

Title: Methamphetamine and Genetically-Predicted Expression of the Cytoskeletal Protein Spectrin Gene (*SPTB*) May Interact to Influence Neurocognitive Function in HIV+ Adults

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Neurocognitive impairment (NCI) remains a common complication of HIV infection, despite effective antiretroviral therapy. Methamphetamine exposure (MA) may have additive or synergistic effects. Our group has been exploring the role of host genetic variation in risk and patterns of NCI in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study. Using CHARTER genome-wide data, we recently predicted the genetically-derived component of gene expression using an approach called PrediXcan. We previously demonstrated the impact of PrediXcan-estimated gene expression traits on the global deficit score (GDS) in 440 CHARTER participants of European ancestry. Expression of 222 genes was associated with continuous GDS at $p < 0.01$. In pilot analyses presented here, we examined the impact of a lifetime history of MA abuse or dependence as determined by Composite International Diagnostic Interview criteria on the most robust of these associations. We selected the top five GDS-associated genes (*ANKRD44*, *IRS2*, *ATF3*, *SLC35C2*, and *SPTB*), and statistically modeled the interaction between lifetime MA and each predicted gene expression trait on GDS. Regression models included adjustment for age, baseline reading comprehension (wide-range achievement test [WRAT]), HIV RNA in plasma, nadir CD4+ T-cell count, and comorbid neurologic conditions, and included terms for the predicted gene expression trait, lifetime MA, and interaction between lifetime MA and the predicted gene expression trait. The main effects of lifetime MA and predicted *SPTB* expression were both statistically significant, with lower GDS (better neurocognitive performance) being associated with lifetime MA ($p < 0.001$) and lower *SPTB* expression ($p = 0.001$). In addition, there was a significant interaction between lifetime MA and predicted *SPTB* expression ($p = 0.005$). These results suggest that germline genetic variants that alter *SPTB* expression contribute to GDS in HIV-infected individuals, and that any lifetime MA abuse or dependence significantly modifies the relationship between these variants and neurocognitive function. *SPTB* encodes spectrin, a cytoskeletal protein involved in calcium homeostasis in the brain and red cell membrane stabilization, and implicated in Alzheimer's disease neuropathology. This novel association supports prior findings from our group linking red-cell indices to NCI in CHARTER, and requires further study to delineate the mechanism by which MA exposure may modulate *SPTB* effects on NC function in HIV-infected adults.