Widespread loss of presynaptic terminal marker SV2A in early Huntington's disease.

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INTRODUCTION

Synaptic damage has been proposed to play a major role in the pathophysiology of Huntington disease (HD), but *in vivo* evidence in humans is lacking. We performed a PET imaging study to assess synaptic damage and its clinical correlates in early stages of HD *in vivo.*

MATERIALS AND METHODS

Eighteen HD mutation carriers (7 premanifest, 11 early manifest [7 Shoulson-Fahn stage 1, 4 stage 2]) and 15 age- and gender-matched healthy controls were included. Subjects underwent a comprehensive clinical assessment of motor and non-motor manifestations, MRI, PET with ^{11}C-UCB-J, a radioligand targeting the ubiquitous presynaptic terminal marker SV2A, and ^{18}F-FDG PET, as regional cerebral glucose consumption is thought to largely reflect synaptic activity. Volumes of interest were delineated based on individual 3D T1 MRI. SUVR-1 images were calculated for ^{11}C-UCB-J with the centrum semiovale as reference region. ^{18}F-FDG PET activity was normalized to the pons. All PET data were corrected for partial volume effects.

1. CLINICAL CHARACTERISTICS

	Controls	HD (total)	*P value*	Premanifest HD	Manifest HD
Age (years)	52.3 ± 3.5	51.4 ± 11.6	0.76	45.0 ± 11.6	55.2 ± 9.6
Gender (M/F)	11/4	12/6	0.72	3/4	9/2
CAG repeat length	NA	41.9 ± 1.7	*NA*	42.3 ± 2.1	41.8 ± 1.4
Disease burden	NA	317.4 ± 50.3	*NA*	289.7 ± 51.0	335.1 ± 43.1
Unified HD Rating Scale – Motor	0.4 ± 0.6	11.6 ± 8.8	***<0.001***	4.0 ± 2.4	16.4 ± 7.9
Unified HD Rating Scale – Total Functional Capacity	13.0 [0.0]	12.0 [2.3]	***<0.001***	13.0 [0.0]	11.0 [2.0]
Montreal Cognitive Assessment	28.9 ± 1.1	25.1 ± 2.6	***<0.001***	26.6 ± 1.4	24.1 ± 2.8
Problem Behaviors Assessment	1.0 ± 1.5	8.9 ± 9.2	*0.004*	0.6 ± 1.0	14.2 ± 7.9

2. ^{11}C-UCB-J PET IMAGING RESULTS

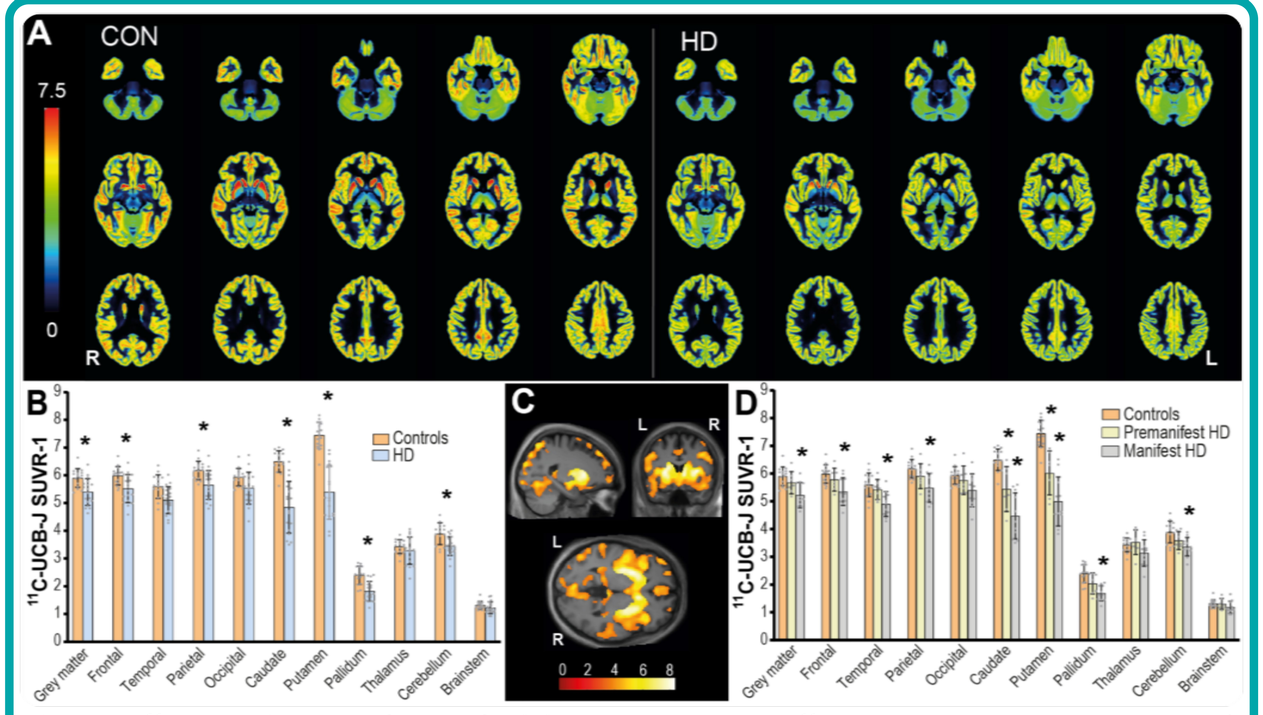

Figure 1. ^{11}C-UCB-J in HD and controls. (A) Transverse average ^{11}C-UCB-J SUVR-1 images in HD and controls (CON). Color bar represents SUVR-1 values. **(B, D)** ^{11}C-UCB-J SUVR-1 values of CON and total HD group (B) and CON, premanifest and early manifest HD subgroups (D) in different brain regions. * Significantly different from CON. Error bars indicate SD. **(C)** Clusters of voxel-based unpaired t-test with significantly lower ^{11}C-UCB-J in HD compared to controls (peak $p_{unc} < 0.001$, cluster $p_{FWE} < 0.05$). Color bar shows T-values.

3. ^{18}F-FDG PET IMAGING RESULTS

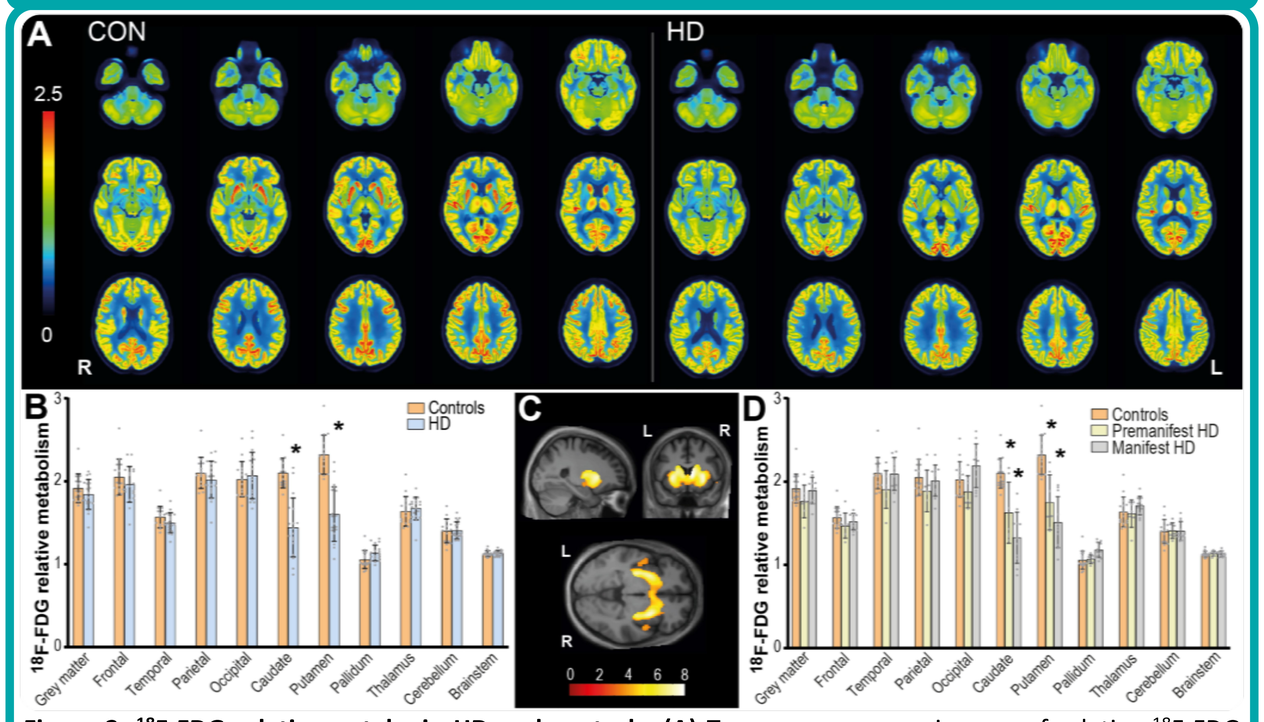

Figure 2. ^{18}F-FDG relative uptake in HD and controls. (A) Transverse average images of relative ^{18}F-FDG uptake in HD and controls (CON). Color bar represents normalized SUV values. **(B, D)** ^{18}F-FDG relative uptake values of CON and total HD group (B) and CON, premanifest and early manifest HD subgroups (D) in different brain regions. * Significantly different from CON. Error bars show SD. **(C)** Clusters of voxel-based unpaired t-test with significantly lower ^{18}F-FDG in HD compared to controls (peak $p_{unc} < 0.001$, cluster $p_{FWE} < 0.05$). Color bar shows T-values.

4. CORRELATIONS ^{11}C-UCB-J PET AND CLINICAL SCORES

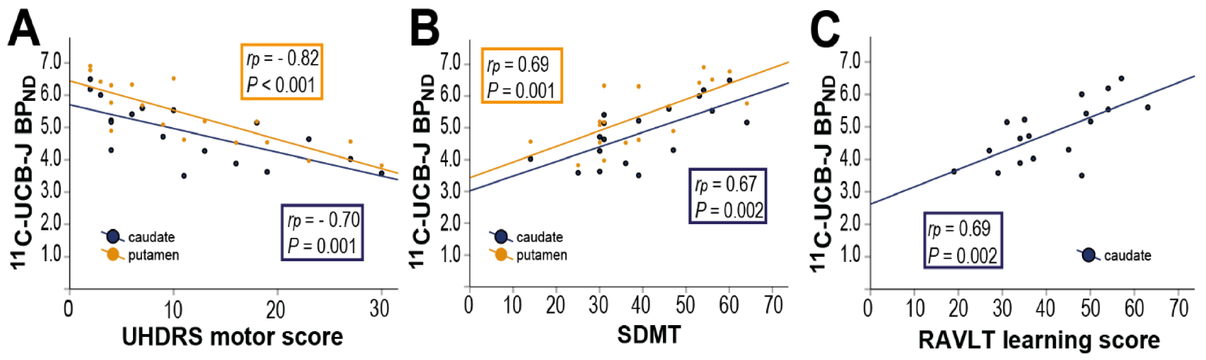

Figure 3. Volume of interest-based correlation between ^{11}C-UCB-J PET SUVR-1 and clinical scores in HD mutation carriers. (A-C) Volume of interest (VOI) based Pearson correlation analysis between clinical scores and ^{11}C-UCB-J SUVR-1.

After adding age and gender as covariates, only the correlation between UCB-J binding in the putamen and UHDRS motor score were significant. Correlations between striatal UCB-J binding and cognitive scores showed strong trends but did not reach significance any more (data not shown).

CONCLUSION

^{11}C-UCB-J PET revealed extensive loss of SV2A in early HD, suggesting widespread synaptic disconnection. SV2A loss in the striatum correlated with motor and cognitive functioning. ^{11}C-UCB-J PET is more sensitive than ^{18}F-FDG PET for detection of extrastriatal changes in early HD.