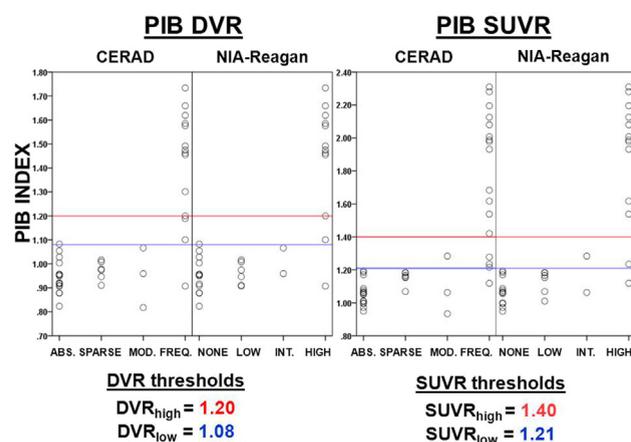


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Background: Variable quantitative thresholds have been proposed to define amyloid positivity on PET, but few studies have compared these thresholds to post-mortem amyloid burden as the “standard of truth.” **Methods:** We included 43 individuals who underwent PIB-PET during life and brain autopsy (mean age at PET=66.8±8.0, T autopsy -T PET =3.0±1.8 years). Patients were evaluated clinically at UCSF (N=36) and UC Davis (N=7), and all underwent PET at Lawrence Berkeley Laboratory. Clinical diagnoses included Alzheimer’s disease (AD, N=10), frontotemporal dementia (N=24), other dementia (N=2), mild cognitive impairment (N=5) and cognitively normal (N=2). Global amyloid was measured with a PIB Index (gray cerebellum reference) via 0-90 minute Distribution Volume Ratios (DVR, N=39) and/or 50-70 min Standardized Uptake Value Ratios (SUVR, N=41). Amyloid at autopsy was classified using CERAD (N=43) and NIA-Reagan criteria (N=33, 10 cases unclassifiable). We compared conservative PIB thresholds in the literature (SUVR high =1.40, DVR high =1.20) and more liberal proposed thresholds (SUVR low =1.21, DVR low =1.08, see Villeneuve et al., submitted) to CERAD frequent neuritic plaques (NP) and NIA-Reagan high-likelihood AD. Receiver operator characteristic (ROC) analyses were performed to empirically derive optimal thresholds. **Results:** The liberal DVR low and SUVR low thresholds captured all but one patient with CERAD frequent NP, and each threshold misclassified one patient with lower amyloid burden (sensitivity 93-94%, specificity 96%, see Figure - blue line). Conservative thresholds were considerably less sensitive (DVR high 71%, SUVR high 77%) but 100% specific (Figure - red line). Liberal thresholds performed similarly well in capturing NIA-Reagan high-likelihood AD (sensitivity 92%, specificity 95% for both DVR low and SUVR low), whereas conservative thresholds were again less sensitive (DVR high 75%, SUVR high 85%) but 100% specific. ROC analyses yielded areas under the curve ranging from 0.929-0.971 (all p<0.001). The optimal thresholds derived from ROC were nearly identical to our a priori liberal thresholds (DVR=1.09 and SUVR=1.20-1.21). **Conclusions:** Liberal thresholds for PIB-positivity were highly sensitive and specific for high-burden amyloid pathology. Conversely, more widely used conservative thresholds appeared to be overly stringent in defining amyloid positivity. More work is needed to verify these findings in subjects with intermediate pathology and independent cohorts.



IC-P-012 **AUTOMATED REPORTING OF AMYLOID PET QUANTIFICATION ON BRAIN SURFACE THROUGH A WEB INTERFACE**

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Background: Molecular brain imaging using Positron Emission Tomography (PET) is a robust diagnostic tool for which several tracers labelled with either 11C or 18F are available. For visual inspection of the images, cortical surface based visualisation presents the advantage of providing a compact and more convenient display than volumetric scans. We have developed an automated reporting tool to display the semiquantitative PET signal for several common tracers without the need of a MRI and using several standard normalisation methods (i.e. using the Pons, the whole Cerebellum WCB and the cerebellum cortex CB-CTX). This tool is available on-line to registered users and the processing is performed remotely (<http://milxcloud.csiro.au/capaibl>). The method was validated by comparing the surface signal computed with and without MRI. **Methods:** Three hundred and thirty nine participants from the AIBL cohort underwent MRI and PET scans with different tracers: 18F-Flutemetamol (n=101), 11C-PIB (n=91), 18F-Florbetapir (n=77), 18F-FDG (n=38), 18F-Florbetaben (n=14) and 18F-NAV4694 (n=18). Each individual PET image was spatially normalised to the MNI space and SUVR corrected with a common mask. Radiotracer retention was then estimated vertex-wise within several GM prior atlases. Atlas selection and Bayesian fusion were then used to estimate retention on the cortical surface. For comparison with MR-based approach, radiotracer retention was also estimated for each vertex with the individual GM segmentation and projected onto the individual cortical surface. The difference in radiotracer estimation between the MRI-dependent and CAPAIBL (Computational Analysis of PET from AIBL) approaches was measured by absolute difference of SUVR values at each vertex. The SUVR differences were averaged over vertices and over the total subjects. **Results:** Visual inspection revealed high concordance between PET only and MRI based surface projection; the surface projection was defined on 8 standard views for consistent reporting (Fig 1). Across the 6 tracers tested, the average absolute error over the brain surface with and without MRI was 0.12, whereas the average variance was 0.018. **Conclusions:** The proposed MRI-less surface projection method demonstrated better estimation of 11C-PIB retention than recently published methods displaying similar accuracy for various 18F labelled radiotracers. CAPAIBL provides an efficient reporting tool for PET imaging easily accessed remotely through a web interface.

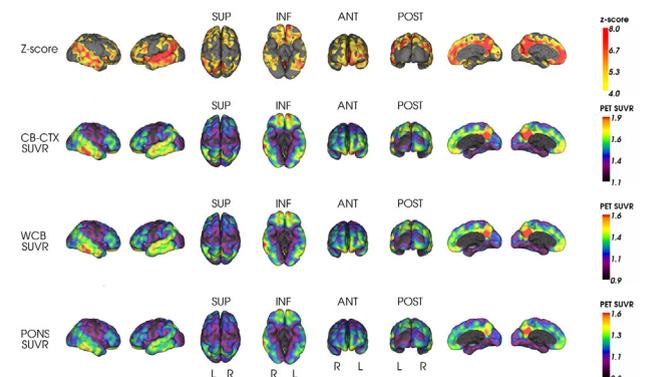


Fig 1. Example of CAPAIBL inspection on a positive 18F-Florbetapir. The report displays the radiotracer retention z-score when compared to a normal negative population followed by normalisation with cortical cerebellum, whole cerebellum and Pons.

IC-P-013 DIAGNOSTIC VALUE OF AMYLOID IMAGING IN EARLY ONSET DEMENTIA

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Background: In early onset dementia approximately one out of three patients has an atypical clinical presentation, which substantially complicates correct etiological diagnosis. [18 F]Flutemetamol PET, an investigational imaging agent, is being studied for detection of amyloid deposition, a pathological hallmark of Alzheimer's Disease (AD). In our ongoing study we examine the diagnostic value of [18 F]Flutemetamol PET in assessing patients with early onset dementia. **Methods:** We included 80 patients with early onset dementia (age <70 years) and physician diagnostic confidence less than 90% after a full routine diagnostic work-up for dementia. All patients underwent a [18 F]Flutemetamol PET scan which were visually assessed as amyloid positive or negative. Scans were performed between 90 and 110 minutes after injection of approximately 185 MBq [18 F]Flutemetamol. Before and after disclosing PET results to the patient's managing physician, clinical diagnosis and confidence in this diagnosis was determined. Also, the impact on patient healthcare management was assessed. **Results:** [18 F]Flutemetamol scans were positive in 48 out of 63 (76%) patients diagnosed (pre-PET imaging) with AD and 4 out of 17 (24%) patients diagnosed with other dementias. Overall, confidence in etiological diagnosis increased from 76±12% to 90±16% after disclosing PET results (p<0.001). Access to PET results led to a change in diagnosis in 16 (20%) patients. In 11 out of 13 patients, a negative PET scan caused a change of the initial AD diagnosis to another dementia. In 3 out of 4 other dementia patients, the initial diagnosis was changed to AD after receiving a positive PET scan. In 27 (34%) patients, PET results led to a change in patient healthcare management (i.e., 25 patients had their medication changed and 9 patients received additional care). These patients predominantly had a clinical diagnosis of AD. For 13 patients additional ancillary investigations were planned after access to the PET scan results. **Conclusions:** [18 F]Flutemetamol PET resulted in changes in the diagnostic process work-up of early onset dementia patients and the diagnostic confidence of the managing physicians. Especially in patients diagnosed with AD prior to PET, a negative PET scan resulted in more changes in clinical diagnosis and patient management.

IC-P-014 USE OF CSF AMYLOID FOR DETECTING CORTICAL AMYLOID DEPOSITION: A MULTICENTER STUDY

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Background: There is a large inter-laboratory variance in local CSF beta amyloid (A β 1-42) cut-points used for clinical and research purposes. Variability may be caused by variability in pre-analytical procedures in measuring CSF markers or approaches to calculate cut-points. We aimed to define an optimal CSF A β 1-42 cut-point for detection of cortical amyloid deposition. Furthermore, we compared concordant and discordant cases. **Methods:** We included 434 subjects (57 controls, 99 Mild Cognitive Impairment patients, 196 Alzheimer's disease (AD) patients and 82 other dementia patients) with available CSF and PIB-PET data from 5 centers. We used local cut-points and calculated optimal cut-points for each center that best predicted cortical amyloid burden using the Youden index. Cortical amyloid

burden was detected by local visual rating of PIB-PET scans. An inter-site rater study of 20 PIB-PET scans showed a 100% accuracy. **Results:** Local cut-points for CSF A β 1-42 levels varied between 400-550 pg/ml. Their sensitivity for detection of cortical amyloid deposition ranged between 0.47-0.80 and specificity between 0.68-0.91. Calculated optimal cut-points that maximised the Youden index varied between 521-616 pg/ml, with a sensitivity ranged between 0.84-0.95 and specificity between 0.58-0.91. The optimal cut-point in the pooled sample was 557 pg/ml with a sensitivity and specificity of 0.87 and 0.79, respectively. Using the optimal CSF A β 1-42 cut-point, concordance between amyloid biomarkers was 86%. Of the 35 discordant subjects with normal CSF A β 1-42 and positive PIB-PET, 50% showed borderline CSF A β 1-42 levels. Furthermore, 62% showed an abnormal CSF tau, 48% was APOE ϵ 4 carrier, and >90% was diagnosed with MCI or AD. Of the 33 discordant subjects with abnormal CSF A β 1-42 and negative PIB-PET, 16% showed an abnormal CSF tau, 64% was APOE ϵ 4 carrier and 49% was diagnosed as non-AD dementia. **Conclusions:** Compared to clinical-based cut-points, the use of cortical amyloid deposition to define CSF A β 1-42 cut-points overall decreased inter-site variability and increased sensitivity and specificity. This suggests that the way clinical cut-points have been calculated introduces substantial variability. Analysis of discordant cases suggests that subjects with abnormal CSF A β 1-42 but negative PIB-PET may be less likely to have AD-related amyloid pathology than subjects with normal CSF A β 1-42 but positive PIB-PET.

IC-P-015 NEW TOOLS FOR AMYLOID PLAQUES DETECTION BY MRI: GADOLINIUM-VHH ANTIBODY CONJUGATES

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Background: The early diagnosis of Alzheimer's disease (AD) is critical for the evaluation of new therapies and for patient follow-up. Aggregation of A β 1-40, A β 1-42 peptides in amyloid plaques, one of the major hallmarks of the pathology, begins more than 15 years before neuropsychological symptoms. Few methods have been developed to detect amyloid plaques by MRI but they always required an invasive process to open the blood brain barrier (BBB). Heavy chain only antibody fragments (VHH), because of their small size and their basic isoelectric point, have the potential to cross the BBB. Hence, in order to detect amyloid plaques by MRI, we developed VHHs with high specificity against A β 1-40, A β 1-42. First, we evaluated the BBB crossing by in vivo multi-photon imaging after conjugation of our VHHs to a fluorochrome. Then, gadolinium (Gd) was conjugated to VHHs via a DOTA cage and the resulting contrast agent (VHH-DOTA/Gd) was evaluated by MRI. **Methods:** Conjugates were synthesized by conjugation of Alexa-Fluor488 or a DOTA/Gd synthon on VHHs. Conjugates were monitored by HPLC/MS, and binding properties were confirmed by ELISA and IHC. PS2APP mice aged of 90-100 weeks were used (n=2/experiment). In vivo multi-photon experiments were realized after intravenous injections of VHH-AlexaFluor488. MRI acquisition were recorded following two different protocols 1) in vitro incubation of one hemisphere with VHH-DOTA/Gd (0.1mg/ml equivalent to 0.1mM of Gd) overnight, 2) Gd-staining, a reference technique to reveal amyloid plaques by soaking the hemisphere in a Gd-solution (2.5mM - 48h). **Results:** Live multi-photon imaging following intravenous injection showed gradual extravasation of the fluorescent VHHs from blood vessels and penetration in brain parenchyma with an exquisite tropism for amyloid plaques, as confirmed by IHC (Figure 1). MR images obtained after in vitro