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The longitudinal and interactive effects of HIV status, stimulant use, and host genotype upon neurocognitive functioning

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Abstract Both human immunodeficiency virus (HIV)-1 infection and illicit stimulant use can adversely impact neurocognitive functioning, and these effects can be additive. However, significant variability exists such that as-of-yet unidentified exogenous and endogenous factors affect one's risk for neurocognitive impairment. Literature on both HIV and stimulant use indicates that host genetic variants in immunologic and dopamine-related genes are one such factor. In this study, the individual and interactive effects of HIV status, stimulant use, and genotype upon neurocognitive functioning were examined longitudinally over a 10-year period. Nine hundred fifty-two Caucasian HIV+ and HIV− cases from the Multicenter AIDS Cohort Study were included. All cases had at least two comprehensive neurocognitive evaluations between 1985 and 1995. Pre-highly active antiretroviral therapy (HAART) data were examined in order to avoid the confounding effect of variable drug regimens. Linear mixed models were used, with neurocognitive domain scores as the outcome variables. No four-way interactions were found, indicating that HIV and stimulant use do not interact over time to affect neurocognitive functioning as a function of genotype. Multiple three-way interactions were found that involved genotype and HIV status. All immunologically related genes found to interact with HIV status affected neurocognitive functioning in the expected direction; however, only C-C chemokine ligand 2 (CCL2) and CCL3 affected HIV+ individuals specifically. Dopamine-related genetic variants generally affected HIV-negative individuals only. Neurocognitive functioning among HIV+ individuals who also used stimulants was not significantly different from those who did not use stimulants. The findings support the role of immunologically related genetic differences in CCL2 and CCL3 in neurocognitive functioning among HIV+ individuals; however, their impact is minor. Being consistent with findings from another cohort,

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dopamine (DA)-related genetic differences do not appear to impact the longitudinal neurocognitive functioning of HIV+ individuals.

Introduction

The prevalence of neurocognitive dysfunction among people infected with human immunodeficiency virus (HIV)-1 remains high, with recent prevalence estimates between 40 and 50 % (Heaton et al. 2011; McArthur et al. 2003, 2005). Chronic HIV infection may result in a persistent neuroinflammatory state, even with relatively effective peripheral viral suppression (Brew 2004; Cysique et al. 2004, 2005; Kraft-Terry et al. 2009). The result of this has been an increase of mild forms of HIV-associated neurocognitive disorder (HAND) (Antinori et al. 2007; Heaton et al. 2010). Common comorbidities, such as substance abuse, can increase the risk for neurologic and neurocognitive dysfunction (Rippeth et al. 2004). With lifetime substance abuse rates ranging between 20 and 50 % among HIV-1-infected (HIV+) individuals, understanding the interactive effects of substance use and HIV upon neuropathogenesis has great importance (Carey et al. 2006; Ferrando et al. 1998; Ferrando and Batki 2000; Levine et al. 2006; Martin et al. 2004; Rabkin et al. 1997, 2004; Rippeth et al. 2004). Perhaps most germane in the context of HIV is stimulant use (e.g., methamphetamine and cocaine), which is one of the more commonly abused classes of drugs among infected and at-risk individuals in the USA (Klinkenberg and Sacks 2004; Stall et al. 2001) and an established neurotoxin known to exacerbate the effects of HIV-1 (Aksenov et al. 2006; Gaskill et al. 2009; Kuczenski et al. 2007; Levine et al. 2006; Rippeth et al. 2004; Silverstein et al. 2011; Zhang et al. 1998).

Evidence from neuroimaging, animal model, and in vitro studies suggests that stimulants and HIV have overlapping neuroanatomical targets (Avison et al. 2004; Aylward et al. 1993; Berger and Nath 1997; Cass 1997; Dal Pan et al. 1992; Itoh et al. 2000; Little et al. 1999; Power et al. 1993) and result in additive or even synergistic adverse impact upon neurophysiology (Aksenov et al. 2006; Cass et al. 2003; Flora et al. 2003; Martin-Thormeyer and Paul 2009; Nath et al. 2001, 2002; Theodore et al. 2007). However, while laboratory studies strongly indicate additive or synergistic adverse neurobiological effects of combined stimulant use and HIV, findings from clinical and epidemiological studies so far have yielded mixed results. Cross-sectional studies indicate increased neurocognitive impairment with the combined effects of HIV and stimulant use (Carey et al. 2006; Rippeth et al.

2004). For example, Rippeth et al. (2004) examined four groups with various combinations of the risk factors of HIV infection and methamphetamine use (HIV+/drug using, HIV+/nondrug using, HIV−/drug using, and HIV−/nondrug using) and found an incremental increase in depression and neurocognitive impairment among those with more risk factors. However, other cross-sectional investigations have not found either an additive or synergistic relationship between HIV and stimulants (Basso and Bornstein 2003; Durvasula et al. 2000), suggesting that additional, unidentified factors likely determine the extent to which stimulant use results in neurobehavioral impairment among individuals with HIV.

Conspicuously lacking are longitudinal studies of neurocognitive outcomes in HIV+ individuals who are abusing stimulants. Such a dynamic model of HAND neuropathogenesis could prove useful in predicting outcomes, identifying salient biological factors, and potentially allowing for the prioritizing of treatments. Towards such an end, consideration of endogenous biological factors can enhance the utility of such studies by identifying viable targets for treatment. Because of the natural variation in host genotype and the known influence of such variation upon neurophysiology and immunology, consideration of genes suspected to contribute to HIV disease progression or to affect neurophysiological functioning is an important dimension to consider in any longitudinal analysis of HIV and stimulant use. There is evidence that sequence variants of chemokine and other immune-related genes results in differences in susceptibility for HIV infection and disease progression and, in some instances, HAND. These include the C-C chemokine receptor type 5 (CCR5) (Liu et al. 1999; Samson et al. 1996), CCR2 (Singh et al. 2004; Smith et al. 1997), C-X-C motif chemokine 12 (CXCL12) (Winkler et al. 1998) (also called stromal cell-derived factor 1), C-C chemokine ligand 2 (CCL2) (Gonzalez et al. 2002) (also called monocyte chemotactic protein 1), CCL3 (Gonzalez et al. 2001) (also called macrophage inflammatory protein 1α), CCL5 (Liu et al. 1999; McDermott et al. 2000) (also called regulated on activation, normal T cell expressed and secreted (RANTES)), tumor necrosis factor alpha (TNF-α) (Quasney et al. 2001), mannose-binding lectin 2 (MBL-2) (Spector et al. 2010), and apolipoprotein E (ApoE) (Burt et al. 2008; Chang et al. 2011; Corder et al. 1998; Soontornniyomkij et al. 2012; Valcour et al. 2004) genes, among others. However, with regards to HAND, none of these allelic associations have been consistently replicated.

In addition to polymorphisms within these largely immunologically related genes, there exist a number of variants of neurobiologically related genes that may impact neurocognitive functioning in the context of HIV and stimulant use. Because HAND has been associated with dopamine (DA) dysfunction, genetic variants that further affect DA availability may augment neurobehavioral impairment.

Among these is the Val158Met allele within the catechol-*O*-methyltransferase (COMT) gene, which is the result of a single nucleotide polymorphism (SNP; rs4680). COMT is an enzyme that catabolizes DA within the prefrontal cortex, an area crucial for a variety of cognitive abilities. This SNP results in a sequence modification and amino acid substitution of methionine (Met) for valine (Val). The Met allele reduces the enzymatic activity of COMT (Lachman et al. 1996), leading to greater availability of DA within the prefrontal cortex. Individuals who are homozygous for the Met allele perform better on neuropsychological tests of working memory and other executive ability tests (Egan et al. 2001; Goldberg et al. 2003; Mattay et al. 2003). Such findings are particularly relevant to HIV, as a recent neuroimaging study found reduced neural processing capacity in working memory networks in those with HIV (Tomasi et al. 2006). Another gene of interest produces dopamine beta-hydroxylase (DBH), which catalyzes the conversion of DA to norepinephrine. A SNP within the DBH gene accounts for 35–52 % of the variation in plasma DBH activity (Zabetian et al. 2001). In addition, another polymorphism within this gene has been associated with biochemical variability in the catecholamine pathway (Wei et al. 1997) and ADHD (Daly et al. 1999; Roman et al. 2002). Dopamine receptors have also been implicated as a bridge between stimulants and HIV progression. For example, Gaskill et al. (2009) found that extracellular DA acts through dopamine receptor 2 (DR2) on monocytes to increase HIV replication, and a SNP in the DR3 gene (rs6280) was recently found to affect risk for neurocognitive impairment among HIV+ stimulant addicts (Gupta et al. 2011). Finally, brain-derived neurotrophic factor (BDNF) is a neurotrophin that promotes neuronal survival and regulates the production and differentiation of neurons. BDNF plays a regulatory role in the DA and serotonin systems (Guillin et al. 2001; Mossner et al. 2000). Both in vitro and in vivo evidences suggest that BDNF may reduce the neurotoxic effects of gp120 in those with HIV (Nosheny et al. 2005). A SNP (rs6265) resulting in the Val or Met is associated with neurobehavioral disorders (Zhang et al. 2006). The Met allele is also associated with diminished episodic memory, abnormal activation, and decreased levels of *N*-acetylaspartate in the hippocampus as determined via brain MRS (Egan et al. 2003).

We propose that there is compelling evidence that some individuals possess genotypes that make them more vulnerable to neurocognitive deficits in the face of environmental stressors such as HIV infection and stimulant abuse. While the results of cross-sectional studies have been equivocal, a number of methodological improvements may elucidate the true relationship. In the current study, we modeled the individual and interactive effects of HIV status, stimulant use, and host genotype upon neurocognitive functioning over a time period of up to 10 years, while controlling for the effect of other important factors known to increase risk of HAND. We hypothesized that both DA-related genes and immunologically related genes would significantly modify the effects of HIV status and/or stimulant use on neurocognitive functioning over time.

Methods

Participants

Genotype, behavioral, medical, and virologic data were obtained from participants in the Multicenter AIDS Cohort Study (MACS). The MACS is a multicenter epidemiological study of the natural history of HIV infection in homosexual men, conducted in four US cities (Baltimore, Chicago, Pittsburgh, and Los Angeles). Recruitment procedures have been described in detail elsewhere (Miller et al. 1990). MACS participants are generally evaluated at semiannual intervals. Evaluations included physical examinations, HIV testing, laboratory testing, structured clinical interviews, and neuropsychological testing as well as collection of information about illicit substance use. From the larger MACS cohort, cases for the current study were selected according to the following criteria: (1) only Caucasian individuals (including Hispanic) were chosen in order to avoid the confounds of population stratification and different neurocognitive test normative data. (2) We excluded individuals with history of HIV-associated dementia, AIDS, loss of consciousness of greater than 1 h (per self-report), learning disability (per self-report), brain neoplasm, stroke, current injection drug use, or current use of the following drugs: ethyl chloride, GHB, MDMA, PCP, hallucinogens, downers, and heroin/opiates. (3) We included only those individuals with at least two comprehensive neurocognitive evaluations between November 1985 and May 1995. This time frame was chosen to avoid the possible confounding effects of highly active antiretroviral therapy (HAART), allowing us to better delineate the interactive effects of stimulant use, HIV status, and genotype. After applying these strict criteria, 1,110 individuals were qualified. Following genotyping quality control, the final sample included 952 individuals (914 Caucasian/non-Hispanic and 38 Caucasian/Hispanic). Participant characteristics are summarized in Table 1.

Primary variables

Neuropsychological functioning

A comprehensive neuropsychological exam is administered every 2 years and consists of a 40-min conventional and computerized neuropsychological test battery designed to cover a broad range of cognitive domains. Raw scores are converted into age- and education-adjusted T-scores using

Table 1 Group characteristics

Variable	HIV−	HIV+
Age	37.3 (7.9)	35.7 (6.6)
Education (%)		
<High school	1 (<1)	6 (1)
High school	21 (5)	55 (10)
Some college	108 (27)	161 (29)
College	107 (26)	133 (24)
Postgraduate	169 (42)	191 (35)
CD4+	991 (329)	589 (282)
Viral load	n/a	44,263 (67,674)
History of IVDU (%)	13 (3)	67 (12)
Time between evaluations	6.5 (2.4)	5.5 (2.3)

normative data derived from HIV-seronegative MACS participants. T-scores for all tests comprising a domain are averaged to obtain a domain T-score. A total of six domain T-scores were derived, including learning and memory (derived from the learning and delayed recall trials of the Rey-Osterrieth Complex Figure Test (Osterrieth 1944; Rey 1964) and Rey Auditory Verbal Learning Test (Rey 1941)), processing speed (Stroop color naming (Comalli et al. 1962) and Symbol Digit Modalities Test (Smith 1982)), motor (Grooved Pegboard (Klove and Matthews 1966)), executive (Stroop interference (Comalli et al. 1962) and Trail Making Test, form B (Reitan 1958)), and sustained attention (CalCAP (Miller 1990)). Domain scores were used as neurocognitive phenotypes, each in separate analyses.

Stimulant use

Stimulant use was recorded at each visit based on self-reported use during the 6 months prior to the visit. Stimulant use was classified as use vs. no use of powder cocaine, crack cocaine, and amphetamines (methamphetamine, speed, ice, crystal).

Genotype

We chose markers that are directly implicated or suspected to tag genetic susceptibility loci for HAND. They included two SNPs within the CCL3 (rs1719134 and rs1130371) (Levine et al. 2009), a three-SNP haplotype within the MBL-2 gene (rs1800450, rs1800451, and rs5030737) (Spector et al. 2010), and SNPs within coding or noncoding regions of the CCL2 gene (rs1024611) (Gonzalez et al. 2002), TNF-α (rs1800629) (Mathis et al. 2008), COMT (rs4680) (Bousman et al. 2010; Kumar et al. 2011), BDNF (rs6265) (Ahmed et al. 2008; Nosheny et al. 2007), DBH (rs1611115) (Kumar et al. 2011), DR2/ANKK1 (rs1800497) (Kumar et al.

2011), DR3 (rs6280), and CXCL12 (rs1801157) (Langford et al. 2002; Peng et al. 2006).

Time

Time was determined as the number of years from baseline testing and was calculated in years.

Additional covariates

Marijuana, injection drug, and alcohol use

Marijuana, injection drug, and alcohol use was recorded at each visit in terms of frequency of use in the last 6 months as well as the average amount used each time. We examined history of injection drug use (IDU) as well as current marijuana and alcohol use. Participants were classified based on their pattern of substance use at each visit examined. Marijuana use was determined at each visit based on self-report and classified as use vs. no use. For alcohol, participants were classified as having no use, 1–3 drinks/week, 4–13 drinks/week, or more than 13 drinks/week. Visits in which intravenous drug (IVD) use was reported were excluded. History of IVD use was included as a covariate (yes vs. no).

CD4

For HIV+ cases, nadir CD4 was included as a covariate. For HIV− cases, mean CD4 for all prior visits was used as a covariate.

Hepatitis C infection (HCV)

Hepatitis C infection (HCV) status in MACS participants was determined via blood testing. Participants were classified as HCV negative if antibody testing was negative. Participants were classified as HCV positive if they were found to be in the process of seroconversion, acute infection, chronic infection, clearing (between RNA+ and RNA−), or previously HCV positive, but now being clear of HCV RNA.

Depression

Depression was determined indirectly with the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). This measure assessed symptoms that are often associated with depression. Scores on the CES-D are entered for each visit in a continuous manner.

Practice effects

Practice effects were controlled for by correcting for the first, second, and later follow-ups.

DNA extraction and genotyping

For most HIV-seronegative participants, DNA was obtained from pelleted peripheral blood mononuclear cells. The Autopure LS™ nucleic acid purification instrument was used for extracting DNA. Samples were quantitated using OD 260/280. DNA was then genotyped with the Sequenom iPlex. Samples submitted for genotyping with the Sequenom iPlex assay were quantitated using a RiboGreen fluorescent assay and normalized to 10 ng per μl. Five microliters of iPlex reactions was set up in 384-well PCR plates using 1 μl (10 ng) of templates DNA and using pooled custom PCR primers normalized to 100 μm per primer using a Tecan EVO 100 workstation and cycled in PE 9700 Dual 384 PCR machines. PCR reactions were prepared for genotyping by treatment with SAP. iPlex primer extension reactions were prepared using custom, mass-tuned, extension primer pools and cycled in PE 9700 Dual 384 PCR machines. Extension products were prepared for detection by resin deionization and spotted onto SpectroChip II chips using the Sequenom Nanodispenser. MALDI-TOF detection was done on the Sequenom MassArray Compact System. Genotype data were reviewed and extracted using Typer v4.0 software and exported to the investigators for analysis. Genotype for most HIV+ participants was obtained from a genome-wide genotyping database, described previously (Levine et al. 2012a). Briefly, genotyping was conducted on the Illumina 1M, 1MDuo, or 550K platform and was either directly obtained or imputed. Imputation was performed using MACH (Li et al. 2010), and all data were imputed to the forward/positive strand. Strand ambiguous AT/GC SNPs were excluded. HapMap2 was used as the reference population (Frazer et al. 2007). SNPs with an imputation quality score (r^2) greater than 0.3 were retained for analysis. All SNPs were examined for Hardy-Weinberg equilibrium (HWE). It was found that rs1130371 in the MIP1α gene was not in HWE, so it was excluded from analyses.

Statistical analysis

Our basic approach involved the use of generalized linear mixed models to take account of repeated observations on the same subjects. One advantage of this family of models is that well-developed procedures exist for diagnosing violations of assumptions and lack of fit of the proposed model (Atkinson 1985; Chatterjee and Hadi 1988; McCullagh and Nelder 1989). These procedures provide checks of the error assumptions, e.g., normally distributed errors with constant variance for continuous outcomes, and can suggest data transformations, such as the log transformation, when these are needed. Procedures are also available to check for outliers and influential points, as well as nonlinear trends, interactions, and multicollinearity.

Linear mixed models with domain-specific T-scores as the outcome variables were used (Table 2). Independent variables in these models included variables for the genotype of interest, stimulant use, HIV serostatus (positive vs. negative), hepatitis C serostatus (positive vs. negative), CD4 (nadir for HIV+, mean CD4 for HIV), marijuana use, alcohol use, history of IVD use, depression, time since the first test administration, and practice effects (between baseline and first follow-up, second follow-up, and any follow-up thereafter) at each visit. All were time-varying covariates in these models. The covariance structure included a random intercept for each subject. Each SNP listed in Table 3 was examined in a separate model with individual cognitive domains. A total of 60 models (ten SNPs×six domains) were run.

The focus of the analysis was the estimation of time trends in the domain-specific test scores, so that time (years from first administration) was treated as a continuous variable. In addition, we examined interactions between time and HIV serostatus (positive vs. negative), current stimulant use (yes or no), and genotype. Genotypes were coded as positive/negative in accordance with a dominant model in most instances. In the case of rs4680 and rs6280, additive models were used, with values 0, 1, and 2 corresponding to the number of minor alleles present, so that only a single parameter was required. Our strategy involved fitting a full model for each of 60 combinations of genotype and domain score. Each model included the four-way interaction between time and the three exposures of interest as well as all four three-way interactions, six two-way interactions, and the four individual main effects. The resulting p values for the significance tests for all of these effects involving time (8) for all 60 full models were adjusted for multiplicity using the false discovery rate. Using the adjusted p values with a cutoff of 0.1, we then determined a reduced model for each of the 60 analyses using the hierarchy principle. That is, the highest order significant interaction was determined for each model, and all interactions of the same or lower order were included in the reduced model. This was done primarily to help with the interpretation of the results, which involved the highest order interactions that were significant in the reduced model. The resulting reduced models were of two types, those with all three-way (and two-way) interactions and the remainder with only two-way interactions. Models with only two-way interactions can be directly interpreted; for the significant three-way interactions, we estimated time trends (slopes) for each of the groups implied by the interaction. Pairwise comparisons among these groups were also examined.

Results

In the reduced models, a p value threshold of 0.05 was used. We did not correct for multiple comparisons at this step, as the false discovery rate correction was already applied when determining significant interactions in the full model. Using

Table 2 COMT and learning functioning: genotype interaction with HIV status

Group[a]	Estimate[b]	Standard error	df	T	p value
HIV− Val/Val 1	−0.1197	0.1552	4,695	−0.77	0.4405
HIV− Val/Met 4	0.1483	0.1146	4,719	1.29	0.1957
HIV− Met/Met 5	0.4163	0.1527	4,696	2.73	0.0064
HIV+ Val/Val 2	0.1711	0.1154	4,811	1.48	0.1380
HIV+ Val/Met 9	0.1051	0.07869	4,893	1.34	0.1817
HIV+ Met/Met 10	0.0390	0.1135	4,770	0.34	0.7306
Post hoc comparisons[c]					
HIV− Val/Val vs. HIV− Val/Met	−0.2680	0.1028	4,665	−2.61	0.0092
HIV− Val/Val vs. HIV− Met/Met	−0.5360	0.2056	4,665	−2.61	0.0092
HIV− Met/Met vs. HIV+ Met/Met	0.3772	0.1579	4,776	2.39	0.0169

[a] All cases included regardless of stimulant use status (i.e., the estimates are averaged over stimulant use)

[b] Estimates are based on a significant three-way interaction (HIV × genotype × time)

[c] Only significant results are shown. Positive estimates indicate that the regression coefficient (slope) for time in the first group is significantly larger than that of the second group

this approach, no four-way interactions were found, indicating that HIV status and stimulant use status do not interact over time to affect neurocognitive functioning as a function of genotype. However, multiple three-way interactions were found that involved genotype and HIV status. Of the 10 genetic markers examined, seven had significant interactions with HIV status upon the trajectory of performances on learning, memory, information processing speed, and working memory over time. No effect on motor functioning, executive functioning, or sustained attention was found. Only one of the 10 genetic markers was found to have a significant interaction with stimulant use over time, affecting the information processing domain. These results are described next.

Three-way interactions

Time × HIV status × genotype interactions

For the learning domain, the COMT genotype had a significant interaction with time and HIV status ($p=0.0004$). Post hoc comparisons shown in Table 2 indicate that the learning ability of HIV+ individuals did not differ across genotypes. However, a dosage effect for the Met allele was observed for the HIV-negative group, such that the Val/Val group declined slightly over time, the Val/Met group remained generally stable, and the Met/Met group improved (Fig. 1a). Also within the learning domain, MBL had a significant interaction with time and HIV status ($p=0.0093$) (Table 3). Post hoc testing revealed that the HIV-negative A/A genotype group differed significantly from the HIV-negative combined O/O and A/O genotype group, in which the former showed greater improvement over time (Table 3, Fig. 1b). Finally, CCL3 genotype (rs1719134) also had a significant interaction with time and HIV status in affecting learning ability ($p=0.0081$). Post hoc analysis did not reveal any significant group differences (Table 4); however, Fig. 1c suggests that the HIV+ AA/AG group declined relative to the other groups over time.

For the information processing domain, DBH (rs1611115) had a significant interaction with time and HIV status ($p=0.0168$). Post hoc testing revealed that the HIV− CC group had significantly greater improvement in these scores over time as compared to the other groups (Table 5, Fig. 1d).

Table 3 MBL and learning functioning: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− A/A	0.3130	0.1479	3,387	2.12	0.0345
HIV+ A/A	0.08419	0.1227	3,499	0.69	0.4925
HIV− O/O|A/O	−0.00128	0.1388	3,428	−0.01	0.9927
HIV+ O/O|A/O	0.1504	0.1306	3,528	1.15	0.2492
Post hoc comparisons[b]					
HIV− A/A vs. HIV− O/O|A/O	0.3143	0.1547	3,379	2.03	0.0423

[a] All cases included regardless of stimulant use status
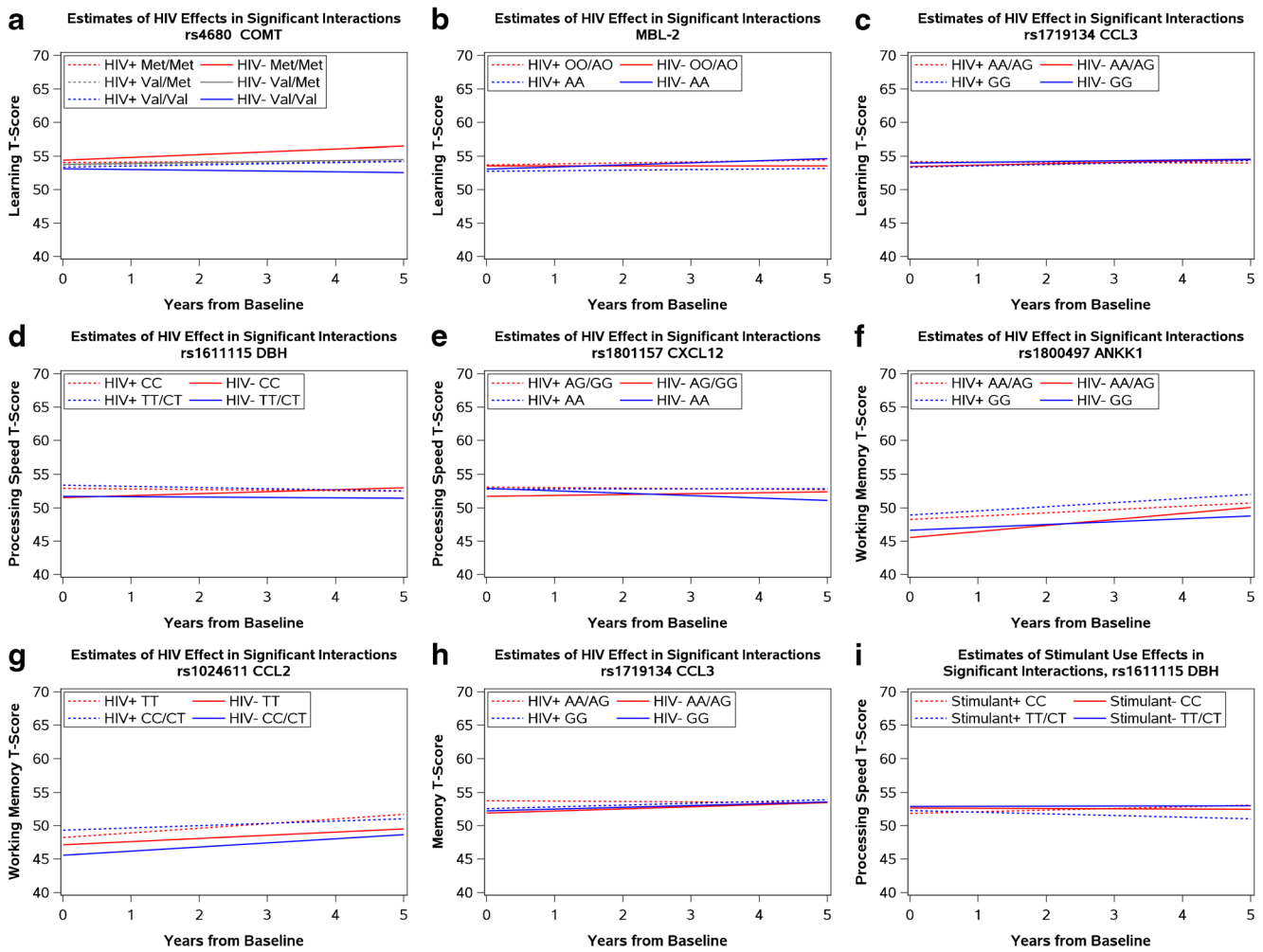
[b] Only significant results are shown

Fig. 1 Slope estimates for significant three-way interactions

CXCL12 (rs1801157) also interacted with HIV status to affect information processing speed ($p=0.0305$). While none of the post hoc tests were significant, it appears from Fig. 1e that the HIV-negative combined AG and GG group had a trend towards improvement relative to that of the HIV-negative AA group (Table 6).

Two genetic markers showed an association with working memory performance over time. ANKK1 (rs1800497) had a

significant interaction with time and HIV status ($p=0.0007$). Post hoc analysis revealed that the HIV-negative AA/AG group had significantly better improvement over time compared to the HIV-negative GG group as well as their HIV+ counterparts (Table 7, Fig. 1f). CCL2 (rs1024611) also affected working memory performance as a function of HIV status and time ($p=0.0021$). Post hoc testing revealed that the HIV+ TT group improved at a faster rate than the HIV+ CC/CT

Table 4 CCL3 and learning functioning: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− GG	0.1173	0.1204	4,732	0.97	0.3300
HIV+ GG	0.1976	0.09153	4,910	2.16	0.0310
HIV− AA/AG	0.2092	0.1543	4,784	1.36	0.1751
HIV+ AA/AG	−0.04407	0.1113	4,802	−0.40	0.6922
Post hoc comparisons[b]					
HIV+ GG vs. HIV+ AA/AG	0.2416	0.1246	4,698	1.94	0.0526

[a] All cases included regardless of stimulant use status

[b] Only near-significant results are shown

Table 5 DBH and information processing speed: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− TT/CT	−0.05803	0.1173	7,745	−0.49	0.6209
HIV+ TT/CT	−0.1742	0.1085	7,893	−1.61	0.1084
HIV− CC	0.3033	0.1066	7,703	2.84	0.0045
HIV+ CC	−0.08448	0.07922	8,089	−1.07	0.2863
Post hoc comparisons[b]					
HIV− TT/CT vs. HIV− CC	−0.3613	0.1250	7,718	−2.89	0.0038
HIV+ TT/CT vs. HIV− CC	−0.4775	0.1632	7,808	−2.93	0.0034
HIV+ CC vs. HIV− CC	0.3878	0.1188	7,944	3.27	0.0011

[a] All cases included regardless of stimulant use status

[b] Only near-significant results are shown

group, but not faster than the HIV-negative groups (Table 8, Fig. 1g).

Finally, memory functioning was affected as a function of CCL3 (rs1719134) genotype and HIV status ($p=0.0062$). It was the HIV+ AA/AG group that differed relative to the other groups, showing a relative decline in memory ability (Table 9, Fig. 1h).

Time × stimulant use × genotype interactions

DBH (rs1611115) had an interaction with stimulant use and time ($p=0.0096$). Specifically, the stimulant users with CC genotype had a more significant improvement in information processing speed over time (Table 10, Fig. 1i).

Time × HIV status × stimulant use

There were no significant interactions between HIV status and stimulant use status over time. In only one model was a three-way interaction involving HIV status, stimulant use, and genotype observed. This occurred in the COMT (rs4680) gene for the learning domain ($p=0.0439$).

Two-way interactions

In those models in which no three-way interactions were found, there were a total of 21 two-way interactions involving time. Twelve involved HIV status, and it was consistently revealed that HIV+ status was associated with a relative decline in motor functioning over time, but improvement of information processing speed over time. In six models, stimulant use was also consistently associated with motor functioning decline over time and, to a greater extent, HIV+ status. In one instance, stimulant use was associated with a very marginal improvement in working memory. In two instances, genotype (DR3 C and BDNF-GG) was associated with poorer motor functioning over time. Results of the two-way interactions are shown in Table 11.

Discussion

Variability in HAND risk, with or without concurrent stimulant abuse, suggests that inherent factors such as genotype may protect some individuals against neurocognitive impairment. Cross-sectional studies and some short-duration longitudinal studies have found genetic markers associated with

Table 6 CXCL12 and information processing speed: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− AA	−0.3597	0.2852	7,646	−1.26	0.2073
HIV+ AA	0.00412	0.2029	7,665	0.02	0.9838
HIV− AG/GG	0.1364	0.09435	7,714	1.45	0.1482
HIV+ AG/GG	−0.07033	0.07500	8,141	−0.94	0.3484
Post hoc comparisons[b]					
HIV− AA vs. HIV− AG/GG	−0.4961	0.2774	7,649	−1.79	0.0738
HIV− AG/GG vs. HIV+ AG/GG	0.2068	0.1122	7,948	1.84	0.0654

[a] All cases included regardless of stimulant use status

[b] Only near-significant results are shown

Table 7 ANKK1 and working memory: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− GG	0.4262	0.1213	3,987	3.51	0.0004
HIV+ GG	0.6181	0.1329	4,204	4.65	<0.0001
HIV− AA/AG	0.9042	0.1938	4,032	4.66	<0.0001
HIV+ AA/AG	0.4951	0.1728	4,163	2.87	0.0042
Post hoc comparisons[b]					
HIV− GG vs. HIV− AA/AG	−0.4780	0.1934	4,032	−2.47	0.0135
HIV− AA/AG vs. HIV+ AA/AG	0.4091	0.2004	4,116	2.04	0.0413

[a] All cases included regardless of stimulant use status

[b] Only significant results are shown

HIV-related neurocognitive deficits; however, very few findings have been replicated. We hypothesized that certain alleles of DA and immunologically related genes would confer protection against neurocognitive deficits resulting from HIV and stimulant use and that this relationship would bear out over time. Our findings indicate that genotype does affect neurocognitive functioning over time as a function of HIV status and, to a lesser extent, stimulant use. However, these effects are insubstantial.

Multiple lines of research implicate that the activation of immunologically related factors, such as cytokines and chemokines, is an important component of HAND neuropathogenesis. Our analyses revealed that all immunologically related genetic markers found to interact with HIV status affected neurocognitive functioning in the expected direction; however, some of these effects were observed in the HIV negatives only. This included MBL, which influenced learning ability over time. An adverse impact of the "O" genotype was observed among the HIV-negative cases only. This genotype was previously reported to increase a risk of neurocognitive impairment at a 1-year follow-up in HIV+ Chinese individuals (Spector et al. 2010). Note that the previous study did not include HIV-negative individuals; therefore, it was not possible to determine if the previously observed decline in neurocognitive status was due to genotype alone or

in combination with HIV serostatus. Our findings suggest that it was the former. CXCL12 genotype (rs1801157) affected information processing speed among HIV negatives only. This interaction appears to have been driven largely by the relative improvement of the HIV-negative AG/GG individuals relative to the HIV-negative AA. As such, it does not appear that this allele plays a significant role in neurocognitive functioning among HIV+ individuals. The AA genotype was previously associated with faster disease progression, including the development of neurocognitive impairment, in a cohort of HIV+ children (Singh et al. 2003). Conversely, this genotype has been associated with slower disease progress in adults, based on a study involving the MACS cohort (Winkler et al. 1998). No association between this allele and HIV-related neurocognitive impairment was found in other studies (Levine et al. 2009; Spector et al. 2010). The CCL2 (MCP-1) rs1024611 marker validated previous findings. In our sample, HIV+ individuals possessing a C allele did not demonstrate improvement in working memory functioning, as compared to HIV+ individuals with a TT genotype or HIV-negative individuals as a whole (regardless of genotype). The C allele has previously been associated with an increased risk for HIV-associated dementia (Gonzalez et al. 2002) and higher HIV DNA in the CSF of children (Shiramizu et al. 2006), although other studies have not observed a relationship between this

Table 8 CCL2 and Working Memory: Genotype Interaction with HIV Status

Group[a]	Estimate	Standard error	df	T	p value
HIV− CC/CT	0.6180	0.1374	3,958	4.50	<0.0001
HIV+ CC/CT	0.3337	0.1710	4,176	1.95	0.0511
HIV− TT	0.4715	0.1448	4,023	3.26	0.0011
HIV+ TT	0.6915	0.1309	4,171	5.28	<0.0001
Post hoc comparisons[b]					
HIV+ CC/CT vs. HIV+ TT	−0.3577	0.1771	4,011	−2.02	0.0434

[a] All cases included regardless of stimulant use status

[b] Only significant results are shown

Table 9 CCL3 and memory: genotype interaction with HIV status

Group[a]	Estimate	Standard error	df	T	p value
HIV− GG	0.2630	0.1270	4,461	2.07	0.0384
HIV+ GG	0.2640	0.1052	4,661	2.51	0.0121
HIV− AA/AG	0.3186	0.1637	4,524	1.95	0.0517
HIV+ AA/AG	−0.05818	0.1233	4,546	−0.47	0.6370
Post hoc comparisons[b]					
HIV+ GG vs. HIV+ AA/AG	0.3222	0.1381	4,452	2.33	0.0197
HIV− AA/AG vs. HIV+ AA/AG	0.3768	0.1630	4,577	2.31	0.0208

[a] All cases included regardless of stimulant use status

[b] Only significant results are shown

allele and neurocognitive functioning in HIV (Levine et al. 2009; Singh et al. 2004; Spector et al. 2010). Finally, those individuals homozygous or heterozygous for the A allele at rs1719134 of the CCL3 gene demonstrated a relatively greater decline in learning and memory ability as compared to HIV-negative individuals with this genotype or individuals with the GG genotype. This SNP is in high linkage disequilibrium with rs1130371, previously shown by our group to be associated with an increased risk of HIV-associated dementia. (As mentioned in the Methods section, we did not use rs1130371 genotype in this analysis due to its violation of Hardy-Weinberg equilibrium, possibly indicating a genotyping error.) Specifically, in Levine et al. (2009), we found that the TT (equivalent to AA, due to the strand of DNA read by the technology) genotype at rs1130371 in the CCL3 gene was associated with a twofold greater risk for HIV-associated dementia in the National NeuroAIDS Tissue Consortium cohort (Morgello et al. 2001). The current results may validate the previous finding in this second cohort.

The hypothesis that variation in dopamine-related genes would affect neurocognitive functioning as a function of stimulant use was not supported. In addition and somewhat surprisingly, two of the three DA-related SNPs showed a significant interaction with HIV status or stimulant use in the opposite direction than expected. The DBH (rs1611115) CC genotype, which is associated with greater DBH activity and therefore increased DA catabolism into norepinephrine (Zabetian et al. 2001), was associated with faster information processing speed for HIV negatives only. This same relationship was observed for stimulant users, with CC genotype showing greater improvement than those with CT or TT genotype. It should be noted that DBH is limited neuroanatomically to the adrenal medulla and synaptic vesicles of postganglionic sympathetic neurons (Kim et al. 2002). Therefore, our findings may indicate that it is increased norepinephrine availability in the adrenal medulla and sympathetic neurons that is related to improved processing speed performance among CC carriers and that whatever decrease in DA availability resulting from this does not influence neurocognitive functioning. Variation at the ANKK1 (rs1800497) SNP, which has been linked to striatal DR2 receptor density and neuropsychiatric illness (Jonsson et al. 1999; Neville et al. 2004), modified working memory performance over time in HIV negatives. Our analysis found that HIV-negative individuals who possessed one or two of the ancestral A alleles had greater improvement in working memory ability over time when compared to HIV+ A carriers and HIV-negative GG carriers. As suggested by Fig. 1f, both

Table 10 DBH and information processing speed: genotype interaction with stimulant use

Group[a]	Estimate	Standard error	df	T	p value
Nonstimulant TT/CT	0.01934	0.05366	7,817	0.36	0.7186
Stimulant TT/CT	−0.2516	0.1709	7,755	−1.47	0.1410
Nonstimulant CC	−0.03136	0.04725	7,937	−0.66	0.5070
Stimulant CC	0.2502	0.1306	7,730	1.92	0.0555
Post hoc comparisons[b]					
Stimulant TT/CT vs. stimulant CC	−0.5018	0.2052	7,711	−2.45	0.0145
Nonstimulant CC vs. stimulant CC	−0.2815	0.1319	7,713	−2.13	0.0328

[a] All cases included regardless of HIV status

[b] Only significant results are shown

Table 11 Main effect and interaction estimates for models with no three- or four-way interactions

Domain (gene)	Interaction	Time estimate[a]	Interaction estimate[b]	Standard error	p value
Motor (DRD3)	Time	0.7441			
Motor	Time×DRD3		−0.1106	0.04146	0.0077
Motor	Time×stimulant		−0.2549	0.09969	0.0106
Motor	Time×HIV+		0.2175	0.06197	0.0005
Speed[c] (BDNF)	Time	−0.02840			
Speed	Time×HIV+		0.3205	0.06075	<0.0001
Motor (BDNF)	Time	0.7181			
Motor	Time×BDNF		−0.1322	0.05997	0.0275
Motor	Time×stimulant		−0.2646	0.09934	0.0077
Motor	Time×HIV+		0.2080	0.06130	0.0007
Speed (MBL-2)	Time	0.01543			
Speed	Time×HIV+		0.3590	0.07094	<0.0001
Motor (MBL-2)	Time	0.7425			
Motor	Time×stimulant		−0.3528	0.1189	0.0030
Motor	Time×HIV+		0.2781	0.07062	<0.0001
Working memory (DBH)	Time	0.3002			
Working memory	Time×stimulant		0.4535	0.1458	0.0019
Speed (ANKK1)	Time	−0.06188			
Speed	Time×HIV+		0.3116	0.05994	<0.0001
Motor (ANKK1)	Time	0.6667			
Motor	Time×stimulant		−0.2620	0.09921	0.0083
Motor	Time×HIV+		0.2250	0.06092	0.0002
Speed (CCL2)	Time	−0.03545			
Speed	Time×HIV+		0.3215	0.06040	<0.0001
Speed (TNF-α)	Time	−0.1018			
Speed	Time×HIV+		0.3108	0.05994	<0.0001
Motor (TNF-α)	Time	0.6896			
Motor	Time×stimulant		−0.2651	0.09920	0.0075
Motor	Time×HIV+		0.2223	0.06095	0.0003
Speed (CCL3)	Time	−0.1197			
Speed	Time×HIV+		0.3166	0.06045	<0.0001
Motor (CCL3)	Time	0.7116			
Motor	Time×stimulant		−0.2751	0.09945	0.0057
Motor	Time×HIV+		0.2165	0.06114	0.0004

[a] Time estimate indicates T-score change per year

[b] Negative interaction estimates indicate a greater decline relative to the overall estimate. Positive estimates indicate relative improvement

[c] Information processing speed

HIV+ genotype groups and the HIV-negative GG carriers have similar trajectories, suggesting that whatever beneficial effects there were of the A allele were not manifested in HIV+ individuals. Of the DA-related genes examined, only COMT (rs4680) showed an expected association. Specifically, the Met allele was associated with stronger learning ability; however, this was observed only for HIV-negative individuals.

Perhaps most notable is that even in those models that demonstrated significant genetic interactions, the influence of genotype was minor. The largest effect due to genotype amounted to three or four T-score points over a 5-year period, while in most models, the effect was indiscernible. Also notable are the results of models that involved two-way interactions, which consistently showed a relative decline in motor functioning among HIV+ individuals and, even more so, among stimulant users. Conversely and unexpectedly, HIV+ individuals demonstrated improvement in information processing speed over time. Due to the large number of comparisons, even with the corrections for multiple testing, some

results are likely to represent false-positive errors. One such likely instance was the finding that stimulant use was associated with a very marginal improvement in working memory over time. This finding was seen in only one model, and the degree of improvement combined with a lack of replication suggests that the finding was spurious. In two instances, variation in DR3 (C) and BDNF (GG) was associated with poorer motor functioning over time, regardless of HIV status or stimulant use.

Contrary to expectation, the trajectory of neurocognitive functioning among HIV+ individuals who also used stimulants was not significantly different from those who did not use stimulants. Note that our design differed from that of previous studies (e.g., (Carey et al. 2006; Rippeth et al. 2004)) in which we did not have defined substance use groups but rather considered substance use on a visit-by-visit basis. As such, the same individual may have been considered as a stimulant user at one visit, but not at another. This approach was necessary, considering the long duration of the retrospective data capture, and may better reflect the actual drug use habits of stimulant users. Regardlessly, the lack of significant interactions may be due to the varying inclusion of substance users, abusers, and dependent individuals across studies. It is also noted that our analysis included only men and that these findings may not generalize to females, who are or may be more vulnerable to stimulant dependence (Lynch et al. 2009) and who may experience different neurocognitive consequences from stimulant use (Meyer et al. 2013). Finally, drug use was determined via participant self-report. While this is the only feasible method for obtaining such information in the population studied, self-report does have inherent flaws, including under- and over-reporting.

To summarize, our findings support the notion that immunologically related genetic differences in the chemokines CCL2 and CCL3 affect the neurocognitive functioning of HIV+ individuals over time, although their influence appears to be minor. This likely reflects the multifaceted nature of HAND pathogenesis, which is influenced by numerous cytokines, chemokines, and other immunological factors. Being consistent with findings from another cohort (Levine et al. 2012b), DA-related genetic differences do not appear to influence the longitudinal neurocognitive functioning of HIV+ individuals, despite a significant evidence for the role of DA dysfunction in HAND. Further, in the pre-HAART era, improvement of processing speed and decline of motor functioning over time among HIV+ individuals were consistently observed, and an unrelated decline in motor functioning due to stimulant use (regardless of HIV status) was also consistently observed. Finally, in addition to the very small effects observed here, we suggest that the inconsistencies in previous cross-sectional genetic association studies of HAND may also be due to a number of factors, including survival bias, use of different neurocognitive phenotypes and/or psychometric measures, and problems inherent in genetic analyses (e.g., population stratification).

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References

Ahmed F, Tessarollo L, Thiele C, Mocchetti I (2008) Brain-derived neurotrophic factor modulates expression of chemokine receptors in the brain. Brain Res 1227:1–11

Aksenov MY, Aksenova MV, Nath A, Ray PD, Mactutus CF, Booze RM (2006) Cocaine-mediated enhancement of Tat toxicity in rat hippocampal cell cultures: the role of oxidative stress and D1 dopamine receptor. Neurotoxicology 27:217–228

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA et al (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799

Atkinson AC (1985) Plots, transformations and regression. Clarendon, Oxford

Avison MJ, Nath A, Greene-Avison R, Schmitt FA, Bales RA et al (2004) Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. J Neurovirol 10:223–232

Aylward EH, Henderer JD, McArthur JC, Brettschneider PD, Harris GJ et al (1993) Reduced basal ganglia volume in HIV-1-associated dementia: results from quantitative neuroimaging. Neurology 43:2099–2104

Basso MR, Bornstein RA (2003) Effects of past noninjection drug abuse upon executive function and working memory in HIV infection. J Clin Exp Neuropsychol 25:893–903

Berger JR, Nath A (1997) HIV dementia and the basal ganglia. Intervirology 40:122–131

Bousman CA, Cherner M, Atkinson JH, Heaton RK, Grant I et al (2010) COMT Val158Met polymorphism, executive dysfunction, and sexual risk behavior in the context of HIV infection and methamphetamine dependence. Interdiscip Perspect Infect Dis 2010:678648

Brew BJ (2004) Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. Aids 18(Suppl 1):S75–S78

Burt TD, Agan BK, Marconi VC, He W, Kulkarni H et al (2008) Apolipoprotein (apo) E4 enhances HIV-1 cell entry in vitro, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. Proc Natl Acad Sci U S A 105:8718–8723

Carey CL, Woods SP, Rippeth JD, Gonzalez R, Heaton RK, Grant I (2006) Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. AIDS Behav 10:185–190

Cass WA (1997) Decreases in evoked overflow of dopamine in rat striatum after neurotoxic doses of methamphetamine. J Pharmacol Exp Ther 280:105–113

Cass WA, Harned ME, Peters LE, Nath A, Maragos WF (2003) HIV-1 protein Tat potentiation of methamphetamine-induced decreases in evoked overflow of dopamine in the striatum of the rat. Brain Res 984:133–142

Chang L, Andres M, Sadino J, Jiang CS, Nakama H et al (2011) Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. NeuroImage 58:1017–1027

Chatterjee S, Hadi AS (1988) Sensitivity analysis in linear regression. Wiley, New York

Comalli PE Jr, Wapner S, Werner H (1962) Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 100:47–53

Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G et al (1998) HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nat Med 4:1182–1184

Cysique LA, Maruff P, Brew BJ (2004) Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J Neurovirol 10:350–357

Cysique LA, Brew BJ, Halman M, Catalan J, Sacktor N et al (2005) Undetectable cerebrospinal fluid HIV RNA and beta-2 microglobulin do not indicate inactive AIDS dementia complex in highly active antiretroviral therapy-treated patients. J Acquir Immune Defic Syndr 39:426–429

Dal Pan GJ, McArthur JH, Aylward E, Selnes OA, Nance-Sproson TE et al (1992) Patterns of cerebral atrophy in HIV-1-infected individuals: results of a quantitative MRI analysis. Neurology 42:2125–2130

Daly G, Hawi Z, Fitzgerald M, Gill M (1999) Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Mol Psychiatry 4:192–196

Durvasula RS, Myers HF, Satz P, Miller EN, Morgenstern H et al (2000) HIV-1, cocaine, and neuropsychological performance in African American men. J Int Neuropsychol Soc 6:322–335

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM et al (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98:6917–6922

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS et al (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269

Ferrando SJ, Batki SL (2000) Substance abuse and HIV infection. New Dir Ment Health Serv 57–67

Ferrando S, Goggin K, Sewell M, Evans S, Fishman B, Rabkin J (1998) Substance use disorders in gay/bisexual men with HIV and AIDS. Am J Addict 7:51–60

Flora G, Lee YW, Nath A, Hennig B, Maragos W, Toborek M (2003) Methamphetamine potentiates HIV-1 Tat protein-mediated activation of redox-sensitive pathways in discrete regions of the brain. Exp Neurol 179:60–70

Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL et al (2007) A second generation human haplotype map of over 3.1 million SNPs. Nature 449:851–861

Gaskill PJ, Calderon TM, Luers AJ, Eugenin EA, Javitch JA, Berman JW (2009) Human immunodeficiency virus (HIV) infection of human macrophages is increased by dopamine: a bridge between HIV-associated neurologic disorders and drug abuse. Am J Pathol 175:1148–1159

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T et al (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60:889–896

Gonzalez E, Dhanda R, Bamshad M, Mummidi S, Geevarghese R et al (2001) Global survey of genetic variation in CCR5, RANTES, and MIP-1alpha: impact on the epidemiology of the HIV-1 pandemic. Proc Natl Acad Sci U S A 98:5199–5204

Gonzalez E, Rovin BH, Sen L, Cooke G, Dhanda R et al (2002) HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. Proc Natl Acad Sci U S A 99:13795–13800

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P (2001) BDNF controls dopamine D₃ receptor expression and triggers behavioural sensitization. Nature 411:86–89

Gupta S, Bousman CA, Chana G, Cherner M, Heaton RK et al (2011) Dopamine receptor D3 genetic polymorphism (rs6280TC) is associated with rates of cognitive impairment in methamphetamine-dependent men with HIV: preliminary findings. J Neurovirol 17:239–247

Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C et al (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75:2087–2096

Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL et al (2011) HIV-associated neurocognitive disorders before and during

the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 17:3–16

Itoh K, Mehraein P, Weis S (2000) Neuronal damage of the substantia nigra in HIV-1 infected brains. Acta Neuropathol (Berl) 99:376–384

Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y et al (1999) Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 4:290–296

Kim CH, Zabetian CP, Cubells JF, Cho S, Biaggioni I et al (2002) Mutations in the dopamine beta-hydroxylase gene are associated with human norepinephrine deficiency. Am J Med Genet 108:140–147

Klinkenberg WD, Sacks S (2004) Mental disorders and drug abuse in persons living with HIV/AIDS. AIDS Care 16(Suppl 1):S22–S42

Klove H, Matthews CG (1966) Psychometric and adaptive abilities in epilepsy with differential etiology. Epilepsia 7:330–338

Kraft-Terry SD, Buch SJ, Fox HS, Gendelman HE (2009) A coat of many colors: neuroimmune crosstalk in human immunodeficiency virus infection. Neuron 64:133–145

Kuczenski R, Everall IP, Crews L, Adame A, Grant I, Masliah E (2007) Escalating dose-multiple binge methamphetamine exposure results in degeneration of the neocortex and limbic system in the rat. Exp Neurol 207:42–51

Kumar AM, Ownby RL, Waldrop-Valverde D, Fernandez B, Kumar M (2011) Human immunodeficiency virus infection in the CNS and decreased dopamine availability: relationship with neuropsychological performance. J Neurovirol 17:26–40

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM (1996) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6:243–250

Langford D, Sanders VJ, Mallory M, Kaul M, Masliah E (2002) Expression of stromal cell-derived factor 1alpha protein in HIV encephalitis. J Neuroimmunol 127:115–126

Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin CH (2006) The effect of recent stimulant use on sustained attention in HIV-infected adults. J Clin Exp Neuropsychol 28:29–42

Levine AJ, Singer EJ, Sinsheimer JS, Hinkin CH, Papp J et al (2009) CCL3 genotype and current depression increase risk of HIV-associated dementia. Neurobehav HIV Med 1:1–7

Levine AJ, Service S, Miller EN, Reynolds SM, Singer EJ et al (2012a) Genome-wide association study of neurocognitive impairment and dementia in HIV-infected adults. Am J Med Genet B Neuropsychiatr Genet. doi:10.1002/ajmg.b.32071

Levine AJ, Sinsheimer JS, Bilder R, Shapshak P, Singer EJ (2012b) Functional polymorphisms in dopamine-related genes: effect on neurocognitive functioning in HIV+ adults. J Clin Exp Neuropsychol 34:78–91

Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR (2010) MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genet Epidemiol 34:816–834

Little KY, Zhang L, Desmond T, Frey KA, Dalack GW, Cassin BJ (1999) Striatal dopaminergic abnormalities in human cocaine users. Am J Psychiatry 156:238–245

Liu H, Chao D, Nakayama EE, Taguchi H, Goto M et al (1999) Polymorphism in RANTES chemokine promoter affects HIV-1 disease progression. Proc Natl Acad Sci U S A 96:4581–4585

Lynch W, Potenza MN, Cosgrove KP, Mazure CM (2009) Sex differences in vulnerability to stimulant abuse. In: BS Brady KT, Cosgrove KP, Greenfield SF (eds) Women and addiction: a comprehensive handbook. Guilford, New York

Martin EM, Pitrak DL, Weddington W, Rains NA, Nunnally G et al (2004) Cognitive impulsivity and HIV serostatus in substance dependent males. J Int Neuropsychol Soc 10:931–938

Martin-Thormeyer EM, Paul RH (2009) Drug abuse and hepatitis C infection as comorbid features of HIV associated neurocognitive

disorder: neurocognitive and neuroimaging features. Neuropsychol Rev 19:215–231

Mathis KL, Dozois EJ, Larson DW, Cima RR, Sarmiento JM et al (2008) Ileal pouch-anal anastomosis and liver transplantation for ulcerative colitis complicated by primary sclerosing cholangitis. Br J Surg 95: 882–886

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A et al (2003) Catechol-O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 100:6186–6191

McArthur JC, Haughey N, Gartner S, Conant K, Pardo C et al (2003) Human immunodeficiency virus-associated dementia: an evolving disease. J Neurovirol 9:205–221

McArthur JC, Brew BJ, Nath A (2005) Neurological complications of HIV infection. Lancet Neurol 4:543–555

McCullagh P, Nelder JA (1989) Generalized linear models. Chapman and Hall, London

McDermott DH, Beecroft MJ, Kleeberger CA, Al-Sharif FM, Ollier WE et al (2000) Chemokine RANTES promoter polymorphism affects risk of both HIV infection and disease progression in the Multicenter AIDS Cohort Study. Aids 14:2671–2678

Meyer VJ, Rubin LH, Martin E, Weber KM, Cohen MH et al (2013) HIV and recent illicit drug use interact to affect verbal memory in women. J Acquir Immune Defic Syndr 63:67–76

Miller E (1990) California computerized assessment package. Norland Software, Los Angeles

Miller EN, Selnes OA, McArthur JC, Satz P, Becker JT et al (1990) Neuropsychological performance in HIV-1-infected homosexual men: the Multicenter AIDS Cohort Study (MACS). Neurology 40:197–203

Morgello S, Gelman BB, Kozlowski PB, Vinters HV, Masliah E et al (2001) The National NeuroAIDS Tissue Consortium: a new paradigm in brain banking with an emphasis on infectious disease. Neuropathol Appl Neurobiol 27:326–335

Mossner R, Daniel S, Albert D, Heils A, Okladnova O et al (2000) Serotonin transporter function is modulated by brain-derived neurotrophic factor (BDNF) but not nerve growth factor (NGF). Neurochem Int 36:197–202

Nath A, Maragos WF, Avison MJ, Schmitt FA, Berger JR (2001) Acceleration of HIV dementia with methamphetamine and cocaine. J Neurovirol 7:66–71

Nath A, Hauser KF, Wojna V, Booze RM, Maragos W et al (2002) Molecular basis for interactions of HIV and drugs of abuse. J Acquir Immune Defic Syndr 31(Suppl 2):S62–S69

Neville MJ, Johnstone EC, Walton RT (2004) Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat 23:540–545

Nosheny RL, Mocchetti I, Bachis A (2005) Brain-derived neurotrophic factor as a prototype neuroprotective factor against HIV-1-associated neuronal degeneration. Neurotox Res 8:187–198

Nosheny RL, Ahmed F, Yakovlev A, Meyer EM, Ren K et al (2007) Brain-derived neurotrophic factor prevents the nigrostriatal degeneration induced by human immunodeficiency virus-1 glycoprotein 120 in vivo. Eur J Neurosci 25:2275–2284

Osterrieth P (1944) Le test de copie d'une figure complexe. Arch Psychol 30:206

Peng H, Erdmann N, Whitney N, Dou H, Gorantla S et al (2006) HIV-1-infected and/or immune activated macrophages regulate astrocyte SDF-1 production through IL-1beta. Glia 54:619–629

Power C, Kong PA, Crawford TO, Wesselingh S, Glass JD et al (1993) Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood-brain barrier. Ann Neurol 34:339–350

Quasney MW, Zhang Q, Sargent S, Mynatt M, Glass J, McArthur J (2001) Increased frequency of the tumor necrosis factor-alpha-308 A allele in adults with human immunodeficiency virus dementia. Ann Neurol 50:157–162

Rabkin JG, Ferrando SJ, Jacobsberg LB, Fishman B (1997) Prevalence of axis I disorders in an AIDS cohort: a cross-sectional, controlled study. Compr Psychiatry 38:146–154

Rabkin JG, McElhiney MC, Ferrando SJ (2004) Mood and substance use disorders in older adults with HIV/AIDS: methodological issues and preliminary evidence. Aids 18(Suppl 1):S43–S48

Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401

Reitan R (1958) Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 8:271

Rey A (1941) L'examen psychologique dans les cas d'encephalopathie traumatique. Arch Psychol 28:286

Rey A (1964) L'examen clinique en psychologie. Presses Universitaires de France, Paris

Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ et al (2004) Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. J Int Neuropsychol Soc 10:1–14

Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH (2002) Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. Am J Med Genet 114:154–158

Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C et al (1996) Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382:722–725

Shiramizu B, Lau E, Tamamoto A, Uniatowski J, Troelstrup D (2006) Feasibility assessment of cerebrospinal fluid from HIV-1-infected children for HIV proviral DNA and monocyte chemoattractant protein 1 alleles. J Investig Med 54:468–472

Silverstein PS, Shah A, Gupte R, Liu X, Piepho RW et al (2011) Methamphetamine toxicity and its implications during HIV-1 infection. J Neurovirol. doi:10.1007/s13365-011-0043-4

Singh KK, Barroga CF, Hughes MD, Chen J, Raskino C et al (2003) Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. J Infect Dis 188:1461–1472

Singh KK, Ellis RJ, Marquie-Beck J, Letendre S, Heaton RK et al (2004) CCR2 polymorphisms affect neuropsychological impairment in HIV-1-infected adults. J Neuroimmunol 157:185–192

Smith A (1982) Symbol digit modalities test. Western Psychological Service, Los Angeles

Smith MW, Dean M, Carrington M, Winkler C, Huttley GA et al (1997) Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. Science 277:959–965

Soontornniyomkij V, Moore DJ, Gouaux B, Soontornniyomkij B, Tatro ET et al (2012) Cerebral beta-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE epsilon4 carriers. AIDS. doi:10.1097/QAD.0b013e32835a117c

Spector SA, Singh KK, Gupta S, Cystique LA, Jin H et al (2010) APOE epsilon4 and MBL-2 O/O genotypes are associated with neurocognitive impairment in HIV-infected plasma donors. AIDS 24:1471–1479

Stall R, Paul JP, Greenwood G, Pollack LM, Bein E et al (2001) Alcohol use, drug use and alcohol-related problems among men who have sex with men: the Urban Men's Health Study. Addiction 96:1589–1601

Theodore S, Cass WA, Nath A, Maragos WF (2007) Progress in understanding basal ganglia dysfunction as a common target for methamphetamine abuse and HIV-1 neurodegeneration. Curr HIV Res 5:301–313

Tomasi D, Chang L, de Castro CE, Telang F, Ernst T (2006) The human immunodeficiency virus reduces network capacity: acoustic noise effect. Ann Neurol 59:419–423

Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P et al (2004) Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii aging with HIV cohort. J Neuroimmunol 157:197–202

Wei J, Xu HM, Ramchand CN, Hemmings GP (1997) Is the polymorphic microsatellite repeat of the dopamine beta-hydroxylase gene associated with biochemical variability of the catecholamine pathway in schizophrenia? Biol Psychiatry 41:762–767

Winkler C, Modi W, Smith MW, Nelson GW, Wu X et al (1998) Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC). Science 279:389–393

Zabetian CP, Anderson GM, Buxbaum SG, Elston RC, Ichinose H et al (2001) A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. Am J Hum Genet 68:515–522

Zhang L, Looney D, Taub D, Chang SL, Way D et al (1998) Cocaine opens the blood-brain barrier to HIV-1 invasion. J Neurovirol 4:619–626

Zhang H, Ozbay F, Lappalainen J, Kranzler HR, van Dyck CH et al (2006) Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. Am J Med Genet B Neuropsychiatr Genet 141:387–393