Imaging age-related effects on amyloid-β deposition in nondemented adults with Down syndrome using [11C]PiB

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Introduction

- The majority (95%) of Down syndrome (DS) cases result from a triplication of chromosome 21.
- It is hypothesized that the overexpression of gene products, like amyloid precursor protein, predisposes young adults with DS to developing Alzheimer disease (AD)-like neuropathology.
- Neurofibrillary tangles and amyloid-β plaques have been observed in virtually all adults with DS by age 40.
- The goal of this UW/UPMC collaborative project was to use [11C]PiB to image the pattern of amyloid-β deposition in nondemented adults with DS and determine the relationship of deposition with normal aging.

Methods

- 68 nondemented adults with DS (age 30-53) underwent [11C]PiB PET scans. Trisomy 21 was confirmed with genetic testing.
- Standard uptake value ratio (SUVR) images were created using the cerebellum as the reference region.
- Regions of interest (ROIs) included the commonly affected regions in AD: anterior cingulate, frontal cortex, parietal cortex, precuneus, striatum, and temporal cortex.
- Multiple linear regression models tested for significant correlations between SUVR and age in six ROIs, correcting for gender and APOE4 allele status.
- Sparse k-means clustering determined PiB positivity.

Results

- All regions showed a slight, but highly significant, positive correlation (corrected $p<0.05$) of SUVR with age.
- The striatum showed the strongest correlation, followed by the precuneus, parietal cortex, anterior cingulate, frontal cortex, and temporal cortex.
- 17 out of 68 subjects were classified as PiB positive. 94% of the PiB positive subjects were above the threshold in the striatum.
- Elevated cortical [11C]PiB retention was observed in subjects above age 35.

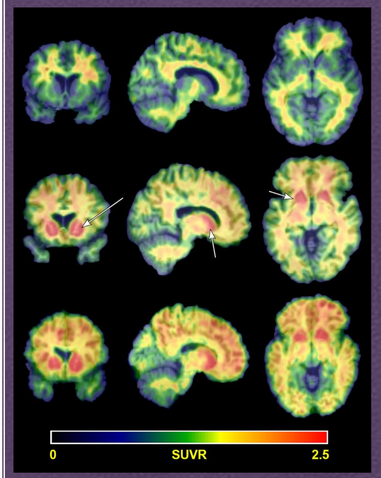


Figure 1 (Above): Three patterns of [11C]PiB retention: nonspecific white matter uptake (top row), elevated striatal uptake (middle row), and elevated cortical uptake (bottom row). Arrows in the middle row denote the striatum.

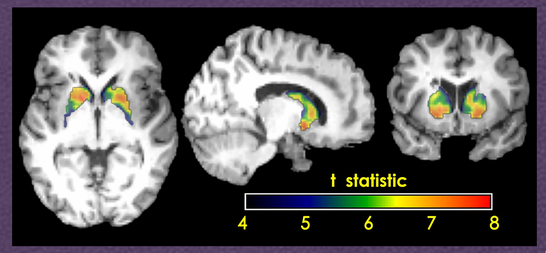
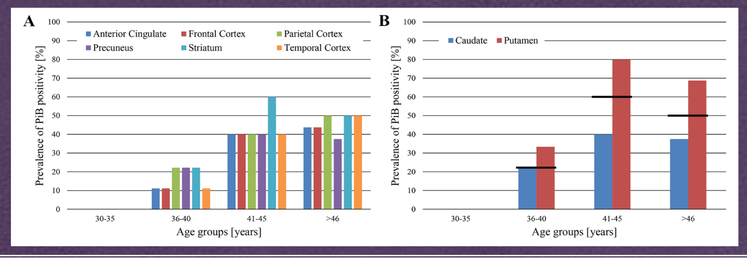


Figure 2: Parametric t-map of the correlation between SUVR and age in the striatum for the whole cohort. The putamen has higher t-stats than the caudate ($P < 0.001$), indicating a statistically stronger correlation between SUVR and age.

Figure 3 (Below): Prevalence of PiB positivity by region of interest and age group. A) The percent of PiB positive subjects generally increases with age. Note that this represents the prevalence of participants being classified as PiB positive per age group and does not represent amyloid deposition or amyloid deposition rates. B) The prevalence of PiB positivity of the striatal components with the value of the whole striatum represented as the black line.



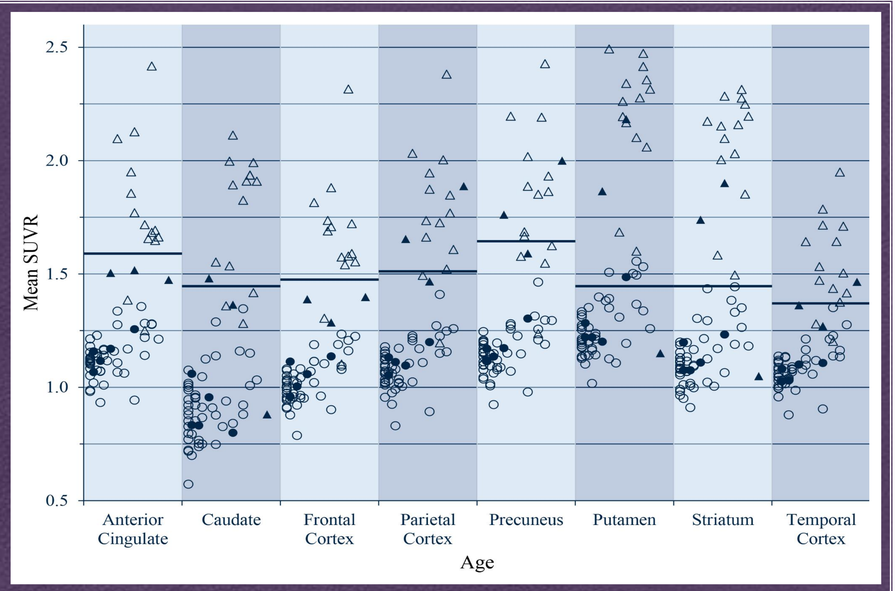


Figure 4: Mean SUVRs plotted against age (30-53 years) for PiB positive subjects (triangles) and PiB negative subjects (circles). Filled shapes are APOE4 positive. The cutoff value for each ROI is represented by the bar.

Discussion

- As a pattern of elevated cortical retention becomes apparent, the correlation loses significance. This suggests that factors unrelated to aging may drive a rapid increase in amyloid-β deposition in the early stages of AD pathogenesis.
- While there are shared aspects of pathogenesis between DS and AD, these data reveal that early involvement of the striatum is a defining pattern among the DS population.

Acknowledgments

- This research is funded by the National Institute of Aging (R01AG031110 to B.H. and B.C.) and the National Institute on Child Health and Human Development (P30 HD03352 to M.M.) and support from the UW and UP Alzheimer Disease Research Centers (ADRC).
- We would also like to thank the adults with DS and their families for their time and commitment to further discovery and understanding into the causes of AD.