The Effects of ApoE4 Allele and Age on Subcortical Brain Atrophy in HIV Positive Subjects

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INTRODUCTION: Stable antiretroviral (ARV) treatments may control the viral replication and partially restore immune function in HIV-infected individuals; however, up to 50% of patients continue to demonstrate HIV-associated neurocognitive disorders (HAND),[1] which may be mediated by various co-morbid issues or genetic vulnerability. The presence of apolipoprotein (Apo) E4 allele has been shown to accelerate the progression of HIV disease,[2] and increase the risk for developing HAND by two-fold.[3] Prior studies demonstrated smaller subcortical brain structures in HIV patients with HAND. Whether the presence of the Apo E4 allele and differences in age may lead to additive or interactive effects on subcortical brain atrophy in HIV patients stable on ARV are unknown and were evaluated in this study.

METHODS: **Clinical**: 71 seronegative (SN) subjects (age: 47.7±9.7 years, 90% men, 24% ApoE4+) and 64 HIV subjects (age: 46.5±12.6 years, 92% men, 31% ApoE4+) were studied. HIV subjects had CD4 counts (450±30/mm^3), nadir CD4 (204±21/ mm^3), plasma viral load (Log 2.6±0.2), HIV dementia scales (14.5±0.2) and Karnofsky scores (91±1.2). HIV patients with and without HAND had a similar proportion of at least one copy of ApoE4+ allele (30.8% vs. 31.6%). **Imaging**: Each subject underwent Magnetization Prepared RApid Gradient Echo (MP-RAGE) volumetric imaging (TR/TE/TI=2200/4.48/1000ms; 160 slices, 1x1x1 mm) on a Siemens 3.0 Tesla Trio MR system. Using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), brain structures were extracted from the skulls and registered to an existing template prior to segmentation of the subcortical structures (caudate, hippocampus, globus pallidus, putamen, thalamus, amydala and cerebellum) and cortical gray and white volumes in both hemispheres. Only subcortical data are presented here.

RESULTS: HIV subjects with HAND had smaller subcortical structures compared to SN controls in all brain regions measured (repeated measure ANOVA, p=0.006), and those with normal cognition also had significantly smaller putamen (p=0.03) and globus pallidus (p=0.001) (**Figure 1**). In addition, presence of at least one ApoE4 allele had a greater atrophic effect on younger (<50 years), but not older (≥50 years) HIV patients compared to controls in the left and right putamen, left caudate, left thalamus and left cerebral white matter (3-way ANOVA-p-values≤0.05; **Figure 2** shows data from 3 of these regions).

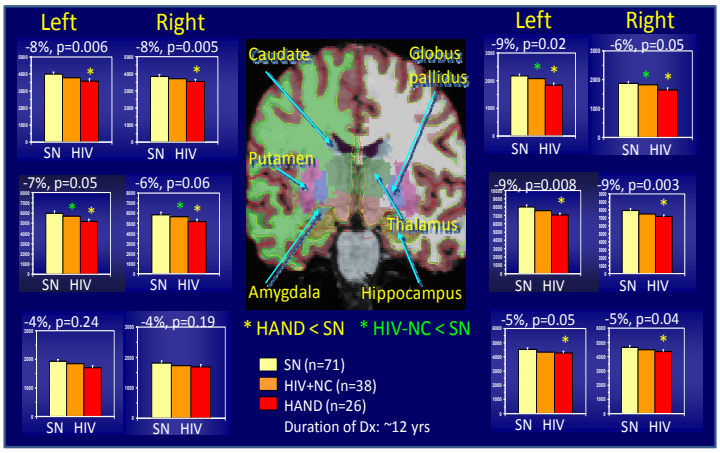

Figure 1: HIV patients with HAND (red bars) show significantly smaller subcortical brain volumes in all regions measured (yellow asterisks, % difference and posthoc p-values are indicated above bargraphs for each region). HIV patients with normal cognition (orange bars) also showed smaller brain volumes, although to a lesser extent, with significance reached in the putamen and globus pallidus (green asterisks).

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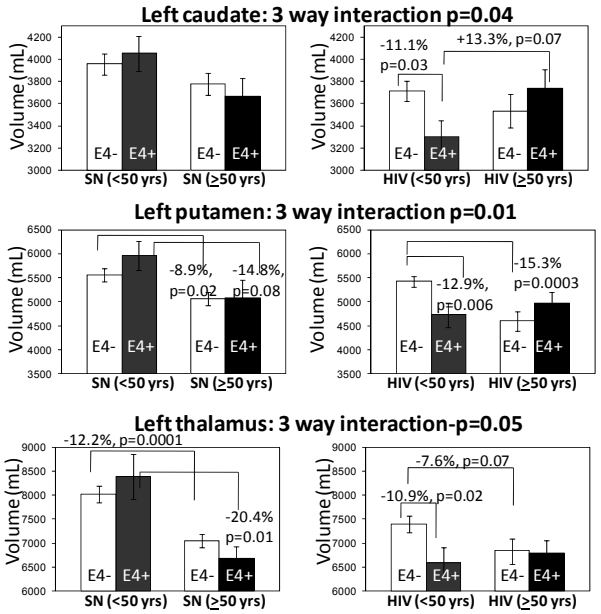

Figure 2: 3-way ANOVA showing interaction effects between HIV, Age and ApoE4+ status, with greater atrophic effects in older individuals with or without HIV, and in younger but not the older HIV patients.

DISCUSSION / CONCLUSION: In a group of clinically stable HIV subjects, we found smaller subcortical structures in those with HAND, and even patients with normal cognition showed smaller putamen and globus pallidus. These findings suggest presymptomatic neurodegeneration in these brain regions. The surprising finding that ApoE4 genotype is associated with greater atrophic effects in the younger but not older HIV patients suggests that ongoing neuro-inflammatory processes in HIV may be more robust and have stronger deleterious effects in the younger HIV patients. We will further evaluate the effects of ApoE4 allele on the progression of brain atrophy in these individuals with longitudinal follow-up studies.

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