Effects of *COMT* Val[158]Met Polymorphism on Resting State Brain Connectivity in HIV Infection and Aging

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INTRODUCTION: Approximately 50% of human Immunodeficiency virus (HIV-1) infected persons have HIV-associated cognitive disorder (HAND).[1] Brain activation during cognitive tasks on functional MRI (BOLD-fMRI) of HIV infected individuals is often abnormal prior to manifestation of cognitive symptoms.[2-4] Even at rest, functional connectivity (rs-fcMRI) was found to be decreased in the visual association areas,[5] the default mode network, the executive control network, as well as the salience network.[6] Given the known dopaminergic deficits in HIV patients[7] and in aging,[8] Catechol-O-methytransferase (*COMT*) polymorphism with Val[158]Met substitution, which increases synaptic dopamine catabolism, may play an important role in regional functional connectivity in HIV patients, especially in older individuals.

Methods: 83 participants [40 HIV+ subjects and 43 HIV-seronegative (SN) controls] were studied on a 3T Siemens Trio scanner. Single-shot gradient-echo echo-planar MRI (TE/TR=30/3000ms, 3 mm slices, ~42 axial slices, 642 matrix, 20cm FOV, 120 NEX) was performed with motion and distortion corrections, and motion monitoring in real-time to assure <1mm translations and <1º rotations. The Melodic FSL software tool was used to perform Probabilistic Independent Component Analysis (ICA) on the fMRI data using linear models. Each subject was genotyped for the *COMT* polymorphism at the single nucleotide (rs4680). Each subject was also evaluated neurologically and with a battery of neuropsychological test.

Results: **Clinical:** The two groups had similar ages (HIV: 50±1.6 years; SN: 52.4±1.8 years), sex proportion (HIV: 93% men; SN: 91% men), education (HIV: 15.0±0.5 years; SN: 15.4±0.4 years) and racial/ethnic distributions. 11 subjects from each group were homozygous for Met/Met; the HIV subjects with Met/Met and those with Val substitution(s) had similar nadir CD4 counts, plasma viral load, duration of HIV diagnosis, and HIV-dementia scale. Although the HIV subjects as a group did not meet diagnostic criteria for HAND, they performed poorer on cognitive tests globally (p=0.03), due to poorer performance on memory (p=0.006), learning (p=0.002) and attention/working memory (p=0.006). All subjects with the Val substitution also had better memory (p=0.02).

rsfMRI: Twelve ICA components that correspond to known networks were identified across all subjects. Compared to SN, HIV subjects had lesser connectivity in the right lateral attention and the bilateral visual networks (**Figure 1**). Age dependent decreases in connectivity were found in the occipital lobes (BA 17, lingual gyrus, max 18, -94, -5, cluster-corrected-p<0.001; BA 18, cuneus, max 0,-97, 1, corrected-p=0.004) and right temporal lobe (BA 39, max 57, -61, 13, corrected-p=0.008), but the slopes were not different between HIV and SN. However, when the *COMT* genotypes were evaluated, only HIV subjects with Met/Met alleles showed age-dependent decrease in BOLD response (**Figure 2**).

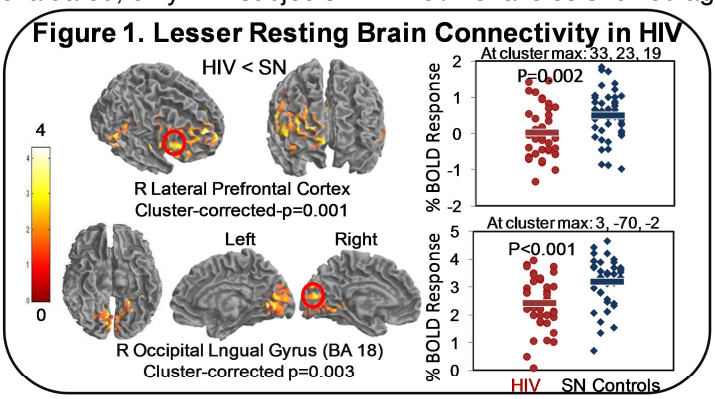

Figure 1. **Top:** Statistical map (**left**) and extracted BOLD signals at the ROI (**red circle and right scatterplot**) showing lesser connectivity in the right attentional network (from ICA, including lateral frontal, temporal and cerebellum) in the HIV subjects than SN controls. **Bottom Row:** Similarly lesser connectivity in the HIV than SN controls is seen in the visual network bilaterally.

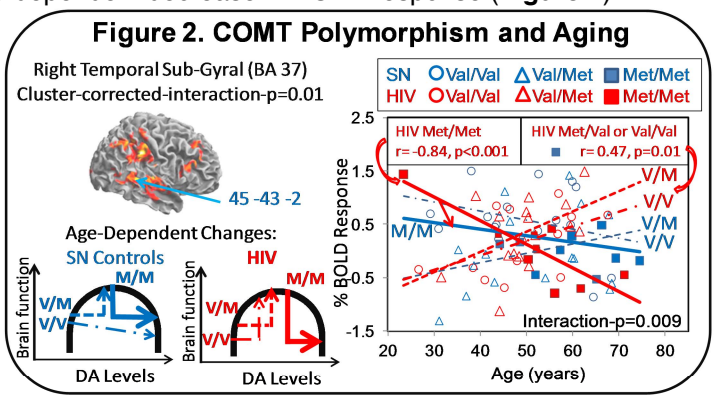

Figure 2. Statistical map (**Top left**) and BOLD signals at the cluster maximum (**Right scatterplot**) showing steepest age-dependent decreases in the right attentional network connectivity in HIV Met/Met subjects, while HIV Met/Val or Val/Val subjects showed age-dependent increases in BOLD responses, due to the inverted U-shaped relationship between brain function and DA levels (**Bottom**).

Discussion: Our finding of lesser resting brain connectivity in the visual and attention networks of HIV subjects is consistent with the two recent reports.[5,6] We further found that HIV subjects with the Met/Met allele(s) had greater than normal age-dependent decline in resting brain connectivity, which is likely due to their lower dopamine function and contributed to the greater age-dependent cognitive decline. Evaluating rsfcMRI in relation to *COMT* polymorphism provides insights into the pathophysiology of HAND and may be useful in predicting cognitive decline in HIV subjects.

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