Emerging β-amyloid pathology is associated with tau, synaptic, neurodegeneration and gray matter volume differences

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Disclosures

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JLM has served/serves as a consultant or at advisory boards for the following for-profit companies, or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, ProMIS Neurosciences. KB has served as a consultant or at advisory boards for Abcam, Axon, Biogen, Lilly, MagQu, Novartis and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. HZ has served at scientific advisory boards for Roche Diagnostics, CogRx, Samumed and Wave, and has given lectures in symposia sponsored by Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. MS is a full time employee of Roche Diagnostics International Ltd. GK is a full time employee of Roche Diagnostics GmbH. RB was a full time employee of Roche Diagnostics International Ltd. The remaining authors declare that they have no conflict of interest.

Sharing

The information included in this presentation may not be shared on other platforms.

Introduction

- Deposition of amyloid-beta (Aβ) is a continuous process happening years before AD symptom onset
- Using cut-offs for established pathology may impede detecting subjects with low Aβ pathological burden
- Individuals classified as Aβ -negative using typical Aβ PET thresholds may have 'subthreshold Aβ values' reflecting low Aβ pathological burden
- There is great interest in understanding the pathophysiological changes occurring in this population and trials targeting this population are underway

> The aim of this study is to describe if there are detectable differences in tau, synaptic, inflammatory, neurodegeneration CSF markers and brain structure in participants with low Aβ pathological burden

Methods: participants

- The initial and consecutive **318 participants of the ALFA+ cohort** with CSF and PET data available were included in this study.
- ALFA + is a cohort comprises middle aged (45 to 65 years) cognitively unimpaired individuals with increased risk for AD, hence located very early in the Alzheimer continuum.

alfa study ALZHEIMER FAMILIES **ALFA parent cohort**

- 2743 CU (45-75 yrs)
- High proportion of AD offspring
- Environmental & Lifestyle factors
- Clinical history, cognition
- GWAS
- Basic MRI

ALFA + (N=400)

- CSF sampling
- Advanced MRI
- PET/CT: A, T, FDG
- Follow-up every 3 y

Molinuevo et al. Alzheimers Dement 2016

Methods: participants

- We measured CSF Ab42, Ab40, t-tau, p-tau, neurogranin, GFAP, IL-6, YKL-40, sTREM2, NFL, S100B and α-synuclein[1].
- The above biomarkers measured are part of the NeuroToolKit. NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers marking some of the main pathologic events described in AD and other neurological disorders
- Abeta42, pTau, tTau, have an identical composition to the commercially available Elecsys® CE/IVD assays.
- Ab42/40 was used to define A+ with CSF, being the cut-off Ab42/40<0.071[2]
- Structural MRI, FDG and Flutemetamol PET were performed.
- PET images were scaled to SUVr using the whole cerebellum as reference region and Centiloid values were calculated.

1. Molinuevo et al. Alzheimers Dement 2016;
2. Milá-Alomá JAPD, 2020 in press

Elecsys® CSF assays are not approved for clinical use in the U.S.

Methods: participants

Low Aβ pathological burden, was defined as:

	Amyloid negative	Low Ab burden pathology	Amyloid positive
Model 1	CSF- and CL<20	**CSF+ and CL<40**	CSF+ and CL>40
Model 2	CL<20	**20-40 CL**	CL>40
Model 3	CSF- and VR-	**CSF+ and VR-**	CSF+ and VR+

Table 1. Amyloid groups definitions

Elecsys® CSF assays are not approved for clinical use in the U.S.

Methods

- We performed one-way analysis of variance (ANOVA) to assess differences in age, education and MMSE performance among the corresponding emerging amyloid pathology, amyloid negative and amyloid positive groups
- All CSF biomarker levels and neuroimaging variables were described and compared between groups using one-way analysis of covariance (ANCOVA), adjusting for the effect of age and sex. FDR multiple comparison correction following the Benjamini-Hochberg procedure
- All CSF biomarker levels and neuroimaging variables were described and compared between groups using one-way analysis of covariance (ANCOVA), adjusting for the effect of age and sex.

Results: demographics and CL values by groups

	MODEL 1				MODEL 2				MODEL 3			
	CSF- CL<20 (n=205, 64.5%)	**CSF+ CL<40** (n= 94, 29.6)	**CSF+ CL>40** (n=19, 6.0%)	***P*-Value**	**<20 CL** (n=281, 88.4%)	**20-40 CL** (n= 18, 5.7%)	**>40 CL** (n=19, 6.0%)	***P*-Value**	**CSF- VR-** (n=202, 64.5%)	**CSF+ VR-** (n= 72, 23.0%)	**CSF+ VR+** (n=39, 12.5%)	***P*-Value**
Age, years	60.5 (4.32)	61.5 (5.16)	65.5 (2.89)[1.2]	**<0.0001**	60.6 (4.61)	64.0 (3.53)[3]	65.5 (2.89)[1]	**<0.0001**	60.5 (4.34)	60.8 (5.23)	64.9 (3.41)[1.4]	**<0.0001**
Female, N (%)	133 (64.9)	53 (56.4)	13 (68.4)	0.32	175 (62.3)	11 (61.1)	13 (68.4)	0.86	131 (64.9)	40 (55.6)	24 (61.5)	0.37
Education, years	13.3 (3.43)	13.2 (3.47)	12.5 (3.99)	0.43	13.5 (3.42)	13.3 (3.85)	12.5 (3.99)	0.53	13.6 (3.40)	13.5 (3.30)	12.5 (3.89)	0.20
MMSE	29.1 (0.95)	29.2 (0.96)	29.1 (1.03)	0.51	29.2 (0.95)	29.2 (1.04)	29.1 (1.03)	0.90	29.1 (0.95)	29.3 (0.90)	29.0 (1.09)	0.25
***APOE ε4* carriers, N (%)**	85 (41.5)	73 (77.7)[1]	14 (73.7)[5]	**<0.0001**	145 (51.6)	13 (72.2)	14 (73.7)	**0.049**	82 (40.6)	57 (79.2)[1]	28 (71.8)[3]	**<0.0001**
Centiloids (CL)	-4.58 (6.51)	8.90 (12.1)[1]	55.6 (10.6)[1.4]	**<0.0001**	-2.17 (7.99)	28.2 (6.10)[1]	55.6 (10.6)[1.4]	**<0.0001**	-4.66 (6.51)	5.52 (9.40)[1]	36.3 (21.7)[1.4]	**<0.0001**
CSF Aβ42/40	0.087 (0.009)	0.054 (0.011)[1]	0.041 (0.008)[1.4]	**<0.0001**	0.078 (0.016)	0.045 (0.010)[1]	0.041 (0.008)[1]	**<0.0001**	0.086 (0.009)	0.056 (0.011)[1]	0.045 (0.011)[1.4]	**<0.0001**

Results: CSF p-tau, t-tau, neurogranin and NFL are increased in the low Aβ burden group

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	MODEL 1				MODEL 2				MODEL 3			
	CSF- CL<20	CSF+ CL<40	CSF+ CL>40	*P*-Value	CL <20	20-40 CL	CL >40	*P*-Value	CSF- VR-	CSF+ VR-	CSF+ VR+	P-Value
p-tau (pg/mL)	13.9 (4.19)	17.1 (6.50)[1]	25.4 (7.08)[1]	**<0.0001**	14.6 (4.97)	19.6 (7.13)[2]	25.3 (7.08)[1]	**<0.0001**	13.8 (4.17)	16.2 (6.03)[2]	23.1 (7.40)[1]	**<0.0001**
t-tau (pg/mL)	176 (48.7)	210 (72.7)[1]	280 (65.8)[1]	**<0.0001**	183 (55.9)	239 (85.4)[2]	280 (65.8)[1]	**<0.0001**	176 (48.5)	199 (66.1)[2]	267 (75.1)[1]	**<0.0001**
NfL (pg/mL)	75.3 (23.6)	86.0 (25.2)[2]	112 (33.4)[3]	**<0.0001**	77.4 (23.6)	98.5 (31.2)	112 (33.4)[3]	**0.0004**	75.4 (23.7)	82.3 (22.9)	105 (31.4)[1]	**<0.0001**
Neurogranin (pg/mL)	722 (252)	841 (356)[2]	1003 (239)[3]	**0.0001**	747 (282)	951 (402)[4]	1003 (239)[2]	**0.0009**	719 (251)	794 (330)	1019 (324)[1]	**<0.0001**
sTREM2 (ng/mL)	7.58 (1.93)	7.98 (2.34)	8.79 (2.66)	0.19	7.63 (2.00)	8.84 (2.74)	8.79 (2.66)	0.065	7.57 (1.93)	7.74 (2.22)	8.83 (2.63)	0.053
YKL-40 (ng/mL)	138 (44.8)	150 (52.5)	200 (64.1)[2]	**0.0041**	140 (46.6)	170 (55.1)	200 (64.1)[2]	**0.0040**	137 (44.6)	143 (51.4)	187 (58.5)[3]	**0.0019**
GFAP (ng/mL)	7.09 (2.13)	7.80 (2.35)	9.71 (2.74)[2]	**0.0032**	7.24 (2.22)	8.51 (1.91)	9.71 (2.74)[2]	**0.0043**	7.08 (2.14)	7.67 (2.39)	9.00 (2.58)[2]	**0.011**
IL6 (pg/mL)	3.86 (1.33)	3.83 (1.53)	3.94 (1.37)	0.58	3.86 (1.38)	3.66 (1.58)	3.94 (1.37)	0.56	3.87 (1.33)	3.90 (1.58)	3.72 (1.39)	0.89
S100 (ng/mL)	0.98 (0.20)	1.07 (0.27)[4]	1.03 (0.18)	**0.033**	1.00 (0.21)	1.16 (0.33)	1.03 (0.18)	0.093	0.98 (0.20)	1.05 (0.25)	1.09 (0.27)	**0.044**
α-synuclein (pg/mL)	189 (80.9)	195 (67.9)	237 (85.1)	0.066	190 (76.6)	210 (82.3)	237 (85.1)	0.069	189 (81.2)	184 (60.9)	239 (79.2)[3]	**0.0011**

Results: CSF p-tau, t-tau, neurogranin and NFL are increased in the low Aβ burden group

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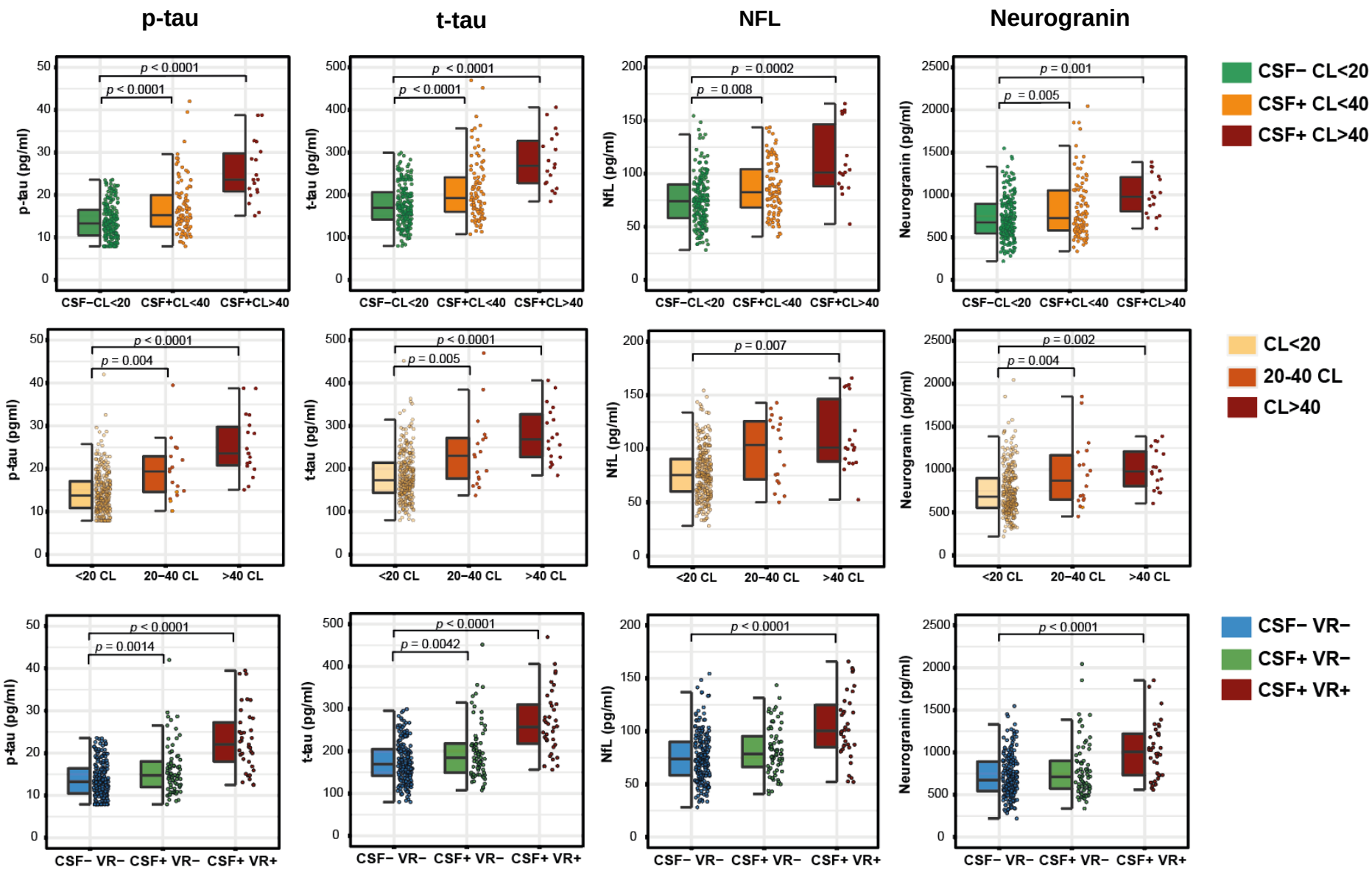
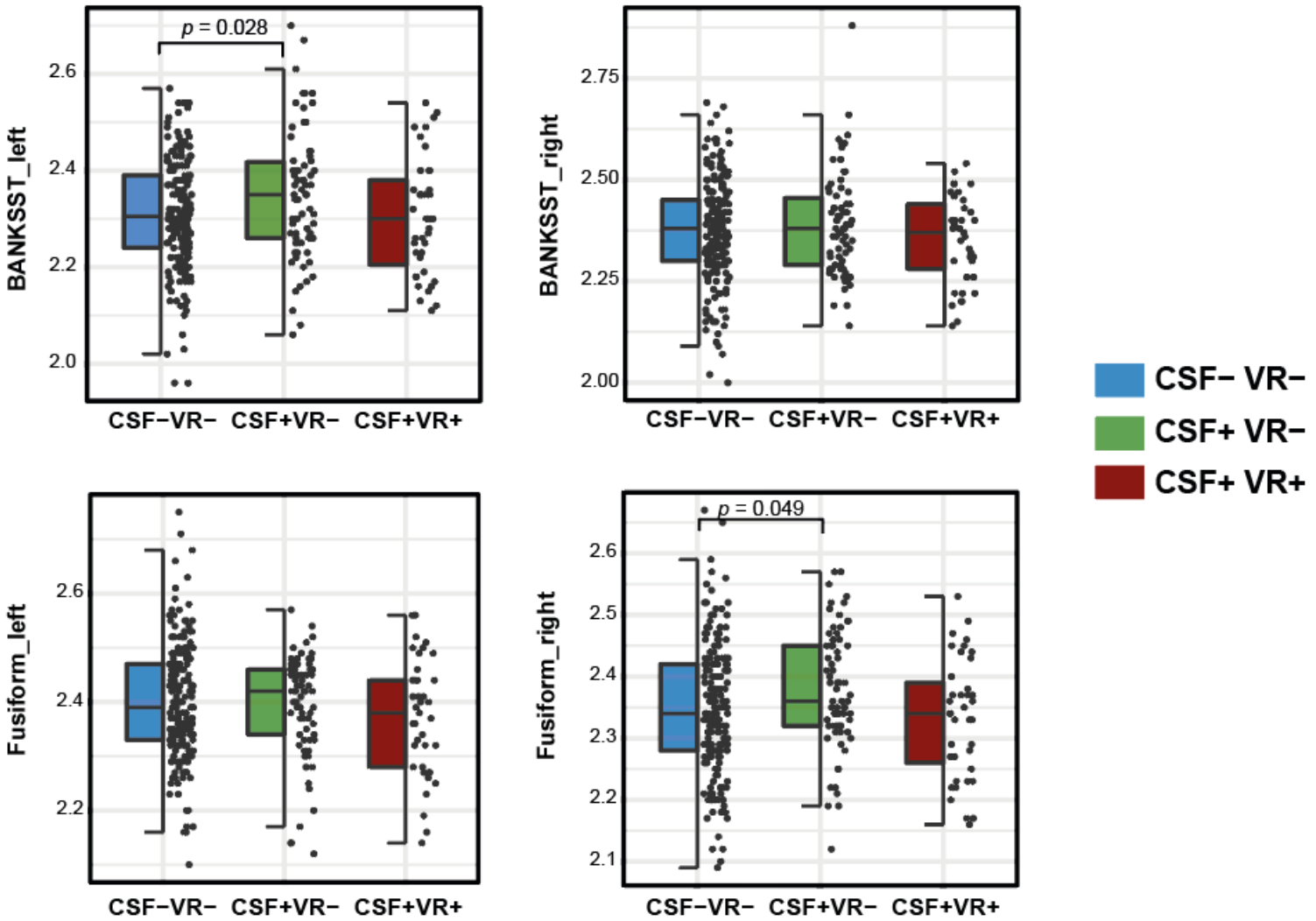


Results: MRI exploratory analysis

- We did not observed differences in cortical thickness in the AD signature MRI Meta-ROI composite when comparing low Aβ burden with the Aβ -negative groups (in any of the 3 models)
- Subjects with low Aβ pathological burden compared with the amyloid negative ones, had an increased in cortical thickness affecting the right fusiform and left BANKSST region (model 3)

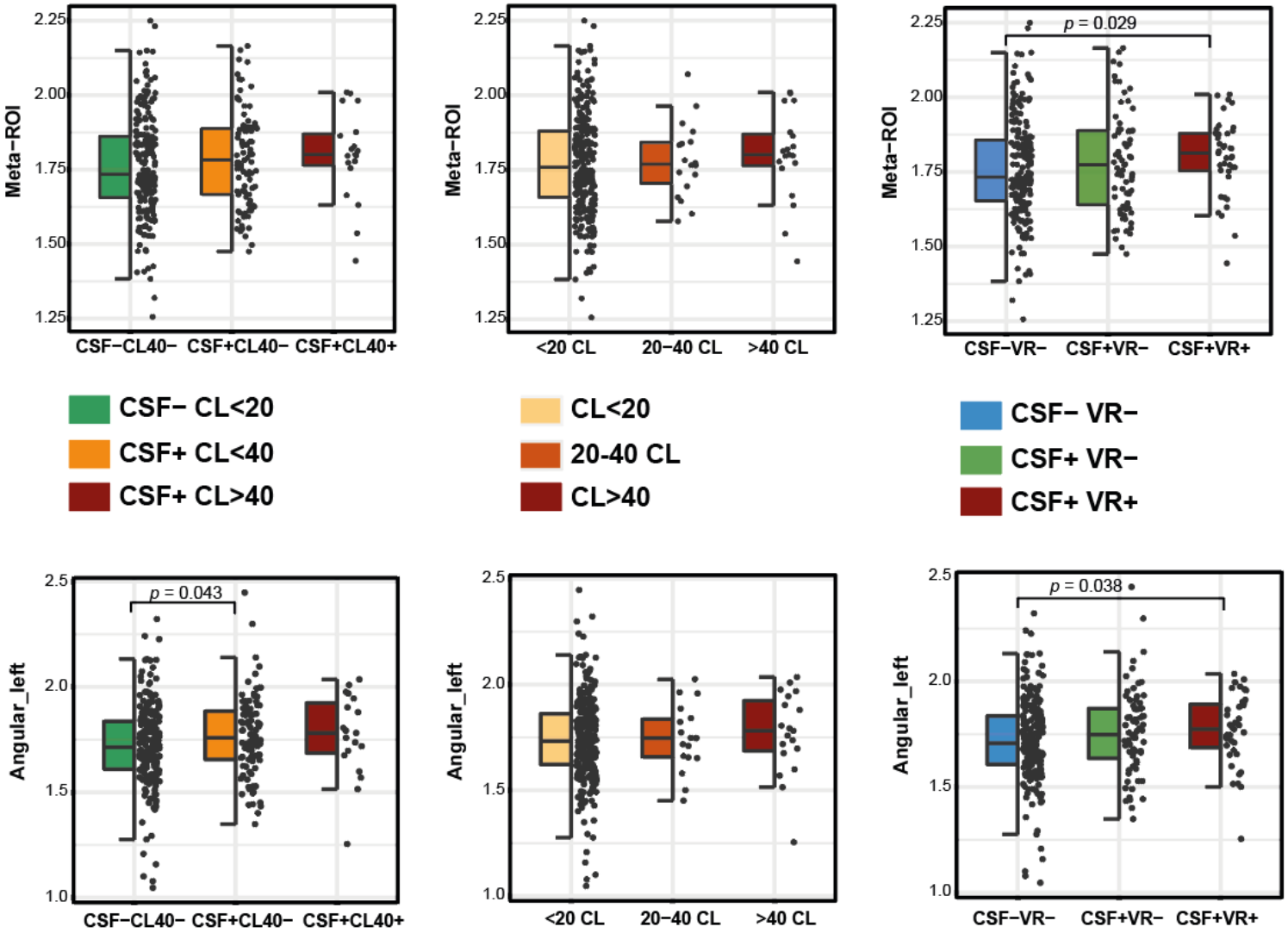
Results: subjects with low Aβ burden present an increased cortical thickness in the right fusiform gyrus and left BANKSST region



Results: Brain FDG metabolism in low Aβ burden pathology

- Analysis of the AD-signature FDG PET Meta-ROI composite showed that Aβ-positive individuals had higher metabolism compared to Aβ -negative ones (P = 0.029, m3; P = 0.077, m1). No significant changes were observed in the low Aβ burden group.
- We observed a higher metabolism in the low Aβ burden group in the left angular gyrus (P = 0.043, m1) and a trend in the right angular gyrus (P = 0.088). In model 3, this increase in metabolism in the angular gyrus was bilateral and significant in the Aβ -positive group but not in the low Aβ burden group

Results: no broad differences in FDG PET metabolism, tendency to increase metabolism



Results: Association between AD CSF biomarkers and FDG PET uptake in low Aβ burden pathology

- In the whole sample, we found a positive association between p-tau, t-tau, neurogranin and α-synuclein and FDG PET Meta-ROI composite. There was also a negative association with CSF Aβ42/40.
- Neurogranin and α-synuclein were positively associated with the FDG PET Meta-ROI composite only in the low Aβ burden group in Model 1 and 3.
- p-tau and t-tau were also positively associated with FDG PET Meta-ROI composite in the low Aβ burden group.
- Remarkably, no significant associations were found in the Aβ-positive groups in any of the 3 models .

Results: Association between p-tau, t-tau and neurogranin with FDG PET uptake in low Aβ burden pathology

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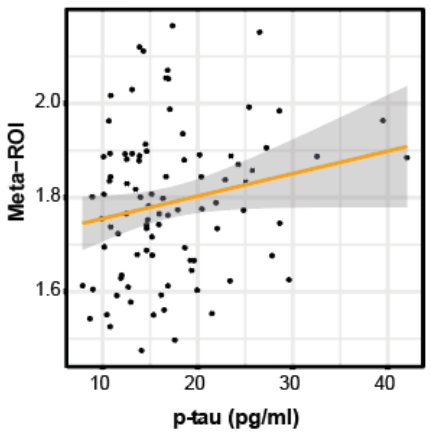
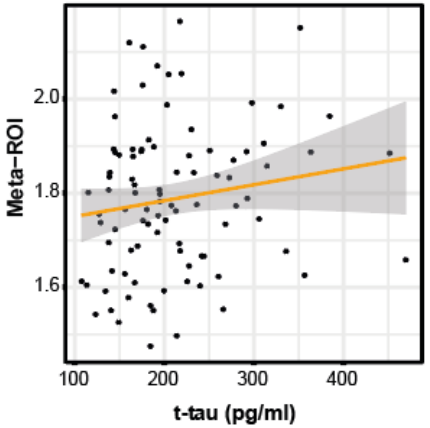
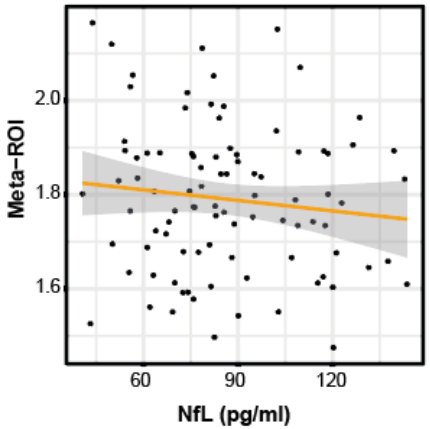
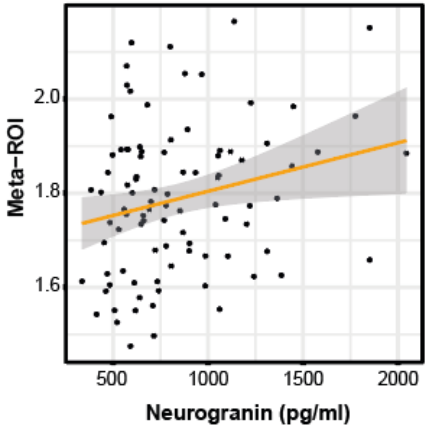
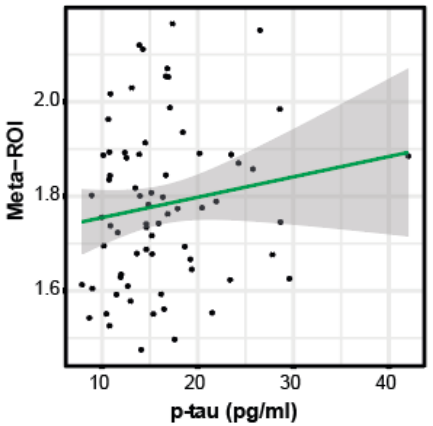
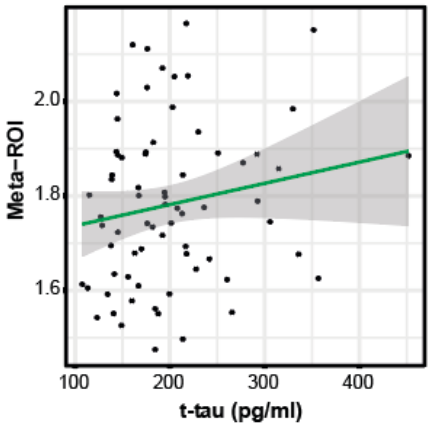
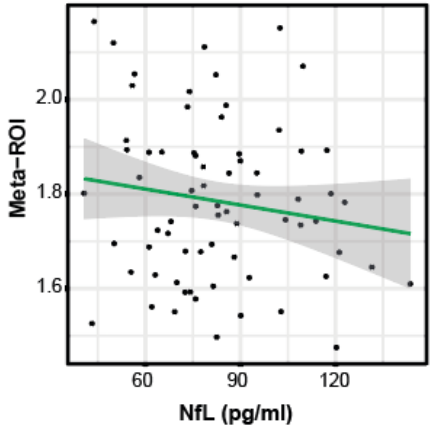
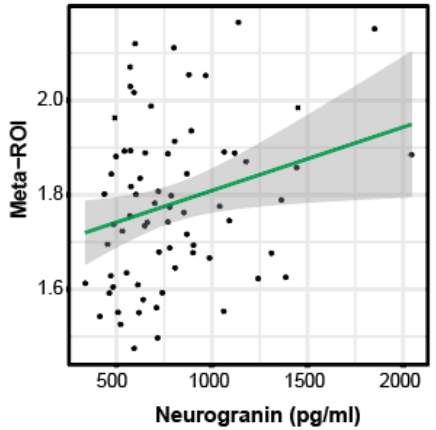
p-tau	t-tau	NFL	Neurogranin
			
β(SE): 0.26 (0.11),	β(SE): 0.25 (0.12)	β(SE): -0.019 (0.15)	β(SE): 0.25 (0.097)
P* = 0.022	***P* = 0.041***	*P* = 0.90	***P* = 0.012***
			
β(SE): 0.22 (0.14)	β(SE): 0.27 (0.15)	β(SE): -0.077 (0.18)	β(SE): 0.28 (0.12)
P = 0.11	*P* = 0.084	*P* = 0.68	***P*=0.025***

CSF+ CL<40

CSF+ VR−

Corrected by age and sex

Discussion

- Tau, synaptic and neurodegeneration pathways are already active in subjects with low Aβ pathological burden
- The NTK panel of neurodegeneration and neuroinflammatory markers represents an important array of tools that confer new insights into the pathogenesis of AD and its eventual clinical manifestations
- Our MRI and FDG PET exploratory analysis mainly suggest that there are no differences in subjects with low Aβ pathological burden compared to Aβ negatives
  - However, an increase in cortical thickness may be happening early in the continuum
  - Low Aβ burden is associated to higher FDG metabolism in the left angular gyrus
  - Higher FDG metabolism is associated with increases in p-tau, t-tau, neurogranin and α-synuclein, suggesting that this early changes parallel those observed in tau, synaptic and neurodegeneration pathways

Take home message

These results provide evidence that multiple biological pathways, such as tau, synaptic and neurodegeneration, are already altered in participants with low Aβ burden, which are associated with brain metabolic changes.

Therefore, intervening very early in the Alzheimer's continuum may be a priority.

Thank you!

BarcelonaBeta Brain Research Center Alzheimer's Prevention Program

ALFA cohort participants

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