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HIV Distal Neuropathic Pain Is Associated with Smaller Ventral Posterior Cingulate Cortex

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Abstract

Objective. Despite modern antiretroviral therapy, HIV-associated neuropathy is one of the most prevalent, disabling and treatment-resistant complications of HIV disease. The presence and intensity of distal neuropathic pain is not fully explained by the degree of peripheral nerve damage. A better understanding of brain structure in HIV distal neuropathic pain may help explain why some patients with HIV neuropathy report pain while the majority does not. Previously, we reported that more intense distal neuropathic pain was associated with smaller total cerebral cortical gray matter volumes. The objective of this study was to determine which parts of the cortex are smaller.

Methods. HIV positive individuals with and without distal neuropathic pain enrolled in the multisite (N = 233) CNS HIV Antiretroviral Treatment Effects (CHARTER) study underwent structural brain magnetic resonance imaging. Voxel-based morphometry was used to investigate regional brain volumes in these structural brain images.

Results. Left ventral posterior cingulate cortex was smaller for HIV positive individuals with versus without distal neuropathic pain (peak $P = 0.017$; peak $t = 5.15$; MNI coordinates $x = -6$, $y = -54$, $z = 20$). Regional brain volumes within cortical gray matter structures typically associated with pain processing were also smaller for HIV positive individuals having higher intensity ratings of distal neuropathic pain.

Conclusions. The posterior cingulate is thought to be involved in inhibiting the perception of painful stimuli. Mechanistically a smaller posterior cingulate cortex structure may be related to reduced anti-nociception contributing to increased distal neuropathic pain.

Key Words. HIV Distal Neuropathic Pain; Structural Magnetic Resonance Imaging; Posterior Cingulate Cortex; Voxel-Based Morphometry

Introduction

HIV-associated distal neuropathic pain (DNP) affects approximately 20% of individuals with HIV and is one of the most prevalent neurological complications of HIV infection in the era of combination antiretroviral therapy (CART) [1]. HIV DNP is typically refractory to current chronic pain therapies [2,3]; and is associated with unemployment, impairment in activities of daily living, and significantly diminished quality of life [1].

Similar to other common peripheral neuropathies such as diabetic and alcoholic peripheral neuropathy [4–7], it is unclear why some individuals with HIV peripheral neuropathy experience DNP and others do not [1,5,6,8]. Approximately half of HIV-infected (HIV+) individuals have sensory neuropathy by physical examination or nerve conduction studies [1,9]. About 40% of them report chronic DNP, while the remainder reports only numbness or paresthesiae or no symptoms at all [1,9]. Most research on HIV DNP mechanisms has focused on the direct effects of HIV or antiretroviral drugs on peripheral nerves (e.g., exposure to dideoxynucleoside reverse transcriptase inhibitors such as stavudine or didanosine) [10,11] and on clinical risk factors for neuropathy (age, height, and lower CD4 nadir) [1]. This research suggests the intensity of DNP is not fully explained by the extent of HIV damage to peripheral nerve fibers [11–14], nor by clinical risk factors [1,8], leaving it unclear why some HIV neuropathy individuals experience DNP and others do not.

Central nervous system pathways exert a major influence on the clinical expression of peripherally-induced pain [15–17] and contribute to the transition from acute to chronic pain states [18,19]. Brain imaging has revealed the impact of peripheral neuropathy on the central nervous system. For example, in diabetic neuropathy the somatosensory cortex is smaller [7] while in painful diabetic neuropathy resting state network connectivity is altered [20–22].

Previously, using conventional morphometric methods which included hand segmentation techniques [23], we reported that total cortical volumes are smaller for HIV+ individuals with higher DNP ratings, when controlling for clinical and imaging covariates associated with changes in total cerebral cortical gray matter volume [24]. This research leaves unresolved which parts of the cortex are smaller for HIV+ individuals with larger DNP ratings. This research also does not address if parts of the cortex are smaller for HIV+ individuals with DNP compared to those without DNP.

The first purpose of this investigation was to use the structural imaging data set from our previous investigation [24] to determine if regional cortical volumes are smaller for HIV+ individuals with DNP compared to those without DNP. The second purpose is to determine if regional cortical volumes are smaller for HIV+ individuals with larger DNP ratings, that is determine if regional cortical volumes are negatively correlated with DNP. Given that it is too laborious to parcelate the total cortex for the hundreds of individuals in this structural imaging data set [24] using hand segmentation methods [23], here we use automated voxel-based morphometry (VBM) to investigate which regions of the cortex are smaller for HIV+ individuals with DNP compared to those without DNP, and whether regions of the cortex are smaller for HIV+ individuals with larger DNP intensity ratings.

In other chronic pain conditions regional cortical gray matter volumes within cortical pain processing structures (such as the anterior cingulate cortex, insula cortex, and prefrontal cortex) and within resting state default mode cortical structures (such as the posterior cingulate cortex) are smaller [25–37]. We therefore hypothesized that regional cortical gray matter volumes within these same structures would be smaller in HIV+ individuals with DNP compared to those without DNP, and would be smaller for those with larger DNP intensity ratings.

Methods

Participants

The Central Nervous System HIV Anti-Retroviral Therapy Effects Research Study (CHARTER), examined 1,556 HIV+ individuals at five United States academic medical centers with a comprehensive battery of neuromedical and neuropsychiatric assessments [1,23]. A subset of CHARTER HIV+ enrollees (N = 699) were recruited to participate in a longitudinal arm of the study which involved follow-up appointments every 6 months. The primary selection criterion for the longitudinal arm was that people were willing to do lumbar punctures at longitudinal visits. Additionally, subgroups were recruited into the longitudinal arm for: 1) presence or absence of peripheral neuropathy; 2) being eligible for magnetic resonance imaging (MRI); and 3) presence of lipodystrophy or lipoatrophy. Of the 699 individuals entering the longitudinal arm, 241 met criteria for MRI and agreed to participate in a sub-study which involved undergoing brain structural MRI studies [23]. Since VBM methods require a relatively normally shaped brain, eight brains with gross structural abnormalities out of the original 241 brains were excluded, so the total number of individuals included in this study was 233. Data reported here are from their first adequate MRI at their second CHARTER visit, which occurred between 2004 and 2007. The sites performing MRI included: Johns Hopkins University (Baltimore, MD; N = 47); Mount Sinai School of Medicine (New York, NY; N = 48); University of California at San Diego (San Diego, CA; N = 70); University of Texas Medical Branch (Galveston, TX; N = 46); and University of Washington (Seattle, WA; N = 30).

Standard Protocol Approvals and Patient Consents

The Human Subjects Protection Committees of each participating institution approved these procedures. Written informed consent was obtained from all study participants as part of enrollment into the CHARTER MRI sub-study.

Measures and Assessments

Diagnosis of HIV Distal Neuropathic Pain

HIV DNP was defined as a specific pattern of bilateral burning, aching, or shooting pain in the lower extremities, which is a standard definition of distal neuropathic pain that has been validated in prior work [1,9]. Recognizing that this specific pattern of pain may occur in small fiber-predominant neuropathies in which abnormalities on clinical examination are sometimes absent due to the relative paucity of large fiber involvement, we included in the diagnosis of DNP those cases that did not have signs of neuropathy (e.g., diminished vibratory sensation). Patients were further diagnosed with sensory neuropathy if examination revealed at least one sign of neuropathy bilaterally (e.g., reduced ankle reflexes, diminished vibratory sense or sharp-dull discrimination). Based on patients' reports of pain intensity, impact on everyday function, and treatment-seeking, study clinicians further classified DNP into five categories of magnitude: none; slight (occasional, fleeting); mild (frequent); moderate (frequent, disabling); and severe (constant, daily, disabling, requiring analgesic medication or other treatment). The DNP grading system used here has been validated against a variety of indices of impact on overall health and daily functioning [1] as well as neuropathy severity as assessed by neurological examination and electrophysiological measures [9]. Because neuropathic pain in HIV is known to wax and wane in severity, and may even remit and then recur, we also asked participants to estimate the duration of their DNP in spans of time: 4 days to 4 weeks, 1 month to 1 year, 1 to 10 years, greater than 10 years. The average time between the DNP clinical assessment and the MRI brain imaging was 10 days. Data related to the validation of the DNP grading system [1,9] as well as DNP clinical case report forms and an associated instruction manual, are available at www.charternntc.org. Alternatively, the DNP clinical case report forms and associated instruction manual can be obtained from the corresponding author for this manuscript.

Neuromedical and Neuropsychiatric Evaluation

Clinicians conducting the neurological examination also performed semi-structured interviews and standardized examinations to ascertain HIV disease status, HIV treatment history, psychotropic medications, and pain treatments. Plasma and cerebrospinal fluid (CSF) HIV concentration were determined [23]. Plasma hepatitis C and plasma CD4 were also determined [23,38].

An extensive treatment history queried for prior and current anti-HIV treatment since exposure to anti-HIV dideoxynucleoside reverse transcriptase inhibitors (didanosine, stavudine, and zalcitabine) may cause neuropathy. Performance on neuropsychological testing was assessed, and a global deficit score was calculated to control for the impact of HIV cognitive deficits on brain structure [13,23,39].

Because psychiatric and substance use disorders may be associated with neuroimaging and cognitive abnormalities, history of major depression (and current Beck depression inventory scores) and psychoactive

substance use disorders were assessed using the Composite International Diagnostic Interview and DSM-IV criteria [40–42]. History of abuse and dependence was collected for alcohol, cannabis, cocaine, hallucinogens, inhalants, methamphetamine, opioids, and sedatives.

Structural Imaging

As described previously [23], structural MRI volumes were acquired on 1.5 Tesla GE scanners at the five participating sites. Image acquisition parameters were sagittal acquisitions with section thickness = 1.3 mm, FOV 24 cm, matrix size 256 x 256 x 124, voxel dimensions 0.94 mm x 0.94 mm x 1.94 mm, 3D T1-weighted SPGR with TR = 20 ms, TE = 6 ms, flip angle = 30.

Voxel-Based Morphometric Analysis

Structural data was analyzed with FSL-VBM [43] (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised VBM protocol [44] carried out with FSL tools [45]. Since the transformation from native brain space to standard space requires a relatively normally shaped native space brain, eight of the original 241 brains were excluded due to gross brain anatomical abnormalities (such as brain tumor, focal encephalomalacia, and hydrocephalus); so the total number of individuals included in this study was 233. The gross brain abnormalities were identified through careful inspection during image analysis and a consensus of the investigators. Not all normal images were reviewed by a neuroradiologist, but all abnormal images were reviewed by a neuroradiologist. Native space structural images were brain-extracted using automated FSL BET with further manual refinement conducted with AFNI [46] as necessary. The native space structural images were then gray matter-segmented [47] before being registered to the MNI 152 standard space using an affine transform [48] that was supplemented by non-linear refinement [49]. The resulting images were averaged to create a study-specific template. In order to eliminate white matter abnormalities in the study-specific template, which have the same intensity as gray matter, we masked the white matter portion of the study-specific template with a mask generated from the avg152T1_gray tissue prior. All native gray matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation [44]. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 (12.25 mm). Finally, voxelwise general linear modeling was applied using permutation-based non-parametric testing that corrected for multiple comparisons across the whole brain using the Threshold-Free Cluster Enhancement method [50]. The corrected alpha was set to 0.05.

Statistical Methods

Demographic and clinical statistical differences between the DNP group and the non-DNP group were determined using the independent samples t-test (age, education, Beck depression inventory, global deficit score) [51], Fisher's exact test (gender, ethnicity, hepatitis C, plasma and CSF viral load, antiretroviral use, dideoxynucleoside reverse transcriptase inhibitors (D-drug) use, history of major depression, history of inhalant use, history of methamphetamine use) [52], and the Goodman and Kruskal ordinal gamma test (CD4) [53].

Two statistical models were investigated for each regional brain volume: First, we used a general linear model to compare regional brain volumes between the HIV+ individuals with and without DNP; second, we used an alternate general linear model to investigate which regional brain volumes were negatively correlated with DNP (volumes are smaller for HIV subjects with larger DNP ratings). DNP was treated as a continuous variable: none (DNP = 0), slight (DNP = 1), mild (DNP = 2), moderate (DNP = 3), and severe (DNP = 4). This is not a region of interest (ROI) analysis where we investigated a priori-defined ROI. Instead, the VBM methods used here investigate the whole brain gray matter to identify clusters of voxels such that the voxel clusters have smaller volumes for HIV+ individuals with DNP compared to individuals without DNP or the voxel clusters have smaller volumes for HIV+ individuals with larger DNP ratings. As described in the Voxel-Based Morphometric Analysis Methods above, all reported P values are corrected for multiple comparisons across space [50].

For each of these statistical models an unadjusted and an adjusted analysis was performed (Table 1). In the unadjusted analysis we did not control for clinical and imaging covariates associated with changes in total cerebral cortical gray matter volume, while in the adjusted analysis we did control for clinical and imaging covariates associated with changes in total cerebral cortical gray matter volume.

The clinical and imaging covariates which have been previously associated with changes in total cortical volume [24] include age, ethnicity, gender, cerebral-vault volume, scanner, history of D-drug use, history of inhalant abuse, history of methamphetamine abuse, and Global Deficit Score – see Table 2. There were two reasons for controlling for these clinical and imaging covariates in the adjusted analysis. First, these covariates may be confounders of the association between DNP and regional brain volumes and thus need to be included to reduce bias in estimating the effect of DNP. Second, these covariates are independent predictors of brain volumetrics. Thus, their inclusion in the model may in fact help to increase the power of our comparisons of interest. To control for bias resulting from inter-scanner variability [54–57], we controlled for scanner as a covariate in the adjusted analysis.

Table 1 Four statistical models used to investigate which regional brain volumes are smaller for HIV+ individuals with DNP compared to HIV+ individuals without DNP as well as HIV+ individuals with larger DNP ratings. Models #2 and #4 control for covariates previously associated with changes in total cortical volume [24]—these control covariates are listed in Table 2

	Unadjusted models not controlling for covariates associated with changes in total cortical volume	Adjusted models controlling for covariates associated with changes in total cortical volume
Statistical models investigating regional brain volumes smaller for individuals with DNP vs individuals without DNP	Model #1	Model #2
Statistical models investigating smaller regional brains in HIV+ individuals with larger DNP ratings	Model #3	Model #4

Table 2 List of clinical and imaging covariates that are associated with changes in total cortical volume [24]. Models #2 and #4 in Table 1 control for these covariates. The definition for each covariate includes its type and range

Variable	Type	Range
Age	Continuous	23 yo–67 yo
Ethnicity	Nominal	See Table 3
Gender	Binary	See Table 3
Log-cerebral vault	Continuous	13.5–14.3
Scanner (# of scanners at site)	Nominal	Univ Wash (1 scanner) Univ Texas (1 scanner) Hopkins (1 scanner) New York (2 scanners) UCSD (2 scanners)
D-drug* ever	Nominal	1 = current 2 = past 3 = never
Inhalant abuse ever	Binary	Yes or no
Methamphetamine abuse ever	Binary	Yes or no
Global deficit score	Continuous	0–3.47

*D-drug = dideoxynucleoside reverse transcriptase inhibitors.

Finally, we performed an additional adjusted analysis to investigate if the pain component of neuropathic pain is associated with changes in regional brain volume independent of contributions of HIV peripheral neuropathy and independent of possible systemic disease associated with HIV peripheral neuropathy. In this additional adjusted analysis, we controlled for clinical and imaging covariates associated with changes in total cerebral cortical gray matter volume and we also controlled for

number of signs of HIV neuropathy. We controlled for signs of HIV neuropathy in both statistical models: the general linear model comparing regional brain volumes between the HIV+ individuals with and without DNP as well as the general linear model investigating which regional brain volumes were negatively correlated with HIV DNP. We controlled for signs of HIV neuropathy using two different methods: 1) we controlled for the number of signs of HIV neuropathy by treating the number of signs as a continuous variable, and 2) we controlled for the number of signs of HIV neuropathy by controlling for the effect of having one or two signs of HIV neuropathy compared to having no signs of HIV neuropathy.

Results

Signs of Neuropathy

Of the 233 evaluable individuals, 132 (57%) met criteria for distal sensory neuropathy by virtue of having at least one objective sign of neuropathy (for example, reduced ability to discriminate vibration sense in the feet and toes bilaterally [58]). Sixty-five individuals (28%) met a more stringent definition of at least two objective signs of neuropathy. The DNP and non-DNP proportions of signs of neuropathy were significantly different using the Goodman and Kruskal ordinal gamma test [53], $P < 0.001$. The proportion of zero signs of neuropathy was higher in the non-DNP group (9/64 = 14% for individuals with DNP and 92/169 = 54% for individuals without DNP). The proportion of two signs of neuropathy was higher in the DNP group (35/64 = 55% for individuals with DNP and 30/169 = 18% for individuals without DNP).

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study participants (Table 3) show that typical individuals were middle-aged men of Caucasian, African-American, or Hispanic ethnicity who had AIDS and were currently

Table 3 Demographic and clinical characteristics of the participants. Column 5 lists the *P* values showing if the characteristic proportions or mean values are significantly different for individuals with DNP compared to individuals without DNP

DNP	All individuals	DNP	No DNP	*P* values DNP vs no DNP
No. of individuals	233	64	169	
Neuropathic pain rating, no. (%)				
No pain	169 (73)	0 (0)	169 (100)	
Slight	18 (8)	18 (11)	0 (0)	
Mild	22 (9)	22 (13)	0 (0)	
Moderate	9 (4)	9 (5)	0 (0)	
Severe	15 (6)	15 (90)	0 (0)	
Age, mean (SD)	44 (8)	46 (8)	43 (8)	<0.01*
Education yrs, mean (SD)	13 (3)	13 (2)	13 (2)	0.734
Male, no. (%)	187 (80)	50 (78)	137(81)	0.712
Race/ethnicity, no. (%)				
Caucasian	92 (40)	32 (50)	60 (36)	0.211
African American	110 (47)	24 (38)	86 (61)	
Hispanic	26 (11)	7 (11)	19 (11)	
Other	5 (2)	1 (2)	4 (2)	
Hepatitis C Virus seropositive, no. (%)	64 (28)	21 (33)	43 (25)	0.324
AIDS, no. (%)	147(63)	41 (64)	106(63)	0.880
CD4, no. (%)				
Current < 200; nadir < 200	34 (15)	7 (11)	27 (16)	0.530
Current ≥ 200, nadir < 200	101(43)	29 (45)	72 (43)	
Current ≥ 200, nadir ≥ 200	95 (41)	27 (42)	68 (40)	
Plasma HIV RNA detectable, no. (%)				
All individuals	121(52)	31 (49)	90 (53)	0.558
ON CART**, no. (%)	61 (26)	19 (30)	42 (36)	0.505
OFF CART**, no. (%)	60 (26)	12 (19)	48 (28)	0.179
Cerebrospinal fluid HIV RNA detectable, no. (%)				
All individuals	68 (30)	16 (25)	52 (31)	0.423
ON CART,** no. (%)	24 (10)	7 (11)	17 (14)	0.813
OFF CART,** no. (%)	44 (19)	9 (14)	35 (21)	0.268
CART** use, no. (%)				
Current	170 (73)	52 (81)	118 (70)	0.107
Past	37 (16)	9 (14)	28 (17)	
Never	26 (11)	3 (5)	23 (14)	
D-drug,** no. (%)				
Current	39 (17)	11 (17)	28 (17)	0.230
Past	87 (37)	29 (45)	58 (34)	
Never	107 (46)	24 (38)	83 (50)	
Beck depression inventory II, mean (SD)	12 (11)	16 (11)	11 (11)	0.001*
Lifetime major depressive disorder,*** no. (%)	51 (22)	21 (33)	30 (18)	0.020*
History of inhalant abuse, no. (%)	5 (2)	3 (5)	2 (1)	0.129
History of methamphetamine abuse, no. (%)	8 (3)	2 (3)	6 (4)	1.000
Global deficit score, mean (SD)	0.4 (0.4)	0.4 (0.4)	0.4 (0.5)	0.991

*DNP and non-DNP characteristics are statistically different.
**D-drug = dideoxynucleoside reverse transcriptase inhibitors; CART = combination antiretroviral therapy.
***Major depressive disorder = Meets DSM-IV criteria for a major depressive episode within the last 30 days.

on antiretrovirals, with good immune recovery and fair virologic control.

The average age of the DNP group was older than the non-DNP group (t = 3.24, degrees of freedom = 231, P < 0.001). In addition, the proportion with a history of depression was higher in the DNP group compared to the non-DNP group (P = 0.02) and the average Beck depression rating was higher for the DNP group compared to the non-DNP group (t = 3.23, degrees of freedom = 231, P < 0.001).

VBM Results

The left ventral posterior cingulate cortex (PCC) was smaller for HIV+ individuals with DNP compared to those without DNP (see Table 4). Figure 1 shows the part of the ventral PCC which is smaller for HIV+ individuals with DNP compared to those without DNP (peak P = 0.017; peak t = 5.15; MNI coordinates x = −6, y = −54, z = 20, cluster volume = 65 voxels; cluster average P = 0.032; cluster average t-score = 4.38). In addition, the ventral PCC volume trends towards statistical significance for being smaller for

HIV+ individuals with larger DNP ratings (see Table 4). Regions within the right precentral gyrus, bilateral insula cortex, bilateral putamen, right orbital frontal cortex, and right caudate are smaller for HIV+ individuals with larger DNP ratings (see Table 4). No regional brain volumes were larger for HIV+ individuals with DNP compared to those without DNP nor for those with larger DNP ratings.

When controlling for signs of HIV neuropathy as well as the covariates listed in Table 2, the PCC is no longer smaller for HIV+ individuals with DNP compared to those without DNP. Also, when controlling for signs of HIV neuropathy as well as the covariates listed in Table 2, the PCC volume is no longer smaller for HIV+ individuals with larger DNP ratings.

Discussion

We hypothesized that regional cortical gray matter volumes within pain processing structures and within default mode network structures would be smaller in HIV+ individuals with DNP compared to those without DNP, and would be smaller for those with larger DNP

Table 4 Results for which regional brain volumes are smaller for HIV+ individuals with DNP compared to HIV+ individuals without DNP and HIV+ individuals with larger DNP ratings. As described in Table 1, statistical models #1 and #2 investigate regional brain volumes smaller for HIV+ individuals with DNP compared to HIV+ individuals without DNP, while statistical models #3 and #4 investigate regional brain volumes which are smaller for HIV+ individuals with larger DNP ratings

Statistical model	Brain region	P value (peak)	T score	MNI coordinates	Cluster volume # voxels P values < 0.05
#1 Unadjusted analysis of brain regions smaller for DNP compared to no DNP	Left ventral PCC	0.034	4.71	X = −6, Y = −52, Z = 18	43
#2 Adjusted analysis of brain regions smaller for DNP compared to no DNP	Left ventral PCC	0.017	5.15	X = −6, Y = −54, Z = 20	65
#3 Unadjusted analysis of brain regions smaller for HIV+ individuals with larger DNP ratings	Left ventral PCC	0.058 (Trend)	3.83	X = −6, Y = −54, Z = 20	0
	R PCG	0.012	4.41	X = 32, Y = −22, Z = 46	174
	R caudate	0.050	2.80	X = 16, Y = 40, Z = 40	18
	R putamen	0.042	3.00	X = 26, Y = 10, Z = 6	91
	L putamen	0.045	3.00	X = −24, Y = 6, Z = 6	84
	R insula cortex	0.038	3.71	X = 30, Y = 28, Z = 4	82
	L insula cortex	0.049	3.00	X = -28, Y = 22, Z = 10	42
	L OFC	0.043	3.93	X = −48, Y = 30, Z = −12	17
#4 Adjusted analysis of brain regions smaller for HIV+ individuals with larger DNP ratings	Left ventral PCC	0.049	4.22	X = −6, Y = −54, Z = 20	3

DNP = distal neuropathic pain; PCC = posterior cingulate cortex; PCG = precentral gyrus cortex; OFC = orbital frontal cortex.
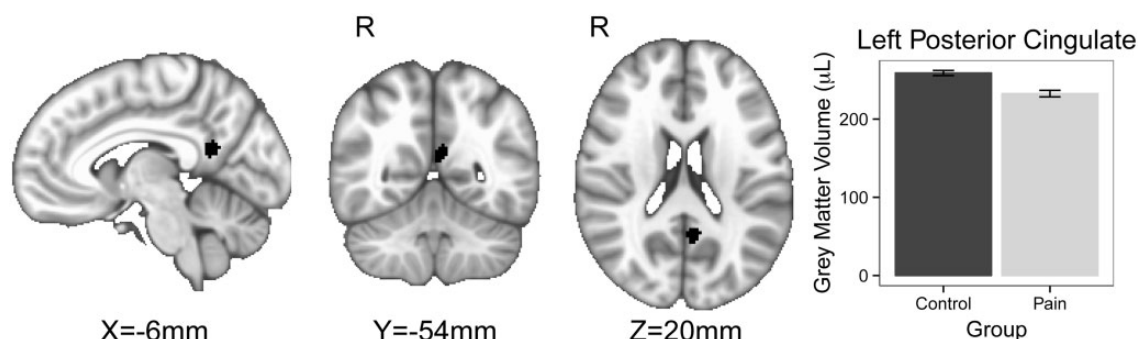
Figure 1 The shaded region in the brain figure is the part of the left ventral posterior cingulate cortex where the gray matter volume is smaller for the group of HIV+ individuals with distal neuropathic pain (DNP) compared to the HIV+ individuals without DNP using the adjusted analysis (see Table 4, statistical model #2). The bar chart shows that the average gray matter volume for the left posterior cingulate cortex cluster is smaller for the HIV DNP group compared with the HIV group without DNP. In the brain figure the shaded volume P values threshold are less than 0.05, cluster volume = 65 voxels, with an average t = 4.38, with an average P = 0.032. The peak P values is 0.017 and the peak t-value is 5.15 with MNI coordinates X = −6, Y = −54, Z = 20. The error bars in the bar chart represent the standard error of the mean.

intensity ratings. Consistent with our hypotheses, regional cortical brain volumes in the left ventral posterior cingulate cortex were smaller in HIV+ individuals with DNP compared to those without DNP. In addition regional brain volumes within the bilateral insula cortex, left orbital frontal cortex, subcortex, and precentral gyrus were smaller for HIV+ individuals with larger DNP ratings. Contrary to our hypotheses, regions within the anterior cingulate cortex, the insula cortex, and prefrontal cortex are not smaller for individual with DNP compared to individuals without DNP.

These observed smaller regional brain volumes in individuals with HIV DNP is consistent with other chronic pain conditions that are associated with smaller regional brain volumes [59–62]. The mechanisms for these smaller regional brain volumes in individuals with chronic pain are not well understood. Possible mechanisms for smaller regional brain volumes in chronic pain include changes in neuronal volume, axonal white matter volume, synaptic volume, glial volume, or vascular volume [60,63–65].

Reduced brain volumes in the posterior cingulate cortex are widely reported in chronic pain: headache [25,33,36], phantom limb pain [26], fibromyalgia [27,28,34], pain disorder [29], temporomandibular pain [30–32], and trigeminal neuralgia [35]. These observations suggest that the PCC could have a role in the development of chronic pain.

Historically it was believed that the PCC was not involved in pain processing [66–68]; however, recent investigations suggest that the PCC may play a role in anti-nociception [69,70]. PCC gray matter density has been shown to be inversely related to cutaneous thermal pain sensitivity [70]. PCC cortical thickness trends towards being inversely related to cutaneous thermal

pain thresholds [71] and is inversely related to rectal sensitivity thresholds [72]. An interpretation of these results is that increased PCC gray matter density/cortical thickness may reflect entrenched introspective thought patterns which function as competitors to processes that contribute to the construction of an experience of pain. That is rumination about non-pain related issues may function to inhibit the experience of pain [70]. This possible antinociceptive role for the PCC is consistent with the PCC participating in attentional disengagement from painful experiences during mind wandering [69,73,74]. A proposed mechanism for the PCC participating in antinociception may involve the default mode network circuit (connectivity between the PCC and medial prefrontal cortex) [37] interacting with descending analgesia brain circuits (connectivity between the periaqueductal gray matter and the rostral ventral medulla) [69,74,75]. This proposed antinociceptive role for the PCC suggests a possible mechanism for chronic pain: Some chronic pain may result from impairment of the PCC participating in antinociception which would make an individual less able to attentionally disengage from the experience of pain.

Reduced volumes in the orbital-frontal cortex and the insula cortex have also been widely reported in chronic pain [59–62]. Chronic pain reduction in orbital-frontal cortex volume may be related to chronic pain changes in reward processing [19,76], while chronic pain reduction in insula cortex volume may be related to chronic pain increased functional connectivity between the salience network [69,74,77,78] and the default mode network [22,75,79–83]. Our observed smaller regional brain volumes in the caudate, putamen, and the precentral gyrus for HIV+ individuals with larger DNP ratings are less commonly reported in other chronic pain conditions [59,60]. These smaller subcortical and precentral gyrus regional brain volumes may be related to

behavioral changes in HIV+ individuals with larger DNP ratings [61].

There are several reports of different pain processing between left and right cortical structures involving the insula [84,85], amygdala [86,87], dorsolateral prefrontal cortex [88], and anterior cingulate [89,90]. In this regard it is interesting that the PCC has reduced regional volume on the left side but not the right side. This difference may suggest different function between the left and right sides of the PCC. Although we are not aware of studies investigating or reporting different function between the left and right PCC, the left region of the PCC has been shown to have abnormal resting state functional connectivity with the insula in another chronic pain condition, ankylosing spondylitis [91].

When we control for signs of HIV neuropathy, the PCC is no longer smaller for HIV+ individuals with HIV DNP compared to individuals without HIV DNP, and the PCC volume is no longer smaller for HIV+ individuals with larger DNP ratings. Interpretation of these results is complicated by two issues. First, it is problematic to attempt to control for a sign of disease when the research variable of interest is a symptom of the same disease. Presence of HIV neuropathy is defined as presence of at least one, or a combination, of three possible symptoms (presence of pain, presence of tingling, loss of sensation) and/or three possible signs (decreased sensation of vibration, decreased sensation of sharpness, decreased ankle reflex) [1]. Second, the purpose of controlling for signs of HIV neuropathy is to attempt to separate the pain aspect of HIV DNP from the neuropathy part of HIV DNP. In fact, the definition of HIV distal neuropathic pain is a pattern of bilateral burning, aching, or shooting pain in the lower extremities that occurs in specific conditions such as HIV peripheral nerve damage. The pain quality of HIV DNP is intimately related to the underlying disease process of damaged peripheral nerves so that it can be argued that it does not make sense to attempt to divide HIV distal neuropathic pain into a separate pain component and a separate neuropathy component. Attempting to control for signs of HIV neuropathy may actually be removing variance fundamental to the group of HIV+ individuals with distal neuropathic pain [92].

The PCC no longer being smaller for HIV+ individuals with HIV DNP compared to individuals without HIV DNP after controlling for signs of HIV neuropathy suggests that PCC volume, HIV distal neuropathic pain, and signs of HIV neuropathy are inter-related. There are multiple possible causal relationships between these three variables: HIV DNP may contribute to smaller PCC volume, smaller PCC volume may contribute to HIV DNP, HIV neuropathy may contribute to smaller PCC volume, HIV neuropathy may contribute to HIV DNP, and/or systemic HIV disease may contribute to smaller PCC volume and HIV DNP and HIV neuropathy. The cross-sectional nature of this study prevents determining which of these possible causal relationships, if any, are true.

This study has several limitations. These include its cross-sectional design, which leaves us unable to explore possible cause and effect relationships between PCC volume and HIV DNP. Our cohort was a convenience sample of individuals enrolled in HIV care at academic clinics, rather than from a random sample of HIV+ individuals in care. Other limitations are that we do not have resting state functional magnetic imaging (fMRI) images, or detailed information about other pain conditions which could confound our results. We also did not include an HIV negative control group. Since we did not collect skin biopsies, we cannot confirm that the DNP individuals without signs of neuropathy have HIV small fiber peripheral neuropathy. Finally, using brain structural MRI images from different scanners may introduce systematic noise [54–57] which could have contributed to why brain volumes for cortical pain processing regions (such as the anterior cingulate cortex, insula cortex, and prefrontal cortex) were not smaller for individuals with DNP compared to individuals without DNP.

Given that HIV DNP is prevalent, treatment resistant, and adversely impacts quality of life [1], additional research is warranted to investigate the mechanisms leading to smaller regional brain volumes in HIV DNP. Future possible studies to investigate mechanistic relationships among regional gray matter volumes, HIV DNP, and signs of HIV neuropathy include cross-sectional VBM studies to examine if associations exist between regional gray matter volume changes and symptoms of HIV neuropathy other than HIV DNP or between regional gray matter volume changes and signs of HIV neuropathy. In addition, cross-sectional functional and diffusion tensor MRI imaging may provide insight into alterations of PCC brain circuit connectivity in participants with HIV neuropathy symptoms and/or signs. Finally, it has recently been shown that approximately 25% of HIV+ individuals in a HIV+ but DNP negative cohort developed new onset HIV DNP in a 2-year period [93]. This suggests that a longitudinal multimodal MRI study may be suited to investigate if changes in PCC regional volumes or changes in PCC circuit connectivity precede onset of HIV DNP. Furthermore, it may also permit examination of whether change in PCC volume over time may be related to variation in HIV DNP over time.

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