HIV-related neurocognitive impairment is related to polymorphisms in *CCR2* and *CD163* in the absence of cocaine and opiate dependency

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Despite the widespread use of efficacious antiretroviral therapies, HIV-associated neurocognitive disorder (HAND) remains highly prevalent, and its dissociation from HIV replication makes it imperative to understand non-viral factors related to its neuropathogenesis. Chronic immune activation has been implicated, but the role of genetics has not been explored. Using an advanced-staged multi-ethnic HIV-positive population (n=276), we examined 230 polymorphisms within 55 genes proposed to play a role in both immune dysregulation and cognition. We examined these polymorphisms for associations with neuropsychological performance in global and cognitive domain T-scores (Motor, Processing Speed, Verbal Fluency, Learning, Memory, Executive Functioning, Working Memory) while controlling for opiate and cocaine dependency using linear regression analysis. While significant associations were observed in nearly every domain across both populations for multiple polymorphisms, one of the most significant effects in Caucasian subjects was observed in the Motor domain with the *CCR2* V64I polymorphism (rs1799864), such that nonsubstance users carrying the mutation had poorer motor performance while substance users with the mutation had better motor performance ($p=0.004$). When we examined levels of *CCR2* mRNA expression in peripheral blood mononuclear cells, we observed that nonsubstance users with the mutation had decreased expression of *CCR2* as compared to those without the mutation; such differences were not seen in drug users. For African- American subjects, the most significant effects were observed for several *CD163* polymorphisms in multiple domains (Global, Processing Speed, Verbal Fluency, and Working Memory). In African-Americans, nonsubstance users carrying *CD163* mutations had poorer performance, as compared to substance using individuals, who had better performance across multiple domains. Gene expression studies for *CD163* are ongoing, as are replication of these results with additional samples from the National NeuroAIDS Tissue Consortium and a separate cohort recruited in New York City, NY. These results suggest that substance use changes that neurobiological relationship of cognitive impairment to inflammatory processes, and should be factored into genetic studies of HAND.