

Existing thresholds for PIB positivity are too high

Sylvia Villeneuve¹, Cindee Madison¹, Nagehan Ayakta¹, Renaud La Joie¹, Brendan I. Cohn-Sheehy², Jacob Vogel¹, Shawn Marks¹, Samia K. Arthur-Bentil¹, Bruce Reed³, Charles Decarli⁴, Gil Dan Rabinovici⁵, William Jagust¹,

¹University of California, Berkeley, Berkeley, California, United States;

Background: There is no consensus among researchers about the thresholds that define amyloid positivity and there is little known about the earliest phases of amyloid accumulation in older adults. The present study had two goals: first, to derive a cutoff that captures early accumulation using both DVR and SUVR data from our subjects and, secondly, to examine their pattern of amyloid accumulation. **Methods:** Amyloid accumulation was investigated in 152 cognitively normal older adults using: (1) a reference group of young adults, (2) Gaussian mixture modeling (GMM), (3) cluster analyses and (4) voxel-wise analyses. All analyses used DVR and SUVR data with a cerebellar gray reference ROI. For voxel-wise analyses, subjects were ranked based on their global DVR status. To track when and where amyloid starts accumulating we compared a group of 22 subjects with a mean DVR of 1 (control group) to the next 22 subjects (group of interest) and iteratively increased the mean DVR of the group of interest by dropping the subject with the lowest value and adding the subject with the next higher value. This procedure was repeated until the subject with the highest DVR was included in the group of interest. **Results:** The threshold 2 SD above the young subjects was a DVR of 1.07 (SUVR = 1.19). Both the GMM and the cluster-derived thresholds were 1.09 (SUVR 1.22). The Figure shows that amyloid starts accumulating in the medial frontal cortex (mean DVR = 1.07, SUVR = 1.19), then spreads to the precuneus, the lateral frontal and parietal lobes, and finally the temporal lobe. **Conclusions:** Amyloid starts to accumulate long before individuals reach the widely used SUVR cutoffs of 1.4 and 1.5. These results support an SUVR cutoff of 1.21 (DVR = 1.08) to capture early amyloid accumulation. This cutoff was confirmed by an autopsy study of 43 dementia cases (Rabinovici et al., submitted).