

Supplementary Information

HIV-Associated Distal Neuropathic Pain is Associated with Smaller Total Cerebral Cortical Gray Matter

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Supplementary information contains:

1. Supplementary text
2. Supplementary Tables

SUPPLEMENTARY RESULTS

Supplementary table S1 shows that for the multivariable model, worse severity of DNP symptoms is significantly correlated with smaller cerebral cortical gray matter volume. Age, ethnicity, gender, cerebral-vault, scanner, history of D-drug use, history of inhalant abuse, history of methamphetamine abuse, and Global Deficit Score are also significantly correlated with smaller cerebral cortical gray matter volume. The definition (type and range) is included for each explanatory variable and the p-values (uncorrected for multiple comparisons) less than 0.20 are listed for each model of DNP and the log brain volumes.

The number of subjects with missing data is listed for each explanatory variable in supplementary table S1. Since the explanatory variable CSF HIV RNA is missing for 28 subjects, in Table 2 the number of subjects without missing data for the association between DNP and log cortical volume is 213. If CSF HIV RNA is removed during the multivariable model selection process the relationship between severity of DNP and smaller cerebral cortical gray matter volume is not significantly changed ($R^2 = .83$; $p = 0.008$)

SUPPLEMENTARY TABLE S1: List of the explanatory variables used for the multivariable models of the association between DNP and log brain volumes. The definition (type and range), number of subjects with missing data for each variable, and the p-values (uncorrected for multiple comparisons) less than 0.20 are listed for each explanatory variable.

VARIABLE	TYPE	RANGE	Number of subjects With Missing Data	Explanatory variables (P<0.20) for each brain volume multivariable model					
				Log Cortical Gray	Log Subcortical Gray	Log Abnormal White	Log Total White	Log Ventricle CSF	Log Sulcal CSF
Distal Neuropathic Pain	Continuous	0 - 4	0	0.0006				0.009	0.16
Age	Continuous	23 yo – 67 yo	0	<0.0001	<0.0001			<0.0001	<0.0001
Education	Continuous	7 yrs – 20 yrs	0			0.122			
Ethnicity	Nominal	See Table 1	0	0.004		0.069			
Gender	Binary	See Table 1	0	<0.0001		0.082	0.022		
Log-cerebralVault	Continuous	13.5-14.3	0	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Scanner	Nominal	1 scanner Univ Wash 1 scanner Univ Texas 1 scanner Hopkins 2 scanners New York 2 scanners UCSD	0	<0.0001	0.039	<0.0001	0.094	0.066	0.885
HCV status	Binary	See Table 1	3			0.002			
Plasma HIV RNA undetectable/detectable	Binary	See Table 1	3			0.100	0.064	0.004	
CSF HIV RNA undetectable/detectable	Binary	See Table 1	28	0.104					
Sqrt CD4 Nadir	Continuous	0-38.7	0		0.097	0.016	0.086		0.042
Sqrt CD4 Current	Continuous	2.64-42.46	3		0.012				
Current D-drug Exp	Continuous	0-110 months	0						
On D-drugs (Y/N)	Binary	On = 30 Off = 211	0	0.171					
D-drug ever	Nominal	1= current 2= past 3= never	0	0.024			0.070		
Total D-drug Exposure	Continuous	0-261 months	0						
# protease inhibitors	Continuous	0-3	0			0.119			
Current Antiretroviral Regimen	Nominal	See Table 1	0					0.014	

Beck Depression Inventory II	Continuous	0-63	0			0.171		0.001	
Major Depression Current	binary	See Table 1	0						
Major Depression Ever	binary	See Table 1	0						
Alcohol Abuse Ever	binary	Yes=29 No=206	6						
Alcohol Dep Ever	Binary	Yes=42 No=193	6						
Cannabis Abuse Ever	Binary	Yes=43 No=198	0			0.016	0.126	0.099	
Cannabis Dependence Ever	Binary	Yes=29 No=206	0			0.074	0.020	0.043	0.037
Cocaine Abuse Ever	Binary	Yes=22 No=219	0				0.136		
Cocaine Dep Ever	Binary	Yes=95 No=146	0				0.002	0.155	0.061
Halucinogen abuse ever	Binary	Yes=11 No=230	0						
Halucinogen Dependence Ever	Binary	Yes=5 No=236	0						
Inhalant Abuse Ever	Binary	Yes=5 No=236	0	0.011					
Inhalant Dependence Ever	Binary	Yes=3 No=238	0					0.102	
Methamphetamine Abuse Ever	Binary	Yes=8 No=233	0	0.020					
Methamphetamine Dependence Ever	Binary	Yes=34 No=207	0		0.092				
Opiate Abuse Ever	Binary	Yes=10 No=231	0						
Opiate Dependence Ever	Binary	Yes=42 No=199	0		0.009			0.185	
Sedative Abuse Ever	Binary	Yes=7 No=234	0	0.055			0.024	0.071	
Sedative Dependence Ever	Binary	Yes=10 No=231	0						
Global Deficit Score	Continuous	0-3.47	0	0.002		0.003		0.004	0.144
Opiate Pain Treatment	Binary	Yes=42 No=199	0					0.072	
Tricyclic Antidepressant Pain Treatment	Binary	Yes=23 No=218	0						
Anticonvulsant Pain Treatment	Binary	Yes=23 No=218	0						

Traumatic Brain Injury	nominal	See Table 1	54	No TBI	No TBI	No TBI	No TBI	No TBI	No TBI
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We repeated the above cortical linear regression and t-test analysis using Minitab (Minitab 16 statistical software, Pennsylvania State University, 2010 - www.minitab.com), obtaining the same reported significance of variables as were previously obtained using JMP.

We then repeated this study using LIBSVM's implementation (Chang et al 2011) of Support Vector Regression (SVR) with Gaussian kernels (Smola et al 2004). By this nonlinear regression (Aksu et al 2010), we again confirmed (Table S2) that DNP was among the top ten most significant variables for predicting total cortical gray matter volume. We ran epsilon-SVR wrapped with recursive feature elimination (RFE) for 50 different random 5-fold splits of the data. For each split (trial) we selected the two SVR hyper-parameters to minimize the average held-out fold mean-squared prediction error. The sample mean and standard deviation of the average RFE-ranking of each feature over the 50 trials is given in Table S2. Note that after eliminating the features mean-ranked 4th, 7th and 8th because of high standard deviations, the DNP feature is mean-ranked 7th most significant variable for predicting total cortical gray matter volume.

SUPPLEMENTARY TABLE S2: The top 10 features by their mean ranks over 50 experimental trials which predict total cortical gray matter volume. Excluding the three bolded features (4th, 7th, and 8th) with negligible statistical significance owing to high sample standard deviation, DNP ranks seventh.

mean feature ranks	Features	Mean	Stdev
1	Log_cerebralVAULT	1	0
2	GDS	2.42	0.55
3	Age	2.61	2.54
4	Sqrt cd4 current	4.36	8.18
5	Gender	5.37	1.47
6	Ethnicity	6.79	0.16
7	Education	7.66	8.04
8	Sed abuse	7.68	6.59
9	Scanner	8.34	0.50
10	DNP	9.52	1.57