Published in final edited form as:
J Neurovirol. 2013 October ; 19(5): . doi:10.1007/s13365-013-0204-8.

HIV-related cognitive impairment shows bi-directional association with dopamine receptor DRD1 and DRD2 polymorphisms in substance dependent and independent populations

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Abstract

It has been postulated that drugs of abuse act synergistically with HIV, leading to increased neurotoxicity and neurocognitive impairment. The CNS impacts of HIV and drug use converge on the mesocorticolimbic dopamine (DA) system, which contains two main receptor subtypes: dopamine receptor 1 and 2. (DRD1, DRD2). DRD1 and DRD2 have been linked to substance dependence; whether they predict HIV-associated neurocognitive disorder (HAND) is unclear. Using an advanced-stage HIV+ population, we sought to determine if drug dependence impacts the contribution of DA receptor polymorphisms on neurocognition. We observed that both DRD1 and DRD2 polymorphisms were associated with opiate and cocaine dependence ($P<0.05$) in Caucasian subjects, but not African-American individuals. Using linear regression analysis, we examined the 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. In the Motor domain, we observed an association for two DRD2 polymorphisms ($P<0.05$) in Caucasian subjects. The effects differed for substance dependence groups as the direction of the correlations with DRD2 were opposite to what was seen in subjects without these dependencies. In African-American subjects, associations were observed in nearly every domain and again, the direction of the correlation differed between substance dependent and independent groups. We conclude that studies to examine genetic risk for HAND must carefully account for substance dependence patterns when assaying dopaminergic systems, as the neurobiological substrates of cognition in HIV populations may vary with tonic alterations secondary to chronic substance exposures.

Keywords

HAND; cocaine; opiate; SNP

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Conflict of Interest The authors declare no conflict of interest.

Introduction

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 neurobiological factors related to its pathogenesis (Heaton *et al*, 2010; Heaton *et al*, 2011; McArthur, 2004; Sacktor *et al*, 2002). Dopamine (DA) dysregulation has been associated with HAND, and converging lines of evidence have implicated brain regions rich in DA (basal ganglia and related structures) as those highly susceptible to the effects of HIV. Decreased levels of DA have been reported in the basal ganglia of HIV+ brains and viral RNA levels are negatively correlated with DA levels (Kumar *et al*, 2009; Kumar *et al*, 2011). As HIV disease progresses, decreased concentrations of DA and homovanillic acid (HVA) have been found in the cerebrospinal fluid (Berger *et al*, 1994; di Rocco *et al*, 2000; Kumar *et al*, 2009; Kumar *et al*, 2011; Larsson *et al*, 1991; Obermann *et al*, 2009). In cognitively characterized subjects, imaging studies have revealed decreases in dopamine transporter in the putamen of those with HIV-associated dementia when contrasted with HIV-negative subjects (Chang *et al*, 2008). Recently, expression of DRD2 in dorsolateral prefrontal cortex has been correlated with the cognitive status of HIV-infected individuals (Gelman *et al*, 2012).

While there is evidence of association between polymorphisms for DA-related genes and neurocognitive functioning in HIV-negative populations (Frank and Fossella, 2011), studies of these associations in HAND have thus far been negative (Levine *et al*, 2012a; Levine *et al*, 2012b). HAND studies are limited in number; a greater number of genetic association studies in HAND have examined immunologic, metabolic and other non-dopaminergic genes (Bol *et al*, 2012; Levine *et al*, 2009; Pemberton *et al*, 2008; Spector *et al*, 2010). More recently, genome-wide association studies (GWAS) have focused on phenotypes such as HIV RNA viral load and disease progression (Aouizerat *et al*, 2011). Only one GWAS in HIV has utilized cognition as an endpoint, and it did not elucidate any dopaminergic associations (Levine *et al*, 2012a).

One limitation in current studies of dopaminergic polymorphisms and HAND is that there has not been a full accounting of substance dependence phenotypes. We are aware of only one study of HAND with a small percentage of substance users (2–5%) that included this variable at the analytic level (Levine *et al*, 2012a). It is well documented that altered dopaminergic function underlies many forms of drug addiction, and despite their varied mechanisms of action, drugs of dependence lead to increased DA release in the central nervous system (Di Chiara and Imperato, 1988). Thus, it is reasonable to postulate that addiction may significantly mediate the relationship between HAND and dopamine genetics.

Substance use is one of the most common comorbidities associated with HIV. Of individuals living with HIV in New York City (NYC) in 2010, 18.5% had injection drug use (IDU) as a risk factor for infection (NYC Dept of Mental Health and Hygiene, 2012). In NYC, nearly one million individuals reported using illicit substances in 2010 regardless of HIV status (NYC Dept of Mental Health and Hygiene, 2010). Among the substances of choice available for use, cocaine and opiate use have greatly increased in NYC in the past ten years; both have direct relevance to dopaminergic function. Chronic cocaine and heroin users have decreased DA receptor availability and expression (Jacobs *et al*, 2012; Volkow *et al*, 1993; Volkow *et al*, 2007). Furthermore, these two substances have been consistently linked to genetic associations with SNPs of both DRD1 and DRD2 (Jacobs *et al*, 2012; Lawford *et al*, 2000; Li *et al*, 2006; Moyer *et al*, 2011; Noble *et al*, 1993; Perez de los Cobos *et al*, 2007; Persico *et al*, 1996; Shahmoradgoli Najafabadi *et al*, 2005).

Given the overlap of HIV, HAND and substance use disorders, it was the goal of this pilot project to investigate whether genetic correlates of HAND are associated with substance dependence, utilizing a population with a high prevalence of well-characterized substance dependence and detailed neuropsychologic assessments. Our hypothesis was that individual polymorphisms of both DRD1 and DRD2 would be significantly and independently associated with cognitive functioning in HIV+ subjects, once their anticipated associations with cocaine and opiate dependency were accounted for.

Materials and Methods

Patient population

The sample consisted of 250 participants in the Manhattan HIV Brain Bank (U01MH083501; U24MH100931). This study operates at the Icahn School of Medicine at Mount Sinai under IRB approval; subjects can opt in or out of genetic analyses. Individuals were included in the current study if they were HIV positive, assented to genetic analysis, and had available neuropsychologic and substance dependence data at study entry. At entry, approximately two-thirds of the MHBB cohort are on combination antiretroviral therapy (cART); of these, over 90% have had prior exposure to ARVs. Thus, this is a highly ARV experienced population. Of 267 individuals identified by substance/neuropsychologic criteria, 17 (approximately 6%) reported being of mixed racial ancestry, or having a racial identity other than White/Caucasian or Black/African American. As analyses were stratified by racial composition (see below), these individuals were not utilized in the study.

Subject characterization

Substance dependence characterization—DSM-IV diagnoses of opiate and/or cocaine dependence were obtained by administration of the Psychiatric Research Interview for Substance and Mental Disorders (Hasin *et al*, 1996; Morgello *et al*, 2001). Additionally, results of urine toxicologies for illicit substances, performed at 6-month intervals, were reviewed. Subjects who did not self-report dependence, but who displayed chronically positive urine toxicology for illicit opiates or cocaine over years of observation, were placed in the substance dependence category (n=8; all subjects were African-American). Subjects without cocaine and opiate dependence were individuals with no DSM-IV diagnoses of opiate or cocaine dependency with the PRISM, and consistent negative toxicology for illicit substances. We studied a total of 76 individuals without substance dependence (45 males, 31 females; average age 52.2 ± 9.5) and 174 substance dependent participants (95 males, 79 females; average age 51.5 ± 6.9). Race and ethnicity were determined by self-report; for first pass analyses in this study, Hispanics identifying as Black were characterized as African American, and those identifying as White were characterized as Caucasian. Additional analyses were then performed on the Hispanic subjects alone. Racially, 59% percent of the population was African American and 41% Caucasian. See Table 1A, Table 1B, and Table 1C for full population information.

Cognitive characterization—Subjects were cognitively characterized with a neuropsychological test battery as previously described (Woods *et al*, 2004). A total of 13 tests spanning 7 cognitive domains (Motor, Processing Speed, Executive Functioning, Learning, Memory, Verbal Fluency, Working Memory), with known sensitivity for the diagnosis of HAND, were administered. Raw scores were transformed to demographically adjusted T-scores to account for effects of age, gender, ethnicity and/or education as appropriate. T-scores were utilized for correlational analyses, as they are normally distributed. In addition to domain T-scores, a summary across all domains of the test battery, the Global T-score, was also examined. The battery performed upon study entry was used

for analysis. For a list of the tests, domains, and normative data sources utilized, see Supplemental Table 1.

Genotyping

DNA was purified from peripheral blood lymphocytes with DNeasy columns (Qiagen, Valencia, CA). All SNP assays were obtained as Taqman Assays-On-Demand (Applied Biosystems, Foster City, CA) and genotyping was performed in triplicate according to the manufacturer's protocol using a LightCycler 480 (Roche Applied Science, Indianapolis, IN).

We selected a total of 10 genetic polymorphisms in the DRD1 (rs4532, rs686, rs265978, rs265975, rs265973) and DRD2 (rs12364283, rs2283265, rs1076560, rs6277, rs1800497) genes for analysis. All of the selected SNPs were either functional, in strong linkage disequilibrium with a functional polymorphism, or were previously associated with addiction-related phenotypes (For a review see: (Le Foll *et al*, 2009)). See Table 2 for a list of all SNPs genotyped, including SNP location, alleles and minor allele frequency with respect to the African American, Caucasian, and Hispanic non-substance dependent subjects in our population. Minor alleles and frequencies agree with that from reference populations for each ethnic group provided by the HapMap and NCBI dbSNP websites.

Statistical Analysis

The PLINK 1.07 genetic association analysis program (Purcell *et al*, 2007) was used to verify SNP data quality, test for departure from Hardy-Weinberg equilibrium, test individual SNPs for statistical association using Fisher's exact test, perform multiple correction testing (Bonferroni), and perform linear regression analyses. SNPs in linkage disequilibrium with each other were analyzed as haploblocks. Analyses were performed within separate racial groups as both minor alleles and allele frequencies of the SNPs differed (see Table 2). Significance was set at $P \leq 0.05$ and trends considered for $P \leq 0.10$.

Results

Polymorphisms of DRD1 and DRD2 are associated with substance dependence

In this population, we genotyped ten SNPs within DRD1 and DRD2 (see Table 2 for a list of SNPs tested), and evaluated their association with opiate and cocaine dependence. In the Caucasian population (n=103, 49 not substance dependent and 54 substance dependent), we found significant associations for one DRD1 SNP (rs265975) and three DRD2 SNPs (rs6277, rs2283265, rs1076560) (Table 3A). No significant associations were observed in the African American sample (n=147, 27 not substance dependent and 120 substance dependent). In addition, a subset of Hispanic subjects were examined separately (n=61, 16 not substance dependent and 45 substance dependent) and a significant association was found for one DRD2 SNP (rs6277) (Table 3A). Thus, in this pilot sample, SNP associations with substance dependence appeared to be confined to Caucasian subjects, as the Hispanic subset is predominately comprised of Caucasian subjects (70%).

Haplotypes were determined from linkage disequilibrium blocks. In the Caucasian population, 2 haploblocks were found. Block 1 consisted of SNPs rs4532 and rs686 within the DRD1 gene and block 2 consisted of SNPs rs2283265, rs1076560, and rs6277 within the DRD2 gene. Association for each of these blocks was tested and significant association was found for each of the 3 possible genotypes within Block 2 of DRD2 (Table 3B). In the African-American population, 1 haploblock was found; SNPs rs2283265 and rs1076560 within the DRD2 gene make up this haploblock but neither of the possible genotypes within this haploblock were significantly associated with substance dependence. In the Hispanic population, 2 haploblocks were found. Block 1 consisted of SNPs rs4532, rs686, and

rsrs265978 within the DRD1 gene and block 2 consisted of SNPs rs2283265 and rs1076560 within the DRD2 gene; neither of these were significantly associated with substance dependence in this population.

To account for increased risk of Type I error related to the multiple SNPs tested, Bonferroni corrections were performed. Following correction in the Caucasian sample, one DRD2 SNP remained significant (rs6277, P=0.002). This same SNP also remained significant in the Hispanic sample (P=0.0007).

Substance dependence has minimal effect on cognitive performance in the sample

To determine the potential effects of substance use on cognition, we examined the association of global and domain T-scores with substance dependence status. In the Caucasian population, substance dependent subjects performed slightly worse than non-substance dependent subjects in tasks of Learning and Memory (Table 4). However, for all other domains and the global scores, performance between non-substance dependent and substance dependent subjects was equivalent. In the African-American and Hispanic populations, there were no differences observed between non-substance dependent and substance dependent individuals in the global T-score or in any cognitive domain (Table 4).

DRD1 and DRD2 associations with HAND in consideration of substance dependence

Using quantitative trait regression models incorporated into PLINK, we next examined our genotyped polymorphisms for their predictive value for cognitive functioning while controlling for opiate and cocaine dependence. We tested the association of DRD1 and DRD2 SNPs with global and domain T-scores while controlling for substance dependency. In Caucasian subjects, significant associations were found between the Motor domain T-scores and two DRD2 SNPs (rs2283265 and rs1076560, Table 5A). In African American subjects, several domains showed significant DRD1 and DRD2 associations, including Motor, Processing Speed, Working Memory and Memory T-scores (Table 5B). In Hispanic subjects, only the Memory domain showed a significant DRD1 association (Table 5C). Importantly, in both Caucasian and African American populations, but not Hispanic, for all but one association in the motor domain (rs265973 in African Americans), the direction of DRD1 and DRD2 effects was opposite in controls and substance dependents (had variably positive or negative beta coefficients). As the analyses were stratified by racial group and there were no gender composition differences between substance users and HIV non substance groups, this difference could not be accounted for by demographic composition of the HIV substance and non-substance populations.

Discussion

Considering the commonalties in fronto-striatal neurocircuitry that underlie both HAND and drug dependence, it is reasonable to postulate that genetic polymorphisms within select genes of the dopaminergic system contribute to both disorders. Dopamine rich regions in the brain, particularly the striatum, are sensitive to the effects of both HIV and substance use. Neuroanatomically, both disorders converge on the mesocorticolimbic DA system, which contains DRD1 and DRD2. The prior literature supports an association between DA receptor polymorphisms and opiate and cocaine dependence; it is unclear whether relationships exist between these same polymorphisms and HAND (Jacobs *et al*, 2012; Lawford *et al*, 2000; Li *et al*, 2006; Moyer *et al*, 2011; Noble *et al*, 1993; Perez de los Cobos *et al*, 2007; Persico *et al*, 1996; Shahmoradgoli Najafabadi *et al*, 2005). As substance dependence is a common feature of HIV populations, and may contribute to HAND through a variety of synergistic neurotoxicities, apportioning genetic risk is a complex problem. Our aim was to determine whether polymorphisms of DRD1 and DRD2 would predict cognitive impairment once

substance dependence and its genetic associations were accounted for. Furthermore, since allele frequencies differed between racial groups (as would be expected), we undertook the analysis within racially segregated samples (analysis of the racially mixed Hispanic subset was undertaken only as a secondary analysis). Importantly, this strategy assured that race-dependent normative scoring in neuropsychological tests could not be responsible for genetic associations with cognitive performance.

As would be expected from the prior literature, the well-characterized substance dependencies in our HIV population had associations with DRD1 and DRD2 SNPs, and the effects differed within the segregated racial groups (Table 3). Effects were limited to the Caucasian and Hispanic (predominantly Caucasian) populations; we found significant associations for one DRD1 SNP (rs265975) and three DRD2 SNPs (rs6277, rs2283265, rs1076560) in Caucasian subjects and one DRD2 SNP (rs6277) in Hispanic subjects. Of particular interest is that these DRD2 SNPs are also part of a haploblock in Caucasian subjects, and all possible genotypes within this haploblock were also significantly associated with substance dependence in the Caucasian population. In the prior literature examining SNP associations with substance dependence, studies that examine DRD1 are limited. One study found associations with DRD1 variants in opiate abuse in three separate populations, entailing Caucasian, African-American, and Hispanic subjects (Jacobs *et al*, 2012). Another study found an association with a single polymorphism in African-American heroin addicts. To date, no study has examined DRD1 variants in cocaine users. Studies of DRD2 variants are much more numerous and several studies have linked polymorphisms to heavy stimulant use in Caucasian subjects (Comings *et al*, 1999; Persico *et al*, 1996), but not racially mixed Europeans or African-American populations (Gelernter *et al*, 1999; Lohoff *et al*, 2010; Moyer *et al*, 2011). In addition, several studies have linked DRD2 polymorphisms to heroin use in Caucasian populations (Lawford *et al*, 2000; Xu *et al*, 2004), but to date, no studies have examined these polymorphisms in African-American or Hispanic populations.

Chronic substance dependence and its genetic associations are likely to have direct relevance to neurocognition and HAND. With chronic substance dependence, adaptive brain changes occur, most notably reduced tonic dopamine levels and increased phasic dopamine neurotransmission following drug dependence (Nestler, 2005). In addition, chronic drug use produces reduced brain metabolism in the frontal cortex that correlates with reductions in DRD2, leading to impairments in working memory and attention (Volkow *et al*, 1993; Volkow *et al*, 2007). In HIV infected subjects, decreased tonic dopamine levels have also been shown with viral replication and advancing disease, both by neuroimaging and direct study of brain tissue. Thus, the environmental effect of long-term substance use should be factored in when studying the relationship between dopaminergic polymorphisms and behavioral outcomes in HIV populations that contain significant numbers of long-term substance dependent individuals. When we employed a strategy to account for gene × environment effects (looking for genetic associations with cognition while controlling for substance dependence), several domains were significantly associated with genotyped polymorphisms, most notably in the African-American population; thus, we detected associations that might not have been evident when simple genetic correlations with cognition without consideration of substance dependence patterns were done (Table 5). This may, in part, account for why our pilot study detected these associations, and prior studies of HIV cognition have not resulted in similar findings. In one, substance users were excluded and only COMT, DAT and BDNF were examined (Levine *et al*, 2012b). In another, a GWAS study that included both HAND and substance use phenotypes in the analysis (Levine *et al*, 2012a), the population had a very low frequency (2–5%) of psychostimulants only (cocaine and methamphetamine), contrasting with our population in which substance dependence had much higher prevalence (69%).

In our population, when controlled for substance dependence status, two SNPs in DRD2 (rs2283265/rs1076560) were significantly associated with the Motor domain T-score in the Caucasian population. These two SNPs play a role in modulating alternative splicing of DRD2 to yield long (DRD2L, expressed mainly postsynaptically) and short (DRD2S, expressed mainly presynaptically) isoforms of the receptor (Khan *et al*, 1998; Usiello *et al*, 2000). While both isoforms regulate presynaptic inhibition of GABAergic neurotransmission in the striatum, DRD2S is preferentially involved in inhibition of glutamate release (Centonze *et al*, 2003; Centonze *et al*, 2004). Recent studies in cognitively normal subjects have revealed roles for these SNPs in a test of working memory and attentional control (N-back working memory task), such that individuals carrying the low expression of DRD2L isoform demonstrated better performance (Zhang *et al*, 2007). Congruently, reduced expression of DRD2L mRNA in dorsolateral prefrontal cortex has been shown in HIV infected subjects with intact cognitive status relative to those with neurocognitive impairment (Gelman *et al*, 2012). When individual neuropsychological test domains were examined in a National NeuroAIDS Tissue Consortium (NNTC) population, significant negative correlations with DRD2L mRNA expression and performance were found for the Verbal Fluency, Attention and Working Memory and Processing Speed Domain T-scores, suggesting that stronger performance was linked to decreased DRD2L expression (Gelman *et al*, 2012). Incidentally, in this study, there were no significant differences in DRD2L mRNA expression in subjects with and without substance use (Gelman *et al*, 2012). Thus, these prior studies together with the current data point to a cognitive impact of DRD2 genetics and expression in HIV and non-infected populations.

Another feature of our analysis was that for all cognitive domains displaying significant genetic associations, the direction of the DRD1 and DRD2 effects in racially segregated populations were, with only one exception, opposite among non-substance using and substance dependent individuals (in the racially heterogeneous Hispanic group, this did not pertain). This supports the hypothesis that the altered tonic dopaminergic milieu of the addicted brain may predicate an altered dopaminergic neurobiology of cognition; elevated levels of transcripts in one setting may be cognitively deleterious, whereas in another may be cognitively beneficial. For example, in the case of the Motor Domain in Caucasians, the preponderance of alleles favoring the DRD2L isoform in substance users (MAF=0.29) compared to non-users (MAF=0.16) in our population suggested that substance users would have greater expression of DRD2L in brain regions relevant to cognitive function (striatum, pre-frontal cortex) in addition to their decreased performance in cognitive tasks (Figure 1). Recently, in a study of healthy controls, increased expression of DRD2L has been linked to greater activity (fMRI BOLD responses) in striatal regions during a visually paced motor task, suggesting individuals with increased DRD2L expression recruit additional neuronal resources during motor tasks, possibly due to less efficient brain activity (Fazio *et al*, 2011). Future studies should confirm DRD2L mRNA expression as well as brain activity changes.

Another aspect of this study was the differences seen between our Caucasian and African American subjects (**Table 5**). In the cognition × substance dependence analyses, we observed a greater number of significant associations in our African American subjects than in the Caucasian subset. This is unusual; in genetic association studies, significant results are more often observed in Caucasian populations that display a greater “genetic bottleneck” than heterogeneous African American populations (Tishkoff and Williams, 2002). Indeed, in our simpler analysis of SNP associations with substance dependency, significant associations were present only in the Caucasian sample. One explanation for the reverse phenomenon in our cognition × substance use analysis might be the inclusion of Hispanics, who had greater representation in our Caucasian than in our African-American subset, and indeed when we examined the Hispanic population separately we only observed single associations for substance dependence as well as cognitive performance. This admixture

would be anticipated to decrease our sensitivity by increasing genetic variability in the Caucasian subset. In addition, with cognitive testing (the endpoint of our analyses) it is well known that Hispanic individuals do not perform as well as would be expected by normative standards or in comparison to non-Hispanic whites (Rivera Mindt *et al*, 2010). Again, inclusion of this group within our Caucasian subset may have worked to diminish effects in an analysis of cognition, but not substance dependency. On the other hand, normative neuropsychological data is also problematic for African American populations; they would be less impacted by inclusion of Hispanics, and their segregation may have eliminated potential test biases that worked to mask results in the entire population, particularly in light of their greater representation in the substance dependent group.

In summary, this study contributes to our understanding of the genetic associations between dopaminergic genes and HAND, importantly showing that substance dependence characteristics must be carefully accounted for when evaluating HIV populations. The distinct and opposing patterns of association displayed by substance users and non-substance users suggest that in an HIV-positive population, neurobiologic processes leading to cognitive impairment may be different, despite the phenotypic similarities of HAND in both groups. Further studies with segregation by substance dependence patterns, to examine brain transcript expression and increase the number of subjects under observation, are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was funded by grants from the National Institutes on Drug Abuse, T32DA007135 (MMJ) and R01DA015446 (YLH), the National Institute of Mental Health, R25MH080663 (MMJ, SM) and U01MH083501 (SM), and the NIH UL1RR029887 (MSSM CTSA).

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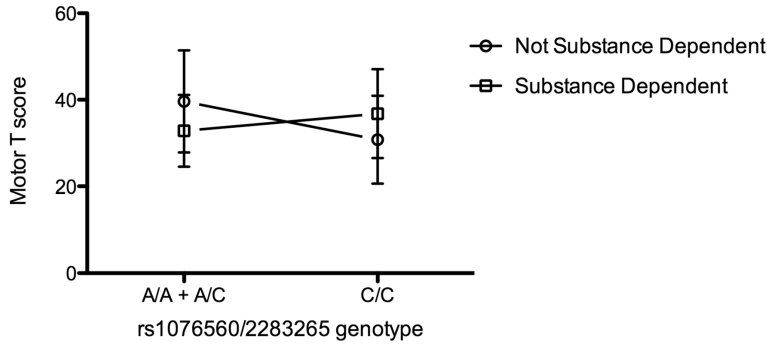

Figure 1. Cognitive performance in the Motor domain is differentially affected by DRD2 genotype

Caucasian substance dependent subjects with the minor alleles at DRD2 rs1076560 and rs2283265 have decreased performance on tasks within the Motor domain as compared with non-substance using subjects of the same race and genotype.

Table 1A

Demographics of the Caucasian study sample.

		Non-Substance Dependent	Substance Dependent	P-value
N		49	54	
Age (mean±SD)		54.7 ± 9.3	51.2 ± 6.1	0.03
Gender				0.99
	Male	34	38	
	Female	15	16	

Table 1B

Demographics of the African-American study sample.

		Non-Substance Dependent	Substance Dependent	P-value
N		27	120	
Age (mean±SD)		49.2 ± 9.0	52.0 ± 7.1	0.05
Gender				0.39
	Male	10	58	
	Female	17	62	

Table 1C

Demographics of the Hispanic subpopulation.

		Non-Substance Dependent	Substance Dependent	P-value
N		16	45	
Age (mean±SD)		50.3 ± 7.6	50.1 ± 5.2	0.91
Gender				0.56
	Male	8	18	
	Female	8	27	

(Note: Of these 61 individuals, 43 identified as Caucasian, and 18 as African-American; they are included in tables 1A and 1B.)

Table 2

Description of polymorphisms tested.

Gene	SNP	SNP Location	Alleles	Minor (AA Freq.)	Minor (Cauc Freq.)	Minor (Hisp Freq.)
DRD1	rs4532	Exon 1 (5'UTR)	C/T	C (0.19)	C (0.36)	C (0.27)
DRD1	rs686	Exon 4 (3'UTR)	A/G	A (0.37)	G (0.43)	G (0.41)
DRD1	rs265978	3.7 kb downstream	C/T	C (0.37)	C (0.43)	C (0.38)
DRD1	rs265975	5.5 kb downstream	C/T	C (0.46)	T (0.25)	T (0.35)
DRD1	rs265973	7 kb downstream	C/T	T (0.42)	T (0.34)	T (0.30)
DRD2	rs12364283	Promoter (1kb upstream)	A/G	G (0.02)	G (0.10)	G (0.10)
DRD2	rs2283265	Intron 5	A/C	A (0.12)	A (0.16)	A (0.22)
DRD2	rs1076560	Intron 6	A/C	A (0.12)	A (0.18)	A (0.22)
DRD2	rs6277	Exon 7 (C957T)	A/G	A (0.14)	G (0.41)	G (0.44)
DRD2/ANKK1	rs1800497	10kb downstream	A/G	A (0.31)	A (0.22)	A (0.25)

Minor alleles and allele frequencies are with respect to the non-substance using population within each subset. Abbreviations: DRD1, dopamine D1 receptor; DRD2, dopamine D2 receptor; Freq: frequency; kb: kilobase; UTR: untranslated region.

Table 3A

SNPs significantly associated with substance dependence.

Population	N (No SUD/SUD)	Gene	SNP	P
Caucasian	103 (49/54)	*DRD2*	**rs6277**	**0.0002**
		DRD2	rs2283265	0.02
		DRD2	rs1076560	0.05
		DRD1	rs265975	0.05
African-American	147 (27/120)	N/A		
Hispanic	61 (16/45)	*DRD2*	rs6277	**0.00007**

Table 3B

Haplotype association tests

Population	Gene	SNPs	Haplotype	P
Caucasian	*DRD2*	rs6277/rs1076560/rs2283265	ACC	**0.0002**
	DRD2	rs6277/rs1076560/rs2283265	GAA	0.02
	DRD2	rs6277/rs1076560/rs2283265	GCC	0.05
African-American	N/A			
Hispanic	N/A			

Abbreviations: SUD, substance dependence; DRD1, dopamine D1 receptor; DRD2, dopamine D2 receptor; SNP, single nucleotide polymorphism. SNP in **BOLD** remains significant after Bonferroni correction for multiple comparisons. Hispanic population comprises a subset of the Caucasian and African American samples.

Table 4

Cognitive Performance T-scores in Caucasian, African-American, and Hispanic subsets.

	Entire	Caucasian		African-American		Hispanic	
Domain	**Population**	**No SUD**	**SUD**	**No SUD**	**SUD**	**No SUD**	**SUD**
Global	37.8 (7.9)	39.9 (9.5)	37.7 (8.1)	37.5 (5.4)	37.0 (7.4)	35.0 (7.3)	35.7 (7.8)
Motor	32.9 (9.8)	33.6 (11.1)	35.0 (9.6)	31.5 (9.5)	31.8 (9.4)	34.9 (11.7)	35.1 (10.5)
Processing Speed	40.6 (9.0)	42.4 (10.4)	41.1 (9.2)	40.5 (7.0)	39.7 (8.7)	39.5 (7.9)	39.5 (9.8)
Working Memory	42.6 (9.3)	43.1 (10.5)	41.9 (10.5)	40.9 (9.4)	43.0 (8.1)	37.8 (6.9)	40.0 (8.8)
Executive Functioning	39.4 (10.0)	40.1 (11.0)	40.6 (9.9)	39.4 (10.1)	38.2 (9.6)	38.7 (9.6)	38.1 (9.6)
Learning	33.3 (10.5)	**36.6 (12.0)**	**31.8 (10.7)**	33.7 (8.8)	32.5 (9.9)	28.8 (9.7)	28.5 (7.8)
Memory	34.1 (11.2)	**38.0 (12.9)**	**33.0 (11.2)**	35.4 (10.3)	32.7 (10.3)	31.1 (11.2)	30.8 (9.1)
Verbal Fluency	47.1 (10.6)	47.2 (12.8)	44.8 (10.1)	49.4 (8.7)	47.6 (10.2)	38.3 (10.5)	42.4 (9.4)

Abbreviation: Substance Dependent (SUD). Cognitive Performance T-scores represented as mean (SD) for the entire population as well as within the Caucasian, African-American, and Hispanic groups. Hispanics are a subset of the Caucasian and African-American individuals. Figures in **BOLD** are significantly different between the no SUD and SUD populations ($P<0.05$).

Table 5A

SNPs associated with cognitive performance T-scores controlling for substance dependence: Caucasian population

Domain	N (No SUD/SUD)	Gene	SNP	β_No SUD	β_SUD	P
Global	97 (45/52)	N/A				
Motor	93 (43/50)	*DRD2*	rs2283265	8.857	−3.253	0.003
		DRD2	rs1076560	7.107	−3.253	0.004
Processing Speed	92 (42/52)	N/A				
Working Memory	95 (45/50)	N/A				
Executive Functioning	94 (42/52)	N/A				
Learning	97 (45/52)	N/A				
Memory	97 (45/52)	N/A				
Verbal Fluency	96 (44/52)	N/A				

Table 5B

SNPs associated with cognitive performance T-scores controlling for substance dependence: African-American population

Domain	N (No SUD/SUD)	Gene	SNP	β_No SUD	β_SUD	P
Global	135 (23/112)	N/A				
Motor	128 (23/105)	*DRD1*	rs265973	10.51	2.186	0.022
		DRD1	rs686	−5.777	1.665	0.010
		DRD2	rs12365283	23.59	−1.815	0.007
Processing Speed	131 (23/108)	*DRD1*	rs4532	−3.124	2.917	0.038
Working Memory	132 (23/109)	*DRD1*	rs265973	−5.221	2.996	0.042
Executive Functioning	129 (22/107)	N/A				
Learning	135 (23/112)	N/A				
Memory	135 (23/112)	*DRD2*	rs2283265*	−10.91	0.0869	0.039
		DRD2	rs1076560*	−10.91	0.0869	0.039
Verbal Fluency	132 (20/112)	N/A				

DRD2 SNPS rs2283265/rs1076560 form a haploblock within the AA subset, which accounts for the identical β and P values observed.

Table 5C

SNPs associated with cognitive performance T-scores controlling for substance dependence: Hispanic subset of above populations

Domain	N (No SUD/SUD)	Gene	SNP	β_No SUD	β_SUD	P
Global	58 (16/42)	N/A				
Motor	54 (14/40)	N/A				
Processing Speed	56 (14/42)	N/A				
Working Memory	56 (16/40)	N/A				
Executive Functioning	56 (14/42)	N/A				
Learning	58 (16/42)	N/A				
Memory	58 (16/42)	*DRD1*	rs4532	−11.33	−2.344	0.046
Verbal Fluency	57 (15/42)	N/A				