A Pilot Study Assessing Central Cholinergic Integrity in Individuals with Down Syndrome Using [18F]-FEOBV and Basal Forebrain Cholinergic Anatomy

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Introduction

- Down Syndrome is associated with an increased risk of Alzheimer's disease due to the presence of the amyloid precursor protein on the triplicated chromosome 21.
- In Alzheimer's disease, degeneration of the cholinergic system is known to play an important role in many of the cognitive deficits observed. However, limited studies assess changes in cholinergic integrity in Down Syndrome individuals.
- In this study, we assess the integrity of the cholinergic system directly in individuals with Down Syndrome utilizing [18F]-FEOBV PET imaging and assess associations with regional-specific amyloid deposition as measured by [11C]-PiB

Methods

Participants

- Seven individuals 19-50 years old with Down Syndrome, not exhibiting Alzheimer's disease symptoms on neuropsychiatric assessment, completed an [18F]-FEOBV PET scan and an MRI scan, with six participants also completing a [11C]-PiB scan
- Participants over 25 years old were recruited from the Trial Ready Cohort – Down Syndrome (TRC-DS) cohort. A cohort study where participants undergo multimodal imaging assessment, including brain amyloid and tau imaging.

FEOBV and PiB PET scan and MRI scan acquisition

- Participants received [18F]-FEOBV (6.5mCi) I.V. with a 30-minute static scan performed following a 3-hour uptake.
- Participants received [11C]-PiB (15mCi) I.V. with a 30-minute static scan performed following a 30-minute uptake.
- PET scans were performed using a Philips Vereos digital PET/CT system.
- MRI scans were performed with a Philips 3T Elition X with T1-weighted scans utilized for registration and volumetric analysis.

FEOBV PET scan data processing and analysis

- A Brodmann area (BA) atlas from MRIcron and FreeSurfer cortical and subcortical parcellations were registered to participants' MRI scans and transformed into native PET space.
- FEOBV SUVRs were calculated using the supraventricular white matter as the reference region.
- PiB SUVRs were calculated using the cerebellum as the reference region.
- Uncorrected Spearman's associations (with SciPy 1.10.1) and linear regressions (with NumPy 1.24.2) in Python 3.11 between FEOBV SUVRs and age, or FEOBV SUVR and PiB SUVR within the same region of interest (ROI) were assessed.

Results

Averaged [18F]-FEOBV Uptake from Seven Individuals with DS and Normal Individuals

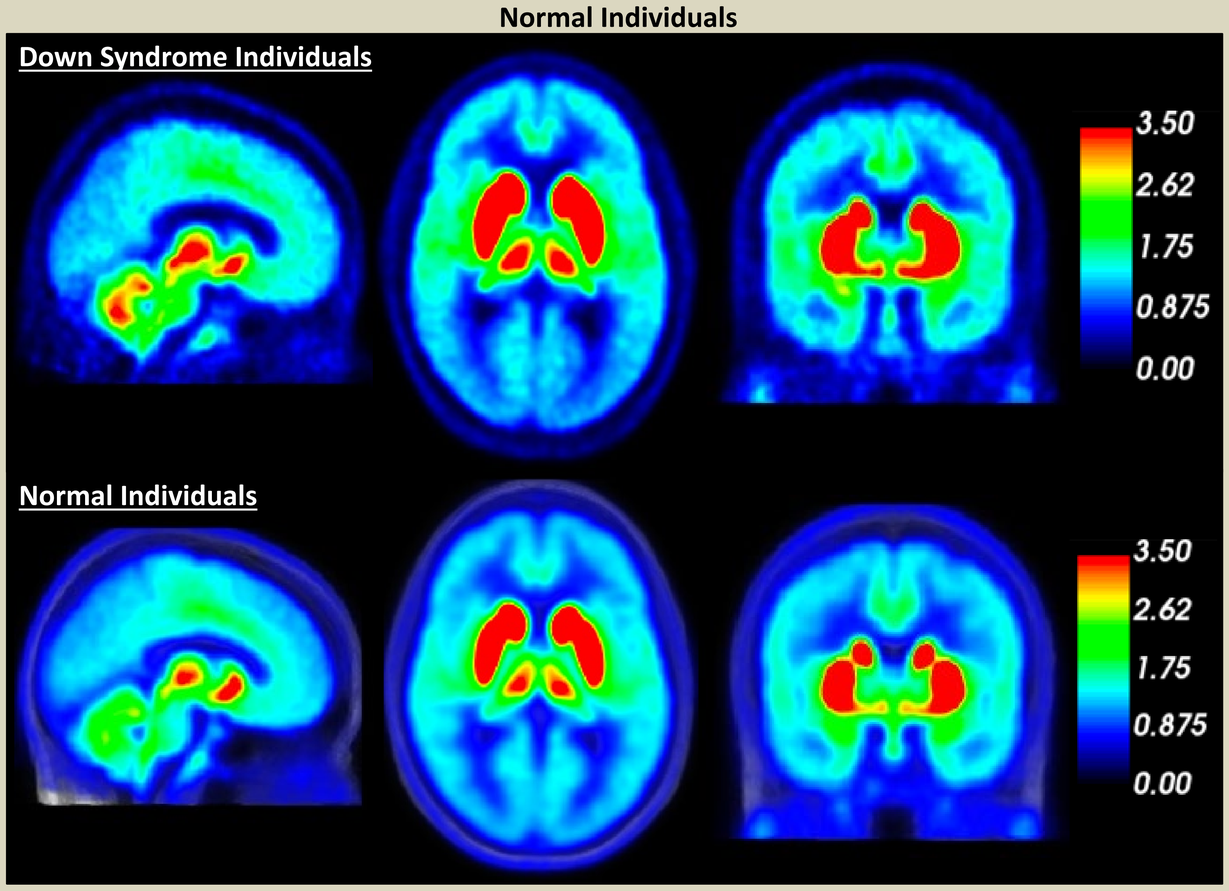
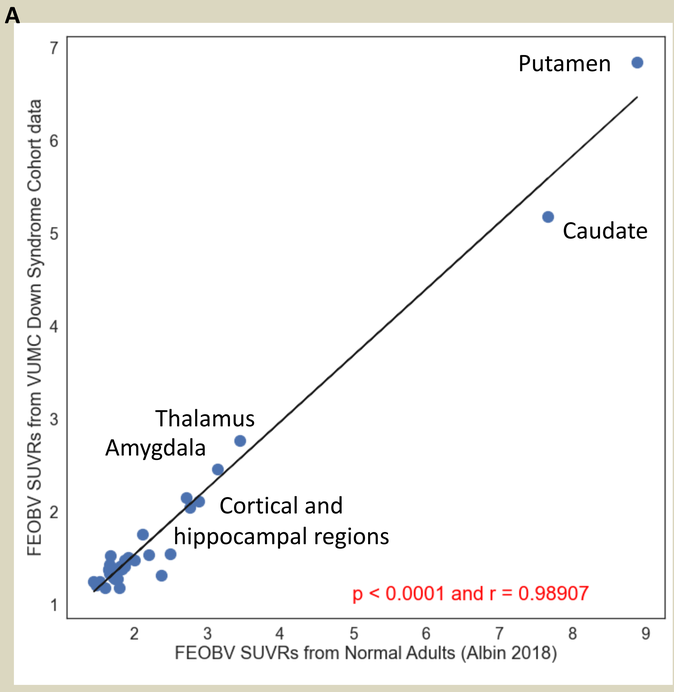


Figure 1. Shown is an averaged image of [18F]-FEOBV uptake in 7 individuals with Down Syndrome and the averaged [18F]-FEOBV uptake in 20 normal individuals. Note the high uptake levels in the putamen and caudate nucleus.

Associations between [18F]-FEOBV uptake and age

Individuals with Down Syndrome Display Regional [18F]-FEOBV Uptake Comparable to Normal Non-Down Syndrome Individuals with Age-Related Decline in Posterior Cingulate Cortex Uptake

A



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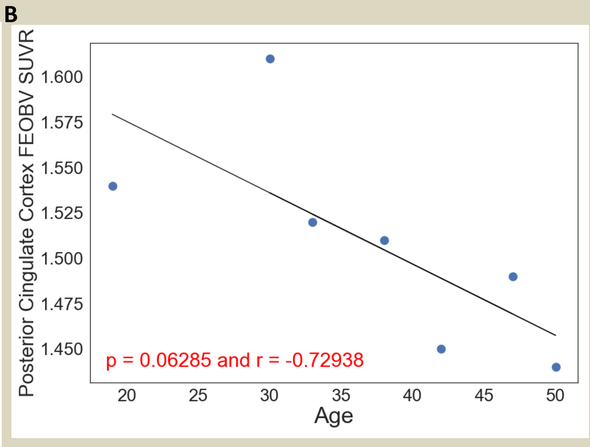

Figure 2. Shown is the correlation between the FEOBV SUVRs in our VUMC Down syndrome cohort and previous published normal adults (Albin 2018) is shown in the linear regression plot. Albin et al 2018, J Comp Neurol. 2018;526:2884–2897 (A). The association between age and posterior cingulate cortex FEOBV uptake is shown in (B).

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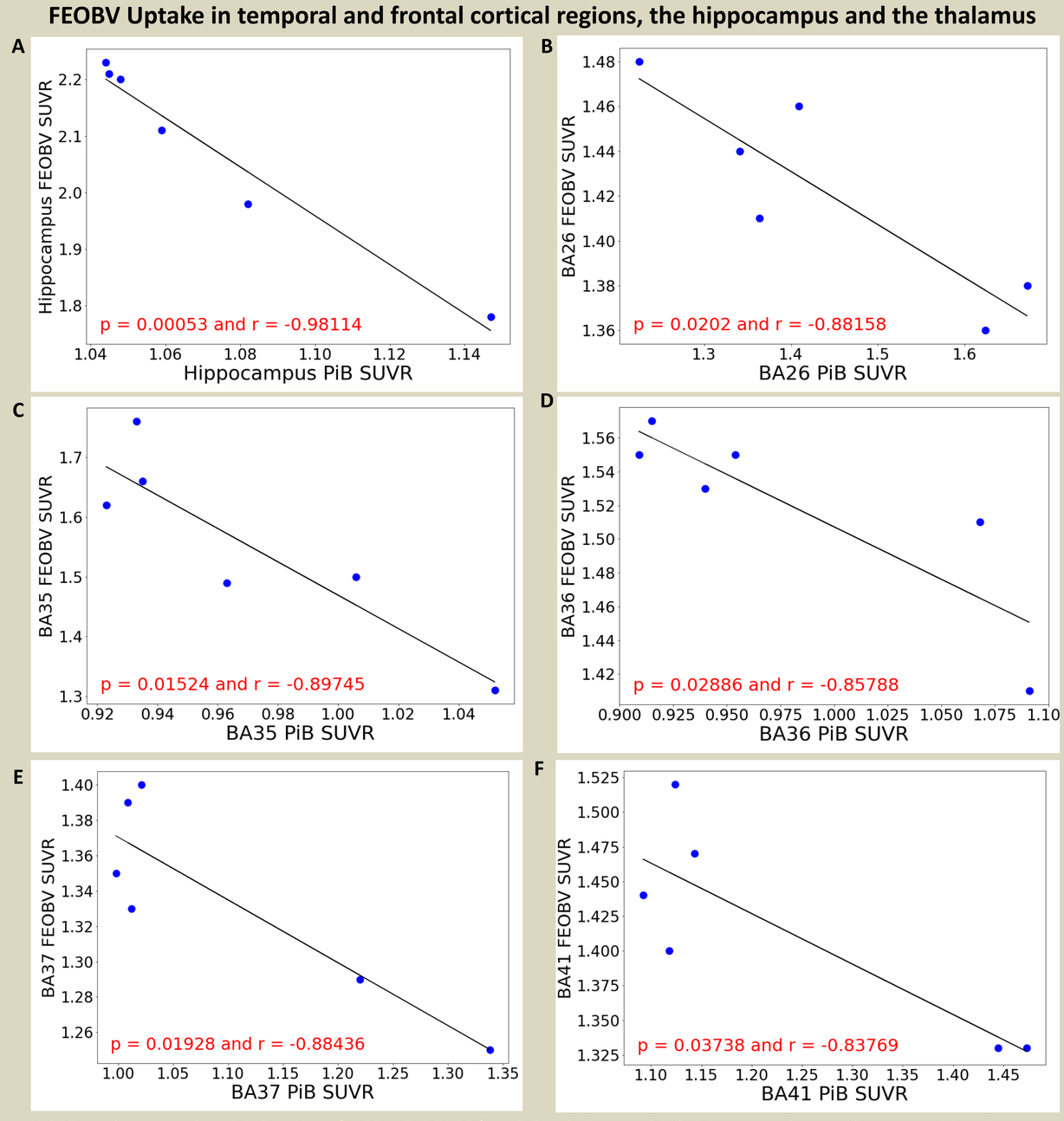
Associations between [18F]-FEOBV uptake and [11]-PiB uptake

Individuals with Down Syndrome Display an Association Between [11C]-PiB Uptake and [18F]-FEOBV Uptake in temporal and frontal cortical regions, the hippocampus and the thalamus



Additional temporal cortical regions (BA20, 21, 28, 29) and the thalamus displaying a trend toward an association between [18F]-FEOBV and [11C]-PiB uptake in temporal and frontal cortical regions and the thalamus (R < -0.75 and P < 0.1)

Figure 3. Shown are associations between region-specific FEOBV and PiB uptake in the Hippocampus (A), Frontocortical regions (B) and Temporocortal regions (C, D, E, F).

Discussion

- Given comparable results to previously published data in normal non-Down Syndrome individuals (Albin 2018), FEOBV PET imaging appears to be a valid modality for assessing cholinergic integrity in individuals with Down Syndrome.
- This data suggests an association between cholinergic nerve terminal degeneration and amyloid deposition in cortical and limbic regions.
- Interestingly, no association between striatal PiB uptake and FEOBV uptake was observed. Although the striatum displays early amyloid deposition in individuals with DS, the lack of striatal FEOBV uptake association with amyloid suggests the intrinsic striatal cholinergic interneurons are relatively preserved despite amyloid accumulation in these non-demented individuals with DS
- These data suggest that FEOBV PET would be useful for future studies assessing cholinergic integrity longitudinally in individuals with Down Syndrome.