schultz[1]; Gustavo Sevlever[1]; Ricardo F. Allegri[2]

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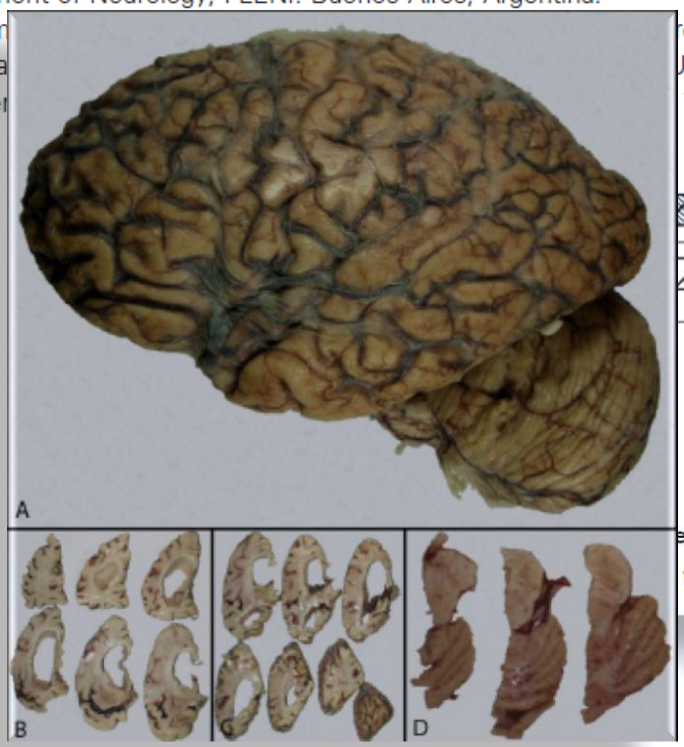

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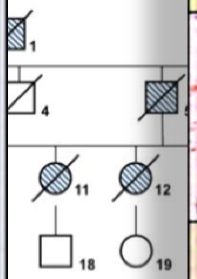

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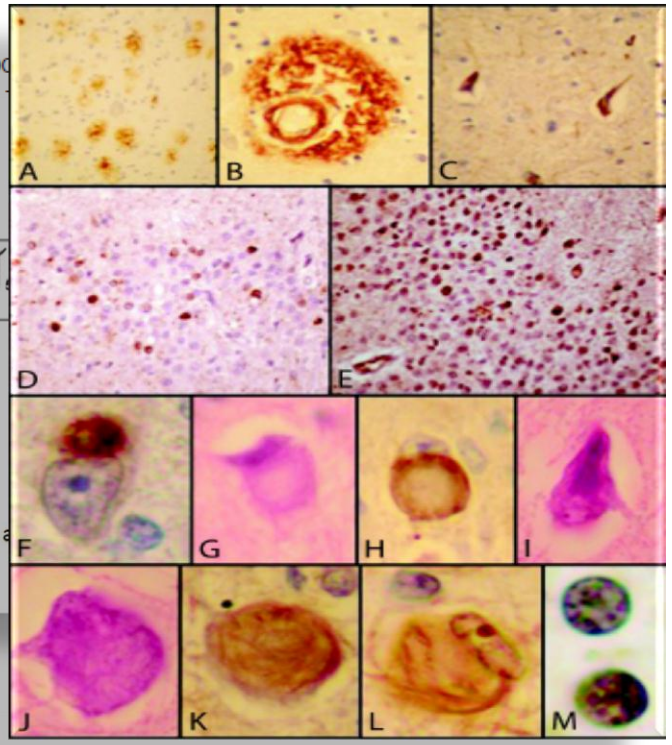


Papers submitted

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

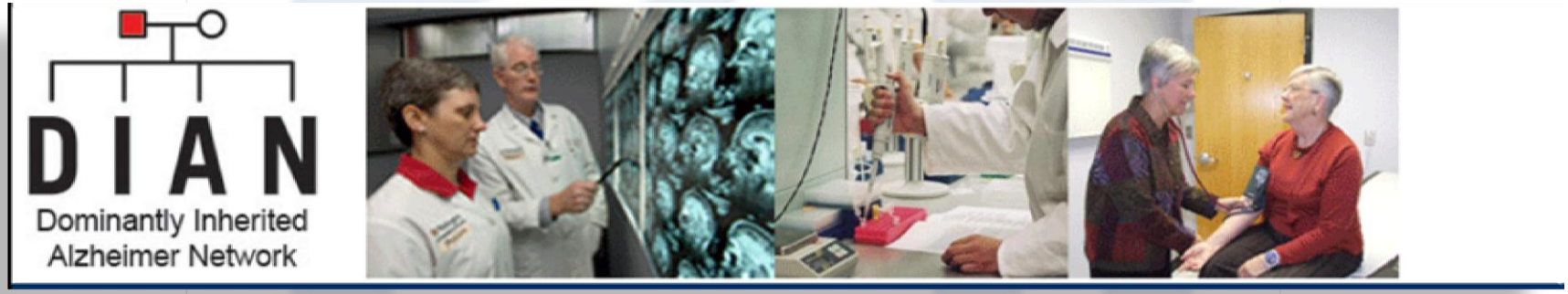
2. Discriminability and Response bias Indices in recognition memory performance in amnestic mild cognitive impairment and Alzheimer's disease. ***Alzheimer & Dementia***

3. Hippocampal atrophy. Automated volumetry vs visual examination: an ARG ADNI cohort analysis

Argentine – ADNI
2011-2014

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

Future Tasks



Arg-DIAN (Dominantly Inherited Alzheimer Network)

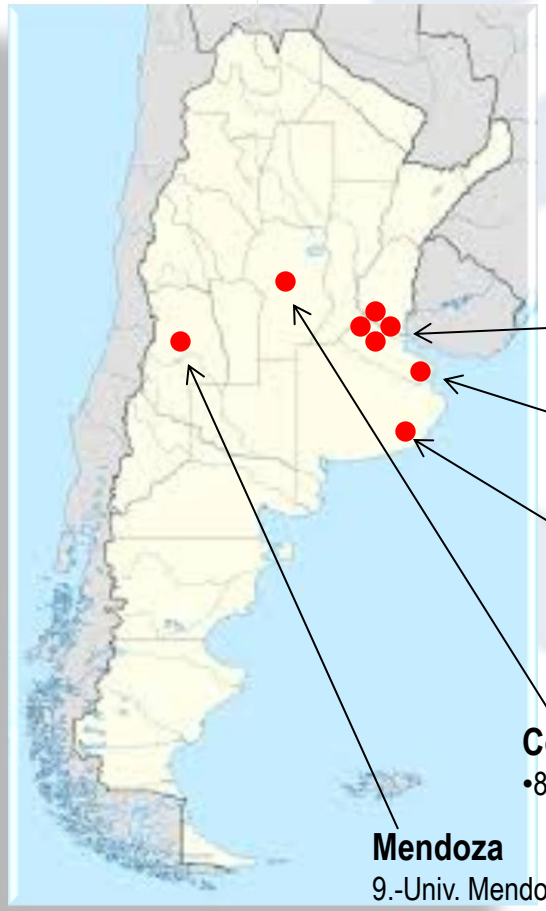
- National grant application (CONICET) June 2014
- to study an Argentine DIAN cohort of 40 participant.

- Start-up October 2014

Future Tasks

Arg-ADNI 2nd 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).



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Thank you
ADNI Argentina