**Brain amyloid in virally suppressed HIV-associated neurocognitive disorder**

***– Supplementary Material –***

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**Table e-1:** Case 1 profile and case statistics

|  |  |
| --- | --- |
|  | HIV+ |
| Age (years) | 62 |
| Education (years) | 10 |
| HIV duration (years) | 15.6 |
| Current cART duration (months) | 6 |
| Nadir CD4 cells/mL | 300 |
| Current CD4 cells/mL | 528 |
| Current CD8 cells/mL | 1224 |
| Predicted WAIS-III VIQ | 98.7 |
| GDS | 1.3 |
| Historical AIDS | Yes |
| CSF Aβ-42 | 168.2 |
| CSF t-tau | 132.2 |
| CSF p-tau | 36.2 |
| CSF AD-like profile | No |
| APOE | ε4/ε4 |
| Hippocampal SUVRc vs NL | 0.057 (1.61) [1.15 to 2.11]\* |
| Hippocampal SUVRc vs MCI | 0.45 (0.12) [-0.62 to 0.86] |
| Hippocampal SUVRc vs AD | 0.11 (1.27) [0.49 to 2.14] |

Case statistics reported as One-tailed p-value (t-value) [Confidence Interval]

GDS: Global Deficit Score; SUVR: Cerebellum standardized uptake value ratio; NL: Cognitive Normal, MCI: Mild Cognitive Impairment; AD: Alzheimer’s disease

\* (trend at p<.06)

**Table e-2:** Case 3 profile and case statistics

|  |  |
| --- | --- |
|  | HIV+ |
| Age (years) | 52 |
| Education (years) | 15 |
| HIV duration (years) | 24.8 |
| Current cART duration (months) | 6 |
| Nadir CD4 cells/mL | 170 |
| Current CD4 cells/mL | 400 |
| Current CD8 cells/mL | 700 |
| Predicted WAIS-III VIQ | 109.9 |
| GDS | 4.73 |
| Historical AIDS | Yes |
| CSF Aβ-42 | Missing |
| CSF t-tau | Missing |
| CSF p-tau | Missing |
| CSF AD-like profile | Missing |
| APOE | Missing |
| Cingulum SUVRc vs NL | 0.07 (-1.47) [-1.94 to -1.02] |
| Cingulum SUVRc vs MCI | 0.02 (-2.55) [-4.39 to -1.04] \* |
| Cingulum SUVRc vs AD | <0.0001 (-5.83) [-8.77 to -3.39] \* |
| Caudate SUVRc vs NL | 0.006 (-2.64) [-3.34 to -1.99] \* |
| Caudate SUVRc vs MCI | 0.01 (-2.97) [-5.06 to -1.26] \* |
| Caudate SUVRc vs AD | 0.005 (-3.16) [-4.83 to -1.75] \* |
| Putamen SUVRc vs NL | 0.07 (-1.48) [-1.95 to -1.03] |
| Putamen SUVRc vs MCI | 0.006 (-3.58) [-6.05 to -1.59] \* |
| Putamen SUVRc vs AD | 0.002 (-3.56) [-5.41 to -2.00] \* |
| Pallidum SUVRc vs NL | <0.04 (-1.80) [-2.34 to -1.31] \* |
| Pallidum SUVRc vs MCI | 0.002 (-4.43) [-7.44 to -2.03] \* |
| Pallidum SUVRc vs AD | 0.007 (-2.98) [-4.57 to -1.63] \* |
| Thalamus SUVRc vs NL | 0.0006 (-3.48) [-4.36 to -2.67] \* |
| Thalamus SUVRc vs MCI | 0.006 (-3.42) [-5.95 to -1.56] \* |
| Thalamus SUVRc vs AD | 0.005 (-3.17) [-4.84 to -1.75] \* |

Case statistics reported as One-tailed p-value (t-value) [Confidence Interval]

GDS: Global Deficit Score; SUVR: Cerebellum standardized uptake value ratio; NL: Cognitive Normal, MCI: Mild Cognitive Impairment; AD: Alzheimer’s disease

p<.05 indicated by \*

**Table e-3:** Case 5 profile and case statistics

|  |  |
| --- | --- |
|  | HIV+ |
| Age (years) | 54 |
| Education (years) | 12 |
| HIV duration (years) | 25.8 |
| Current cART duration (months) | 16 |
| Nadir CD4 cells/mL | 266 |
| Current CD4 cells/mL | 528 |
| Current CD8 cells/mL | 1150 |
| Predicted WAIS-III VIQ | 104 |
| GDS | 4.55 |
| Historical AIDS | Yes |
| CSF Aβ-42 | 553.4 |
| CSF t-tau | 538.5 |
| CSF p-tau | 115.9 |
| CSF AD-like profile | Yes |
| APOE | Missing |
| Cingulum SUVRc vs NL | 0.15 (-1.04) [-1.44 to -0.65] |
| Cingulum SUVRc vs MCI | 0.03 (-2.20) [-3.83 to -0.84] \* |
| Cingulum SUVRc vs AD | 0.0002 (-5.10) [-7.70 to -2.95] \* |
| Caudate SUVRc vs NL | <0.03 (-1.97) [-2.54 to -1.45] \* |
| Caudate SUVRc vs MCI | 0.02 (-2.54) [-4.37 to -1.03] \* |
| Caudate SUVRc vs AD | 0.01 (-2.65) [-4.08 to -1.42] \* |
| Putamen SUVRc vs NL | 0.14 (-1.08) [-1.48 to -0.69] |
| Putamen SUVRc vs MCI | 0.01 (-3.12) [-5.31 to -1.35] \* |
| Putamen SUVRc vs AD | <0.005 (-3.19) [-4.88 to -1.77] \* |
| Pallidum SUVRc vs NL | 0.003 (-2.90) [-3.67 to -2.21] \* |
| Pallidum SUVRc vs MCI | 0.0007 (-5.61) [-9.38 to -2.62] \* |
| Pallidum SUVRc vs AD | 0.001 (-3.83) [-5.81 to -2.17] \* |
| Thalamus SUVRc vs NL | 0.01 (-2.32) [-2.95 to -1.73] \* |
| Thalamus SUVRc vs MCI | <0.02 (-2.68) [-4.59 to -1.11] \* |
| Thalamus SUVRc vs AD | <0.03 (-2.28) [-3.55 to -1.18] \* |

Case statistics reported as One-tailed p-value (t-value) [Confidence Interval]

GDS: Global Deficit Score; SUVR: standardized uptake value ratio; NL: Cognitive Normal, MCI: Mild Cognitive Impairment; AD: Alzheimer’s disease

p<.05 indicated by \*

**Table e-4**: Long-term clinical outcomes of the HIV+ cases

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Deceased** | **Clinical evidence of progressing neurocognitive impairment** | **Clinical evidence of neuropsychiatric symptoms & worsening** | **New (old) Diagnosis of dementia (HIV, other)** | **Comorbid conditions** | **Stable and virally suppressed HIV (yes/no)** | **Functional impairment/dependence** |
| **Case 1**  Abnormal trend for amyloid in hippocampi | No | Yes (2008, 2011) | Yes (depressive symptoms) | (ANI) MND (MSK1) + PSP-like illness | Suspicion of Progressive Supranuclear Palsy like-illness, with worsening gait ataxia and falls. A brain MRI also reveals micro-infarcts and hyperintensities to the white matter consistent with vascular injury | Yes | Partially independent with carers’ assistance |
| **Case 2**  AD-like amyloid | Yes (2019) | Yes (2018) | Yes (aggressive at times) | (Clinically moderate HAD, MSK2) AD | Aortic valve replacement, chronic obstructive pulmonary disease, ischaemic heart disease, type 2 diabetes, hypercholesterolaemia, peripheral neuropathy progressive | Yes | Fully dependent on carers’ assistance |
| **Case 3**  Decreased basal ganglia amyloid | Yes (2018) | Yes (already severe in 1995) | Yes (agitation) | (Clinically severe HAD, MSK3) | Bicuspid aortic valve with mod-severely dilated aortic root, hypercholesterolaemia, chronic obstructive pulmonary disease late in life recurrent aspiration pneumonia and urosepsis lead to hospitalisation & death | Yes (viral failure 2004) | Was in institution since initial HAD diagnosis |
| **Case 4**  Decreased basal ganglia amyloid | Yes (2016) | Yes (already moderate to severe 1998) | No | (Clinically severe HAD, MSK2) | Peripheral neuropathy, Hep C left untreated long-term, T1N3 anal squamous cell carcinoma (2015) leading to death | Yes | Was partially independent with carers/family assistance |
| **Case 5**  Decreased basal ganglia amyloid | Yes (2014) | Yes (2008) (already severe in 1997) | Yes | (Clinically severe HAD, MSK3) | Polyneuropathy, hypercholesterolaemia, hypertension, chronic kidney disease, Burkitt lymphoma (2014) ultinately leading to death | Yes | Was in institution since initial HAD diagnosis |
| **Case 6**  Normal amyloid | No | No | No | (MND, MSK1) Stable | Duodenal adenocarcinoma requiring whipples procedure & chemo complicated by pancreatic insufficiency, hyperlipidemia, hypertension, sigmoid colectomy for colon cancer (2013) partial penectomy for penile cancer (2016). Groin lymph node (2017) treated with right groin dissection & chemo-radiotherapy | Yes | Mostly independent |
| **Case 7**  Normal amyloid | No | No | No | (Clinically mild HAD, MSK1) | Painful neuropathy, functional neurological disorder, Intermittent medication compliance, type 2 diabetes intermittent control complicated by cellulitis, epilepsy, depression, hypercholesterolaemia, concussion, migraine, anal epithelial neoplasia | No (intermittent viral suppression due to ARV stopped due to other medical issues) | Partially independent with carers’ assistance |
| **Case 8**  No amyloid uptake | No | Yes (2011, self-report 2013) | Yes (comorbid diagnosis of possible bipolar disorder) | (ANI) (MND with psychiatric features, MSK 1) | Hyperlipidemia, Type 2 diabetes, hypertension, possible bipolar disorder, ART-related myalgias, lipodystrophy | Yes | Independent |
| **Case 9**  Normal amyloid | No | No | No | (ANI) Stable | Gastrooesophageal reflux disease, hypercholesterolaemia, peripheral neuropathy | Yes | Independent |
| **Case 10**  No amyloid uptake | No | Yes (2019) mild neurocognitive impairment as noted by GP | No | (ANI) MND (MSK1) | Anal dysplasia, hypercholesterolaemia, ischaemic heart disease, peripheral neuropathy, mouth, pharynx and lung cancer (2018) | Yes | Independent |

**Color coding: Red**: amyloid increase; **black**: amyloid within the normal age-range; **green**: amyloid decrease: **blue**: no amyloid uptake

**Table e-5: 22 ROIs**

|  |  |
| --- | --- |
| **Regions of Interest from AAL** | **Aggregated regions-of-interest** |
| Precentral\_L | **Central Region** |
| Precentral\_R |
| Rolandic\_Oper\_L |
| Rolandic\_Oper\_R |
| Postcentral\_L |
| Postcentral\_R |
| Frontal\_Sup\_L | **Lateral Frontal** |
| Frontal\_Sup\_R |
| Frontal\_Mid\_L |
| Frontal\_Mid\_R |
| Frontal\_Inf\_Oper\_L |
| Frontal\_Inf\_Oper\_R |
| Frontal\_Inf\_Tri\_L |
| Frontal\_Inf\_Tri\_R |
| Frontal\_Sup\_Medial\_L | **Medial Frontal** |
| Frontal\_Sup\_Medial\_R |
| Supp\_Motor\_Area\_L |
| Supp\_Motor\_Area\_R |
| Paracentral\_Lobule\_L |
| Paracentral\_Lobule\_R |
| Frontal\_Sup\_Orb\_L | **Orbito Frontal**  **Orbito Frontal** |
| Frontal\_Sup\_Orb\_R |
| Frontal\_Mid\_Orb\_L |
| Frontal\_Mid\_Orb\_R |
| Frontal\_Med\_Orb\_L |
| Frontal\_Med\_Orb\_R |
| Frontal\_Inf\_Orb\_L |
| Frontal\_Inf\_Orb\_R |
| Olfactory\_L |
| Olfactory\_R |
| Rectus\_L |
| Rectus\_R |
| Heschl\_L | **Superior Temporal** |
| Heschl\_R |
| Temporal\_Sup\_L |
| Temporal\_Sup\_R |
| Temporal\_Mid\_L | **Middle Temporal** |
| Temporal\_Mid\_R |
| Temporal\_Inf\_L | **Inferior Temporal** |
| Temporal\_Inf\_R |
| Parietal\_Sup\_L | **Superior Parietal** |
| Parietal\_Sup\_R |
| Parietal\_Inf\_L | **Inferior Parietal** |
| Parietal\_Inf\_R |
| SupraMarginal\_L |
| SupraMarginal\_R |
| Angular\_L |
| Angular\_R |
| Precuneus\_L | **Precuneus** |
| Precuneus\_R |
| Occipital\_Sup\_L | **Lateral Occipital** |
| Occipital\_Sup\_R |
| Occipital\_Mid\_L |
| Occipital\_Mid\_R |
| Occipital\_Inf\_L |
| Occipital\_Inf\_R |
| Fusiform\_L | **Medial Inferior Occipital** |
| Fusiform\_R |
| Calcarine\_L |
| Calcarine\_R |
| Cuneus\_L |
| Cuneus\_R |
| Lingual\_L |
| Lingual\_R |
| Temporal\_Pole\_Sup\_L | **Temporal Pole** |
| Temporal\_Pole\_Sup\_R |
| Temporal\_Pole\_Mid\_L |
| Temporal\_Pole\_Mid\_R |
| Cingulum\_Ant\_L | **Cingulum**  **Cingulum** |
| Cingulum\_Ant\_R |
| Cingulum\_Mid\_L |
| Cingulum\_Mid\_R |
| Cingulum\_Post\_L |
| Cingulum\_Post\_R |
| Hippocampus\_L | **Hippocampus** |
| Hippocampus\_R |
| ParaHippocampal\_L | **Parahippocampus** |
| ParaHippocampal\_R |
| Insula\_L | **Insula** |
| Insula\_R |
| Amygdala\_L | **Amygdala** |
| Amygdala\_R |
| Caudate\_L | **Caudate** |
| Caudate\_R |
| Putamen\_L | **Putamen** |
| Putamen\_R |
| Pallidum\_L | **Pallidum** |
| Pallidum\_R |
| Thalamus\_L | **Thalamus** |
| Thalamus\_R |

L: Left; R: Right

The AALs were collapsed into 22 ROIs based on anatomical organisation and function. Unfortunately, there is no consensus of a standard by which all regions of the brain are compared or used. Herein, we collapse the AALs, according to the neuroanatomical groups in the most cited atlas of the human brain (Mai et al., 2015), as well as Prices work on neuroanatomy organisation by function (Price and Drevets, 2010, Price, 2007). Hierarchically, this is first done by physical organisation, i.e. gyri and lobes, then by function, i.e. emotional, then juxtaposed together to create broad regions representative of both, i.e. central region, orbitofrontal. In some places, i.e. Thalamus, instead of dividing into left and right, these were simplified into thalamus. These regions are not unfamiliar, the orbitofrontal ROI, for example, is commonplace within the literature. The AALs regions are presented in white, with the ROI they collapse into highlighted in blue. i.e. the first six regions collapse into the Central Region.

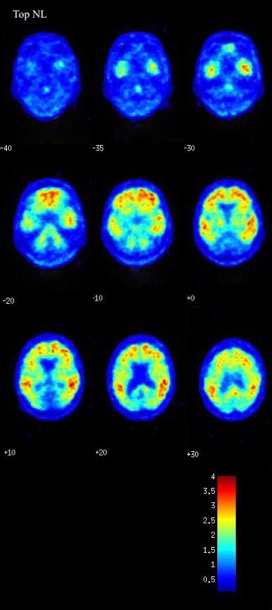
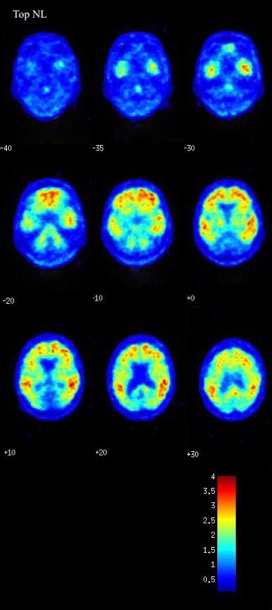
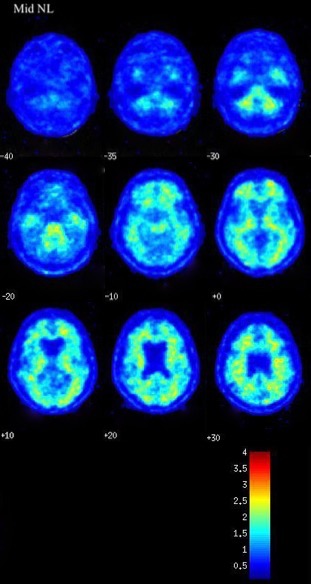
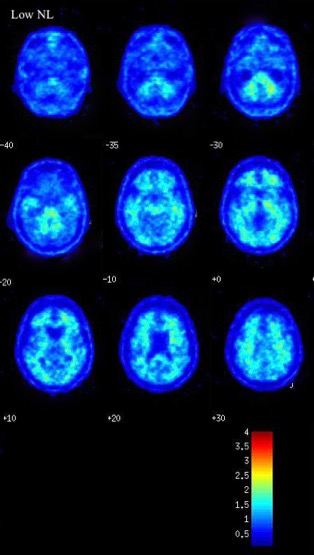
References:

Mai JK, Majtanik M, Paxinos G. Atlas of the human brain, 4th Ed.: Academic Press, 2015.

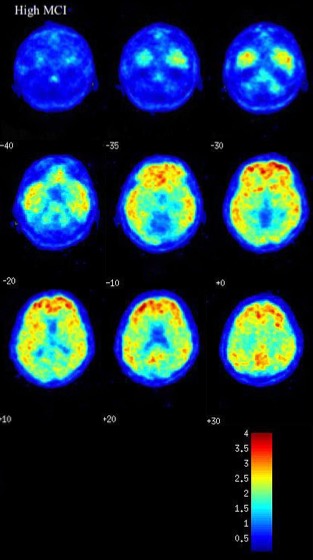
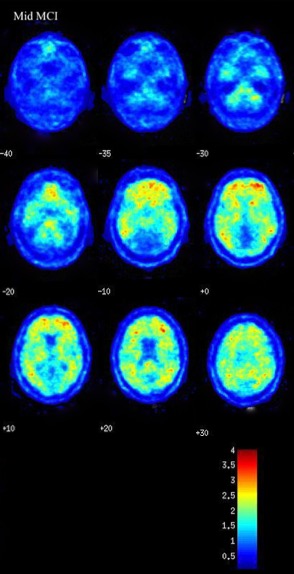
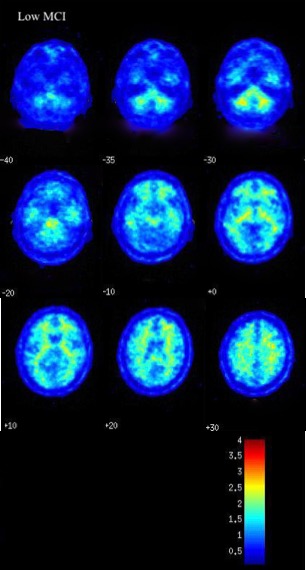
Price JL. Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. Ann N Y Acad Sci 2007;1121:54-71.

Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010;35:192-216.

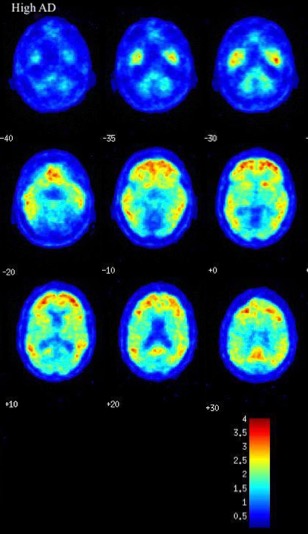
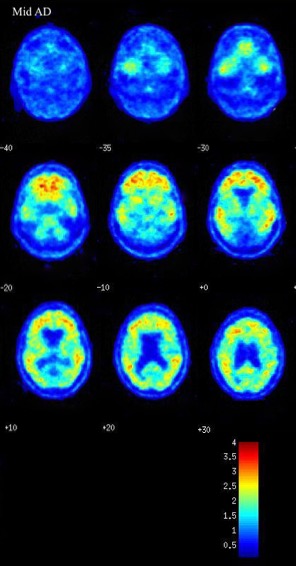
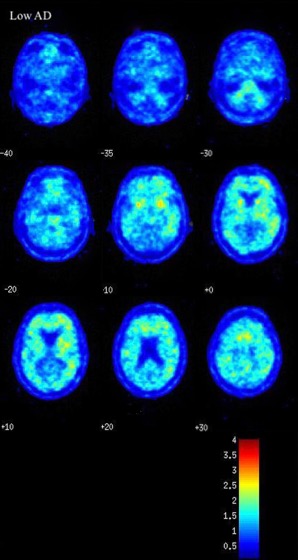
**Figure e-1:** SUVRcin the aged AIBL controls selecting case with lowest, average and highest deposition



**Figure e-2:** SUVRc in the aged AIBL MCI sample selecting cases with lowest, average and highest deposition



**Figure e-3:** SUVRcin the aged AIBL AD sample selecting case with lowest, average and highest deposition



**Figure e-4:** HAND cases 8 and 10 with abnormal PIB PET update (raw data)

