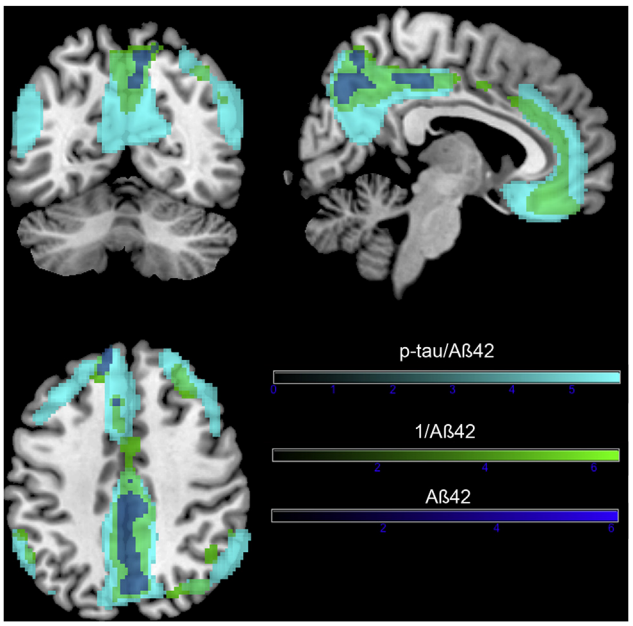

IC-P-008 REGIONAL PIB DEPOSITION AND CSF Aβ42 LEVELS SEVERAL YEARS PRIOR TO AMYLOID POSITIVITY

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Background: The development of Alzheimer disease (AD) pathology in cognitively normal (CN) adults can be characterized by the rate of transition to beta-amyloid (Aβ) positivity with PIB PET. Here we evaluate the appearance of regional beta-amyloid (Aβ) deposition using serial PIB PET scans in relation to the levels of CSF A β 42 for detection of AD pathology in CN older adults. **Methods:** Standardized uptake value ratio (SUVR), corrected for partial volume effect using a regional spread function approach, was calculated for cortical gray matter and subcortical regions of interest (ROI) defined with FreeSurfer software. PIB -positivity was defined using the mean cortical SUVR from precuneus, prefrontal and temporal cortical FreeSurfer ROIs; the threshold for PIB -positivity was an SUVR of 1.4. Levels of CSF A β 42 were obtained by ELISA (interval between CSF and PIB-1 measurements 0.1 $\pm$ 0.7 years). **Results:** Sixty-seven individuals were PIB-negative on both PET scans (PIBnn); 11 individuals who were PIB-negative on the PIB-1 scan demonstrated PIB-positivity on the follow-up (interval between scans 4.6 $\pm$ 2.1 years) PET scan (PIBnp); 18 individuals were PIB-positive on both PET scans (PIBpp). All participants remained CN throughout the follow-up period. At the time of PIB-1 scan, PIBnp demonstrated higher levels of regional and mean cortical PIB deposition compared to PIBnn and lower values compared to PIBpp; CSF A β 42 in PIBnp were lower compared to PIBnn and higher compared to PIBpp. A high correlation between PIB and CSF A β 42 was demonstrated for mean cortical region and ROIs in prefrontal and parietal cortex in PIBnp; the correlation for these ROIs was lower but significant in PIBpp, and not significant in PIBnn. **Conclusions:** Our findings suggest that reductions in CSF Aβ42 are coupled with regional amyloid deposition throughout the process of Aβ accumulation and are evident years prior to reaching the global brain threshold for preclinical AD detected by amyloid imaging.

IC-P-009 NEURODEGENERATIVE AND COGNITIVE PROFILE OF PATIENTS WITH A TYPICAL PHENOTYPE OF AD BUT WITH A NEGATIVE AMYLOID SCAN

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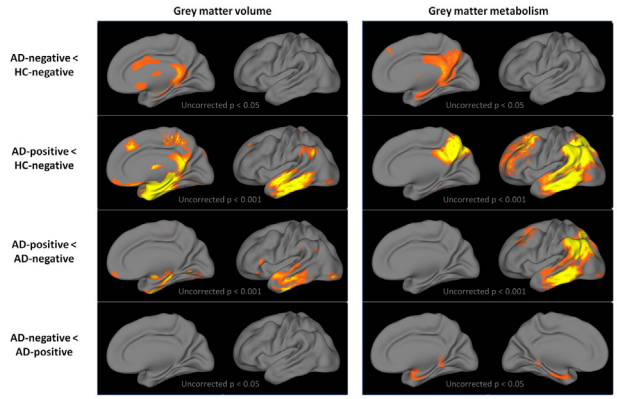
Background: A small proportion of clinically diagnosed probable AD cases present with a negative amyloid PET scan (AD-negative). Understanding this finding may explain the pathological mechanisms of the disease and the significance of amyloid PET scan results. Our objective is to provide a comprehensive assessment of AD-negative cases by assessing their neuropsychological and neuroimaging profiles. **Methods:** All AD-negative (visual reading) patients at the time of clinical diagnosis of probable AD were selected from 4 centres (Amsterdam, Melbourne, San Francisco and Caen). For this study, only those cases with a typical clinical AD presentation (predominant and initial episodic memory deficits), and whose diagnosis didn't change after the clinical knew the results of the amyloid-PET scan, were selected for further analyses (detailed Table). Each of these 9 AD-negative cases was matched for age, education, gender (and MMSE for the AD) to 2-to-4 amyloid-positive AD cases (AD-positive) and 2-to-4 amyloid-negative healthy controls (HC-negative) from the same center. Neuropsychological, MRI and FDG-PET data obtained at the time of the amyloid-PET scan were compared between the three groups after voxelwise SPM processing of neuroimaging data (including MNI normalization, segmentation for MRI and cerebellum scaling for PET). **Results:** The cognitive profile of AD-negative cases was not significantly different from that of the AD-positive. AD-negative cases showed typical hippocampal and lateral temporal atrophy, which was less marked than that observed in the AD-positive cases (p-uncorrected $<$0.001, see Figure). In addition, AD-negative cases showed significantly less hypometabolism in temporo-parietal cortex than the AD-positive cases (pFWE-corrected$<$0.05), while they tended to show greater hippocampal hypometabolism (p-uncorrected $<$0.01). **Conclusions:** AD-negative cases show less cortical neurodegeneration compared to AD-positive, despite similar cognitive impairment. The pattern of atrophy and hypometabolism is similar, but, except for hippocampal hypometabolism, less severe in the AD-negative cases who also lack the AD-characteristic temporo-parietal hypometabolism. The AD-negative cases likely represent a mixed population of initially misdiagnosed limbic predominant AD-mimics (e.g. hippocampal sclerosis, neurofibrillary tangle-predominant dementia or argyrophilic grain disease), other non-amyloid-driven pathologies, and false negative amyloid PET scans. These results demonstrate the importance of multimodality imaging in the clinical evaluation of dementia patients which still requires longer longitudinal observation and autopsy correlation.

Table
Demographic characteristics of the samples

	AD-negative	AD-positive	HC-negative
N (males)	9 (5)	26 (12)	30 (14)
Age (mean±SD)	70.6±14.7	72.5±10.9	71.1±11.6
Education (mean±SD)	12.1±5.8	12.5±2.8	14.1±3.7
MMSE (mean±SD)	24.6±3	22.8±4.4	28.8±1
ApoE4 (n / n available)	14%	81%	14%



IC-P-010 CLINICALLY DIAGNOSED PROBABLE AD CASES WITH A NEGATIVE AMYLOID PET SCAN: CLINICAL FINDINGS

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Background: 10%-20% of patients clinically diagnosed with Alzheimer's disease (AD) in expert centers do not show high tracer retention on amyloid PET. The present study investigates the clinical and demographic features and longitudinal trajectory of this intriguing subgroup. **Methods:** 41 amyloid PET-negative patients carrying a pre-PET diagnosis of AD from 4 centers (Amsterdam, Melbourne, San Francisco, and Caen) were included in this study. Amyloid status was determined by visual reading and confirmed by quantitative analyses. Detailed clinical histories of all patients was collected, including the clinical diagnosis before and after results of the PET scan were known by the clinician, and at long term follow-up, when available. Patients were then classified according to their clinical phenotype as either typical (memory predominant), atypical (predominant language, visual or frontal symptoms), or aclassical (nonspecific presentation), both before and after the PET scan. **Results:** There were 17 typical, 15 atypical, and 8 aclassical AD-negative cases plus one unclassified. Subgroups didn't differ in age, education or MMSE except that typical cases had higher MMSE than atypical ones (p=0.03, see Table). After the PET scan, clinicians altered the diagnosis in 22 of the 34 cases in which they received results. Diagnosis changed to frontotemporal dementia (FTD, n=8), corticobasal syndrome (CBS, n=4), dementia with Lewy bodies (DLB, n=3), epilepsy-depression (n=1), primary progressive aphasia (n=1), non-fluent aphasia (n=1) and unknown diseases (n=4, see detailed table). Clinicians did not change their clinical diagnosis in 60% of typical patients, but nearly always changed the diagnosis in atypical and aclassical cases (83%, p=0.03). Typical cases were most often reclassified as FTD, atypical as FTD or CBS, and aclassical as DLB or unknown. **Conclusions:** Negative amyloid PET scans impacted clinical diagnosis, particularly in patients with non-amnestic clinical presentations. Amyloid PET negative AD likely represents a mixed population of initially misdiagnosed neurodegenerative or non-degenerative conditions, AD-mimics (e.g. hippocampal sclerosis or argyrophilic grain disease), and false negative scans.

Table
Demographic and clinical characteristics of the amyloid-negative AD patients by clinical phenotype subgroups

	All	Typical	Atypical	Aclassical
n	41	17	15	8
Age (mean±SD)	67.2±9.2	68.7±11.5	65.5±7.1	68.1±8.1
Education (mean±SD)	12.3±4.7	12.7±5.6	16.5±4.8	13.7±5.7
MMSE (mean±SD)	22.6±4.8	24.3±2.7	20.9±5.3	23.5±4.9
ApoE4 (n / n available)	5/27	3/14	1/6	1/6
Diagnosis change (n / n available)	22/34	6/15	10/12	5/6
Diagnosis when changed		FTD (n=4) DLB (n=1) Epilepsy-depression (n=1)	FTD (n=4) CBS (n=4) Primary progressive aphasia, no specific subtype (n=1) Non-fluent aphasia (n=1)	DLB (n=2) Unknown (n=3)

IC-P-011 COMPARING LIBERAL AND CONSERVATIVE THRESHOLDS FOR AMYLOID PET POSITIVITY IN AUTOPSY-PROVEN CASES

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