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Authors

Keltner, John R

Tong, Alan

Visser, Eelke

et al.

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Evidence for a novel subcortical mechanism for posterior cingulate cortex atrophy in HIV peripheral neuropathy

John R. Keltner[1,2,3], **Alan Tong**[1], **Eelke Visser**[4], **Mark Jenkinson**[4], **Colm G. Connolly**[5], **Alyssa Dasca**[1], **Aleks Sheringov**[1], **Zachary Calvo**[1], **Earl Umbao**[1], **Rohit Mande**[1], **Mary Beth Bilder**[1], **Gagandeep Sahota**[1], **Donald R. Franklin**[1], **Stephanie Corkran**[1], **Igor Grant**[1], **Sarah Archibald**[1], **Florin Vaida**[6], **Gregory G. Brown**[1], **J. Hampton Atkinson**[1,2], **Alan N. Simmons**[1,2], **Ronald J. Ellis**[7], **CHARTER Group**

[1]Department of Psychiatry, University of California San Diego, San Diego, CA, USA [2]VA San Diego Healthcare System, San Diego, CA, USA [3]UCSD Department of Psychiatry, UCSD HIV Neurobehavioral Research Program, 220 Dickinson Street, Suite B, Mailcode 8231, San Diego, CA 92103-8231, USA [4]Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, England [5]Department of Biomedical Sciences, Florida State University, Tallahassee, FL, USA [6]Department of Family and Preventative Medicine, University of California San Diego, San Diego, CA, USA [7]Departments of Neurosciences and Psychiatry, University of California San Diego, San Diego, CA, USA

Abstract

We previously reported that neuropathic pain was associated with smaller posterior cingulate cortical (PCC) volumes, suggesting that a smaller/dysfunctional PCC may contribute to development of pain via impaired mind wandering. A gap in our previous report was lack of evidence for a mechanism for the genesis of PCC atrophy in HIV peripheral neuropathy. Here we investigate if volumetric differences in the subcortex for those with neuropathic paresthesia may contribute to smaller PCC volumes, potentially through deafferentation of ascending white matter tracts resulting from peripheral nerve damage in HIV neuropathy. Since neuropathic pain and paresthesia are highly correlated, statistical decomposition was used to separate pain and paresthesia symptoms to determine which regions of brain atrophy are associated with both pain and paresthesia and which are associated separately with pain or paresthesia. HIV+ individuals (N = 233) with and without paresthesia in a multisite study underwent structural brain magnetic resonance imaging. Voxel-based morphometry and a segmentation/registration tool were used to investigate regional brain volume changes associated with paresthesia. Analysis of decomposed

John R. Keltner, jkeltner@ucsd.edu.

Compliance with ethical standards

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.

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Conflict of interest Mark Jenkinson receives royalties from commercial licensing of FSL—other authors have no conflicts of interest to disclose.

variables found that smaller midbrain and thalamus volumes were associated with paresthesia rather than pain. However, atrophy in the PCC was related to both pain and paresthesia. Peak thalamic atrophy ($p = 0.004$; MNI $x = -14$, $y = -24$, $z = -2$) for more severe paresthesia was in a region with reciprocal connections with the PCC. This provides initial evidence that smaller PCC volumes in HIV peripheral neuropathy are related to ascending white matter deafferentation caused by small fiber damage observed in HIV peripheral neuropathy.

Keywords

HIV; Paresthesia; Brain; Imaging; Peripheral neuropathy

Introduction

Despite modern antiretroviral therapy, HIV distal sensory–predominant polyneuropathy still affects 30–50% of individuals with HIV infection, causing distressing or disabling symptoms including pain and paresthesia (Atkinson and Keltner 2016; Benevides et al. 2017; Bilgrami and O'Keefe 2014; Chen et al. 2013; Ellis et al. 2010; Evans et al. 2011; Keltner et al. 2017a; Keltner et al. 2017b; Keltner et al. 2012; McArthur et al. 2005; Robinson-Papp et al. 2010; Wiebe et al. 2011; Zhou et al. 2007). Paresthesia is often overlooked due to a clinical focus on pain (Atkinson and Keltner 2016). In fact, paresthesia affects 30–40% of HIV patients (Ellis et al. 2010; Keltner et al. 2017b; Morgello et al. 2004; Robinson-Papp et al. 2010; Verma 2001), and both HIV and non-HIV paresthesia are frequently experienced as unpleasant, distressing, or disabling (Baliki et al. 2011; Beran 2015; Berger 2014; Grovle et al. 2010; Henderson et al. 2014; Huang and Sengupta 2014; Jones 1974; Marchettini et al. 2006; Maunsell et al. 1993; Prazeres et al. 2013; Roerink et al. 2013; Singleton 2005).

While pain has been linked to atrophy of the PCC (Keltner et al. 2017b), a mechanism for atrophy of the PCC in neuropathic pain is lacking. One hypothesis is that this PCC atrophy in HIV individuals with peripheral neuropathy is due to decreased ascending signaling caused by damage to distal peripheral nerves. This hypothesis would suggest that the subcortical brain areas that feed into the PCC should also show atrophy. Thus, identification of what aspects of HIV neuropathy relate to subcortical atrophy may be key in better understanding this hypothesis that HIV distal peripheral nerve damage contributes to ascending white matter atrophy causing PCC atrophy in HIV neuropathy.

It is known that paresthesia can be produced acutely by decreasing perfusion to normal nerves and by nerve injury (Albin and Simons 2010; Ellis et al. 2010; Lennertz et al. 2010; Mogyoros et al. 2000; Nora et al. 2005; Robinson-Papp et al. 2010). Paresthesia mechanisms have also been associated with central nervous system pathophysiology in the midbrain and thalamus in a number of diseases and case studies outside of the research into peripheral neuropathy (Brigo et al. 2012; Caplan et al. 1988; Drake and McKenzie 1953; Kim and Choi-Kwon 1999; Kim et al. 1995; Lee et al. 2001; Lim et al. 2016; Nakashima et al. 2001; Seo and Jang 2013; Vilela Filho 1996). Here we argue that a better understanding of

mechanisms for paresthesia may improve prevention and treatment for paresthesia and neuropathic pain.

Recent investigation of mechanisms for non-HIV peripheral neuropathies has shown evidence for subcortical and cortical brain pathophysiology. Non-HIV associated peripheral neuropathy has been associated with molecular, cellular, and structural changes in the spinal cord, brain stem, and thalamus (Casseb et al. 2016; Eaton et al. 2001; Feldman et al. 2017; Jaggi and Singh 2011; Navarro et al. 2007; Selvarajah et al. 2006; Selvarajah et al. 2008; Selvarajah et al. 2011; Sorensen et al. 2008; Tesfaye et al. 2016). Non-HIV peripheral neuropathies have also been associated with cortical brain pathophysiology (Cauda et al. 2009; Lee et al. 2017; Maeda et al. 2014; Maeda et al. 2016; Meldgaard et al. 1984; Nudelman et al. 2016; Selvarajah et al. 2014; Tseng et al. 2013; Wang et al. 2015). In particular, non-HIV-associated peripheral neuropathies are associated with changes in BOLD fMRI activity and brain circuit connectivity in the posterior cingulate cortex (PCC) (Boland et al. 2014; Hsieh et al. 2015; Rocca et al. 2014), but a mechanism for this PCC dysfunction has not been proposed.

Most research on HIV-associated peripheral neuropathy mechanisms has focused on the effects of HIV or antiretroviral drugs on peripheral nerves (Cherry et al. 2003; Moore et al. 2000) and on clinical risk factors for neuropathy (age, height, and lowest known CD4+ T lymphocyte count – CD4 nadir) (Ellis et al. 2010). This research suggests the intensity of HIV-associated peripheral neuropathy symptoms is not fully explained by the extent of HIV damage to peripheral nerve fibers (Cherry et al. 2003; Dorsey and Morton 2006; Herrmann et al. 2004; Skopelitis et al. 2007), nor by clinical risk factors (Ellis et al. 2008; Ellis et al. 2010), leaving it unclear why some HIV neuropathy individuals experience HIV-associated peripheral neuropathy symptoms and others do not.

Central nervous system pathophysiology associated with HIV distal sensory–predominant polyneuropathy is not well studied. Recent research suggests that brain mechanisms contribute to HIV distal sensory–predominant polyneuropathy symptoms (Keltner et al. 2017b; Keltner et al. 2014). Neuropathic pain has been associated with smaller total cerebral cortical gray matter volumes (Keltner et al. 2014) and smaller posterior cingulate cortex volumes (Keltner et al. 2017b). Since pain and paresthesia are both positive symptoms related to HIV distal sensory–predominant polyneuropathy (Morgello et al. 2004), here we hypothesized that the posterior cingulate regional cortical volumes may be smaller for more severe paresthesia. Given that brainstem, midbrain, and thalamus pathophysiology has been associated with paresthesia in other samples (Brigo et al. 2012; Caplan et al. 1988; Drake and McKenzie 1953; Kim and Choi-Kwon 1999; Kim et al. 1995; Lee et al. 2001; Lim et al. 2016; Nakashima et al. 2001; Seo and Jang 2013; Vilela Filho 1996), we also hypothesized that neuropathic paresthesia may be associated with structural changes in the brainstem or thalamus.

We have observed in the clinical setting that paresthesia predicts the subsequent development and persistence of neuropathic pain (Monica et al. 2019). This clinical observation suggests that ascending deafferentation due to small fiber neuropathy in HIV may be associated differently with symptoms of pain and paresthesia.

Since neuropathic pain and paresthesia are highly correlated (Ellis et al. 2010), we also investigated statistically decomposed pain and paresthesia HIV peripheral neuropathy variables which are orthogonal to investigate which parts of brain atrophy are associated with both pain and paresthesia as well as which parts of brain atrophy are associated separately with either pain or paresthesia. Voxel-based morphometry (FSL-VBM) was used to investigate changes in regional brain volume associated with paresthesia. A model-based segmentation/registration tool (FSL-FIRST) was used to specifically investigate subcortical regional brain volume and shape changes associated with paresthesia.

Materials and methods

Participants

A subset of CHARTER HIV+ enrollees (N = 241) met criteria for MRI and agreed to participate in a sub-study which involved undergoing brain structural MRI studies (Jernigan et al. 2011). This sample of patients and brain images have been used in 3 previous publications from our lab (Jernigan et al. 2011; Keltner et al. 2017b; Keltner et al. 2014). The current re-analysis of this brain imaging data set was conducted in order to investigate if paresthesia is associated with smaller PCC volumes and smaller subcortical volumes.

Since VBM methods require a relatively normally shaped brain, 8 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 the following: 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.

Diagnosis of neuropathic paresthesia

Neuropathic paresthesia was defined as a specific pattern of abnormal paresthesia sensations in the distal bilateral lower extremities, which is a standard definition of neuropathic paresthesia that has been validated in prior work (Ellis et al. 2010; Robinson-Papp et al. 2010). Patients were 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 neuropathic paresthesia intensity, impact on everyday function, and treatment-seeking, study clinicians further classified paresthesia into four categories of severity: no abnormal paresthesia sensations, occasional fleeting abnormal paresthesia sensations, mild to moderate frequent abnormal paresthesia sensations, frequent disabling abnormal paresthesia sensations. Because neuropathic paresthesia 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 paresthesia in spans of time: 1 to 3 days, 4 days to 4 weeks, 1 month to 1 year, 1 to 10 years, greater than 10 years. The average time between the paresthesia clinical assessment and the MRI brain imaging was 10 days. Data related to the validation of the neuropathic paresthesia grading system as well as neuropathic paresthesia clinical case report forms and an associated instruction manual are available at www.charternntc.org.

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 HIV concentration were determined. Presence of plasma hepatitis C infection, risk for vascular disease, and plasma CD4 count were also determined.

An extensive treatment history queried for prior and current anti - H I V treatment since exposure to anti - H I V dideoxynucleoside reverse transcriptase inhibitors (didanosine, stavudine, and zalcitabine) may cause neuropathy. Performance on neuropsychological testing was assessed, and a global deficit score (Carey et al. 2004) was calculated to control for the impact of HIV cognitive deficits on brain structure.

Because psychiatric and substance use disorders may be associated with neuroimaging abnormalities, psychoactive substance use disorders were assessed using the Composite International Diagnostic Interview and DSM-IV criteria. History of abuse and dependence was collected for alcohol, cannabis, cocaine, hallucinogens, inhalants, methamphetamine, opioids, and sedatives.

Structural imaging

As described previously, structural MRI volumes were acquired on 1.5 Tesla GE scanners at the five participating sites (Jernigan et al. 2011). Image acquisition parameters were sagittal acquisitions with section thickness = 1.3 mm, FOV 24 cm, matrix size 256 × 256, voxel dimensions 0.94 mm × 0.94 mm × 1.3 mm, T1-weighted SPGR with TR = 20 ms, TE = 6 ms, and flip angle = 30.

Statistical decomposition of neuropathic pain and paresthesia

Due to the high overlap (overlap = 54 of 96; see Fig. 1) and shared variance between the symptoms of pain and paresthesia (R^2 = 0.476), determining whether differences in brain structure are due to pain or paresthesia is challenging. Variable whitening (Kessy and Strimmer 2018) provides a method for equitably decomposing the covariance of variables. The fundamental steps in this procedure are (1) to determine orthogonal components in a data matrix, such as through a principle component analysis, and (2) to determine a rotation of the variables to match the original, or non-decomposed, variables. Specifically, zero-phase component analysis finds the whitening transformation that minimizes distance between the original and whitened variables (Eldar and Oppenheim 2003) independent to variable scaling. The resultant decomposed variables have no correlation with each other while maximizing the correlation with the non-decomposed data. In the current dataset, non-

decomposed and decomposed variables are highly similar for pain (R^2 = 0.903) and paresthesia (R^2 = 0.815), while non-decomposed pain did not correlate strongly with decomposed paresthesia (R^2 = 0.097), or vice versa (R^2 = 0.185).

Voxel-based morphometric methods

Structural data was analyzed with FSL-VBM, an optimized VBM protocol carried out with FSL tools. For both the non-decomposed paresthesia variable and the statistically decomposed paresthesia variable, VBM methods were used here to investigate the regional brain gray matter to identify clusters of voxels that have smaller volumes for HIV+ individuals with larger neuropathic paresthesia ratings. 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. Any images with gross abnormalities were reviewed by a neuroradiologist with appropriate clinical follow-up. Native space structural images were brain-extracted using automated FSL BET with further manual refinement conducted with AFNI—as necessary. The native space structural images were then gray matter-segmented before being registered to the MNI 152 standard space using an affine transform that was supplemented by non-linear refinement using FSL-FNIRT. 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. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 (FWHM ~ 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 using FSL-randomise. The corrected alpha was set to 0.05.

FIRST subcortical morphometric methods

For both the non-decomposed paresthesia variable and the statistically decomposed paresthesia variable, subcortical structures were segmented using FSL-FIRST that applies a Bayesian shape and appearance model to fit a mesh-based boundary model of a structure to a T1-weighted image. The method was trained on a set of 336 manually annotated T1-weighted images, covering a wide range of ages and pathologies, and can segment 8 different subcortical structures (caudate, putamen, pallidum, thalamus, nucleus accumbens, hippocampus, amygdala, brainstem; separately for left and right in each case, with the exception of the brainstem). Following the mesh fitting, a boundary-based shape analysis can be performed which is based on a signed distance of each boundary point to the average mesh (measured along the normals of the average mesh) and done after alignment to the MNI152 standard T1-weighted template. Finally, voxelwise general linear modeling was applied using permutation-based non-parametric testing that corrected for multiple

comparisons across the boundary voxels using the threshold-free cluster enhancement method. The corrected alpha was set to 0.05.

Statistical analysis

Demographic and clinical statistical differences between the neuropathic paresthesia group and the non-paresthesia group were determined using the *t* test (age, global deficit score, Framingham CVD risk, log skull vault size, CD4 nadir, CD4 current) and the Chi-square test (gender, presence of global deficit, scanner, race, dideoxynucleoside reverse transcriptase inhibitors, hepatitis C, lifetime history of inhalant abuse, lifetime history of methamphetamine abuse, history of diabetes, lifetime history of alcohol dependence). Using the Chi-square test, the relationship between symptoms of pain and loss of sensation as well as presence of signs of HIV neuropathy (vibration, sharp, reflex) for each of the four levels of paresthesia was evaluated.

A general linear model was used to investigate which regional brain volumes were correlated with neuropathic paresthesia. Neuropathic paresthesia was treated as a continuous variable: none (paresthesia = 0), occasional fleeting (paresthesia = 1), mild to moderate frequent (paresthesia = 2), and frequent disabling (paresthesia = 3). As described in the VBM and FIRST analysis methods above, all reported *p* values are corrected for multiple comparisons across space.

For each of the VBM and FIRST statistical models above, an unadjusted and adjusted analysis was performed. Specifically, in the unadjusted analyses we did not control for clinical and imaging covariates associated with changes in regional brain volumes. In the adjusted analyses we did control for clinical and imaging covariates associated with changes in regional brain volume changes.

There are two reasons for controlling for clinical and imaging covariates which are associated with changes in regional brain volumes in the adjusted analysis. First, these covariates may be confounders of the association between neuropathic paresthesia and regional brain volumes and thus need to be included to reduce bias in estimating the effect of neuropathic paresthesia. Second, these covariates are independent predictors of regional 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, we controlled for scanner as a covariate in the adjusted analysis.

Finally, we performed an additional adjusted analysis to investigate if neuropathic paresthesia is associated with changes in regional brain volume independent of contributions of neuropathic pain for the VBM and FIRST analyses. In this additional adjusted analysis, we controlled for clinical and imaging covariates associated with changes in regional brain volume and we also controlled for presence of pain or severity of neuropathic pain. For the VBM analyses, we also repeated the adjusted general linear model comparing regional brain volumes between the HIV+ individuals with and without pain from our previous manuscript (Keltner et al. 2017b) where in this new model we controlled for clinical and imaging covariates associated with changes in regional brain volume and we also controlled for severity of neuropathic paresthesia.

Results

Demographic and clinical characteristics

Typical individuals were middle-aged men of Caucasian, African-American, Hispanic, or other ethnicity who had AIDS and were currently on antiretrovirals, with good immune recovery and fair virologic control (Table 1). The average age of the paresthesia group was older than the non-paresthesia group ($p < 0.001$).

Signs of neuropathy

Of the 233 evaluable individuals, 132 (57%) met criteria for peripheral sensory neuropathy by virtue of having at least one objective sign of neuropathy (reduced sensation to vibration or sharpness, or reduced reflexes) and 64 met criteria for the symptom of HIV neuropathic pain (Gonzalez-Duarte et al. 2008). Sixty-five individuals (28%) met a more stringent definition of at least two objective signs of neuropathy. The brain imaging analyses presented in this manuscript included participants with symptoms of paresthesia who did not have signs of neuropathy. Since we did not collect skin biopsies, it is possible that some of our participants had undetected small fiber neuropathies. Recognizing that paresthesia symptoms may occur in small fiber-predominant neuropathies in which clinical exam abnormalities are sometimes absent due to the relative paucity of large fiber involvement, we included in the paresthesia group those who did not have abnormal clinical exam findings. Indeed, some cases of HIV-SN have been shown to manifest predominantly small fiber involvement. Twenty of the participants without signs of neuropathy had symptoms of paresthesia. Sixty-six of the participants with signs of neuropathy had symptoms of paresthesia.

Original and statistically decomposed symptoms of paresthesia and pain

The non-decomposed paresthesia and pain variables were significantly correlated (Pearson correlation coefficient = 0.686). Fifty-four of the patients with neuropathic pain at the initial visit also had neuropathic paresthesia, while 10 of the patients had neuropathic pain without paresthesia (Fig. 1, Table 2). Also, 32 of the patients had paresthesia without neuropathic pain (Fig. 1, Table 2).

Clinical and imaging covariates associated with changes in regional brain volumes

The clinical and imaging covariates which we determined to be associated with or not associated with changes in regional brain volume are listed in Table 3. The variables which are associated with differences in regional brain volumes are controlled for in the adjusted analyses. These covariates were previously associated with changes in brain structure (Jernigan et al. 2011; Keltner et al. 2014).

VBM results for non-decomposed and statistically decomposed paresthesia symptoms

Adjusted VBM analysis showed that more severe non-decomposed neuropathic paresthesia was associated with smaller bilateral midbrain, bilateral smaller thalamus, smaller left putamen, and smaller left posterior cingulate cortex (Fig. 2). The right midbrain cluster in Fig. 2 appears to extend into the temporal lobe in the hippocampus/amygdala region. This

finding motivated our use of FIRST to investigate volume changes in the temporal lobe in the region of the hippocampus and amygdala. Adjusted VBM peak p values and associated t-values and voxel cluster sizes for Fig. 2 are listed in Table 4. In Table 4, we have also included the cluster characteristics for the adjusted VBM cluster for the left PCC that was smaller for presence of pain from Fig. 1 of our 2017 previously published manuscript (Keltner et al. 2017b).

The peak thalamic volume change ($p = 0.004$; $t = 4.17$; MNI coordinates $x = -14$, $y = -24$, $z = -2$) for more severe paresthesia was in a region that projects to posterior cortical regions, in particular the PCC (Cunningham et al. 2017). This region of peak thalamic atrophy is the same for both non-decomposed and decomposed paresthesia.

When controlling for presence or severity of neuropathic pain as well as clinical and imaging covariates associated with changes in regional brain volume (see Table 3), the PCC, midbrain, and thalamus were not significantly smaller for HIV+ individuals with more severe paresthesia. Similarly, when controlling for severity of paresthesia as well as for clinical and imaging covariates associated with changes in regional brain volume, the PCC volume was not significantly smaller for HIV+ individuals with neuropathic pain compared with those without. Thus, the multicollinearity of pain and paresthesia obscured these relationships.

After statistical decomposition, the PCC was no longer smaller for either more severe decomposed paresthesia or for the presence of more severe decomposed pain. Similar to the adjusted non-decomposed paresthesia variable, the bilateral midbrain and left thalamus were still smaller for the adjusted decomposed paresthesia variable (see Fig. 2) with the same location for peak regional atrophy in the left thalamus (see Table 4).

FIRST results

Unadjusted FIRST analysis showed that the bilateral thalamus surface was displaced inward (consistent with a smaller thalamic volume) for larger non-decomposed paresthesia values compared with smaller non-decomposed paresthesia values (Fig. 3). Similar results were obtained when adjusted models were run (Fig. 3). Adjusted FIRST analysis also showed a trend ($p < 0.07$) that the left thalamus surface was displaced inward for worse paresthesia values compared with better paresthesia values. Although the VBM right midbrain cluster in Fig. 2 appears to extend into the temporal lobe in the region of the hippocampus and the amygdala, unadjusted and adjusted FIRST analysis for both non-decomposed and decomposed paresthesia variables showed no displacement in the surface of the bilateral hippocampus, bilateral amygdala, or brain stem. FIRST was unable to investigate volume changes in the midbrain.

When controlling for presence or severity of neuropathic pain as well as clinical and imaging covariates associated with changes in regional brain volume (see Table 3), the thalamus was no longer displaced inward for individuals with more severe non-decomposed paresthesia.

Unadjusted FIRST analysis showed that the bilateral thalamus surface was displaced inward for worse decomposed paresthesia values compared with better values. The adjusted FIRST analysis for the decomposed paresthesia did not show that the thalamus surface was displaced inward for both left and right thalamus.

Discussion

In the current study, a re-analysis of a large cohort of individuals with HIV peripheral neuropathy was undertaken to disentangle the effects of pain and paresthesia on changes in brain structure for patients with HIV peripheral neuropathy. Through statistical decomposition of these two symptoms, we found that while the posterior cingulate atrophy was contingent upon both of these symptoms, subcortical atrophy in the midbrain and medial posterior thalamus was statistically attributable to paresthesia. This finding highlights a potential mechanism for ascending atrophy in those with HIV peripheral neuropathy, such that subcortical atrophy from paresthesia may lay the foundation for cortical atrophy in the posterior cingulate that has been found in HIV patients with pain due to peripheral neuropathy. This is the first report in any peripheral neuropathy, including diabetic or alcoholic etiologies, providing evidence for a subcortical mechanism for the development of a smaller PCC.

To investigate brain atrophy differences between neuropathic pain and paresthesia, instead of controlling for one of the variables and losing significant signal since the variance is not distributed equitably, we chose instead to statistically decompose pain and paresthesia into new orthogonal variables (Kessy and Strimmer 2018). We found that statistically decomposed paresthesia was significantly related to bilateral midbrain and left thalamus atrophy. No regions were found to be significantly related to the decomposed pain symptoms. This suggests that atrophy in the mid-brain and thalamus may be related to paresthesia and not pain. Notably, when not decomposed (i.e., raw scores) pain and paresthesia symptoms each separately and significantly correlated with PCC atrophy. However, if while investigating either pain or paresthesia one controls for the other covariate, then neither pain nor paresthesia is associated with PCC atrophy. Furthermore, once decomposed neither symptom shows a significant correlation to PCC atrophy. These results indicate that PCC atrophy depends upon the presence of both pain and paresthesia, and also suggest that the symptoms of pain and paresthesia share a common brain mechanism related to smaller PCC volumes. It is important to note that clinically paresthesia often precedes pain (Monica et al. 2019); thus, if paresthesia independently impacts the mid-brain and thalamus, this could shed light on how paresthesia contributes to the development of pain and cortical atrophy.

The central hypothesis of this manuscript is that peripheral nerve damage may cause atrophy of ascending white matter structures and ascending neuronal signaling which contributes to smaller midbrain volumes and smaller thalamus volumes, which in turn contribute to early paresthesia symptoms and then smaller PCC volumes, and finally to symptoms of paresthesia and pain. The specific mechanisms for these smaller regional volumes in the midbrain, thalamus, and posterior cingulate volumes in HIV+ individuals with paresthesia are not well understood. Possible mechanisms for these smaller regional brain volumes

include changes in neuronal volume, axonal white matter volume, synaptic volume, glial volume, or vascular volume (Baliki et al. 2011; Kucyi et al. 2013; Thomas et al. 2012; Zatorre et al. 2012). Given the known pathophysiology of damaged peripheral nerves in HIV distal sensory–predominant polyneuropathy (Ellis et al. 2010; Morgello et al. 2004; Robinson-Papp et al. 2010; Simpson et al. 2006; Verma 2001), it is likely that these changes in regional brain volumes are due to downstream afferent white matter tract atrophy resulting from HIV peripheral nerve damage. Possible downstream afferent white matter tract atrophy would be consistent with subcortical pathophysiology observed in non-HIV peripheral neuropathies (Casseb et al. 2016; Eaton et al. 2001; Feldman et al. 2017; Jaggi and Singh 2011; Navarro et al. 2007; Selvarajah et al. 2006; Selvarajah et al. 2008; Selvarajah et al. 2011; Sorensen et al. 2008; Tesfaye et al. 2016). Molecular, cellular, and structural plastic changes have been observed in the spinal cord, brainstem, and thalamus in peripheral nerve injuries including traumatic and diabetic peripheral neuropathy (Feldman et al. 2017; Jaggi and Singh 2011; Navarro et al. 2007; Tesfaye et al. 2016). Similarly, smaller spinal cord cross-sectional area has been observed in those with diabetic peripheral neuropathy (Eaton et al. 2001; Selvarajah et al. 2006). In fact, in diabetic peripheral neuropathy, diffusion tensor imaging techniques found posterior column damage in the cervical spinal cord (Casseb et al. 2016). Also, diabetic peripheral neuropathy has been associated with changes in the thalamus. A decreased thalamic NAA/creatinine ratio is suggestive of thalamic neuronal dysfunction (Selvarajah et al. 2008; Sorensen et al. 2008), and thalamic microvascular perfusion changes have also been observed (Selvarajah et al. 2011). The region of the left thalamus showing peak atrophy in the current paper has projections to posterior cortical regions and, critically, reciprocal connections with the posterior cingulate cortex and precuneus cortex (Cunningham et al. 2017). Thus, any hypothesized ascending white matter deafferentation due to HIV peripheral nerve damage that impacts the PCC could be anticipated to pass through the posterior ventral thalamus.

Alternatively, these reduced regional brain volumes may result directly from the HIV virus itself. An argument against the idea that HIV may be the cause for the changes in regional brain volume reported here was that current and nadir CD4 were not associated with any changes in regional brain volume (see Table 3). Another possibility is that another unknown factor such as a systemic disease other than HIV (that causes direct effects on the brain, such as encephalitis) may contribute to the changes in regional brain volumes reported here. The cross-sectional nature of this study precludes determining which of these possible causal relationships, if any, are true.

The correlation between worse paresthesias and smaller posterior cingulate cortical volumes is consistent with changes in cerebral pathophysiology observed in other peripheral neuropathies (Cauda et al. 2009; Lee et al. 2017; Maeda et al. 2014; Maeda et al. 2016; Meldgaard et al. 1984; Nudelman et al. 2016; Selvarajah et al. 2014; Tseng et al. 2013; Wang et al. 2015). Specifically, other small fiber peripheral neuropathies are associated with changes in function in the posterior cingulate cortex (Boland et al. 2014; Hsieh et al. 2015; Rocca et al. 2014). Acquired and hereditary peripheral neuropathies are associated with increased functional connectivity of the left precuneus/posterior cingulate cortex in the default mode network (Rocca et al. 2014). The default mode network is most commonly shown to be active when a person is daydreaming or mind wandering (Cavanna and Trimble

2006; Hagmann et al. 2008; Vogt et al. 2006). This increased connectivity in the default mode network is correlated with duration of peripheral neuropathy and severity of clinical total neuropathy score (Rocca et al. 2014). In other small fiber neuropathies, decreased functional connectivity between the left posterior cingulate cortex and the left anterior cingulate cortex has been observed (Hsieh et al. 2015). Chemotherapy-induced peripheral neuropathy has been associated with increased precuneus brain activity response to painful peripheral heat stimulation (Boland et al. 2014).

An unresolved question is why does putative ascending deafferentation in the thalamus selectively target the PCC instead of also targeting the leg region of the somatic cortex? Historically it was believed that the PCC is not involved in processing of physical sensations; however, recent research suggests that the PCC may play a role in anti-nociception (Emerson et al. 2014; Kucyi et al. 2013). We previously argued that PCC function may be related to introspective thought patterns which compete with thoughts that contribute to the construction of an experience such as pain (Keltner et al. 2017b). That is, daydreaming thoughts or mind wandering thoughts may function to inhibit the experience of painful physical symptoms. This possible anti-nociceptive role for the PCC is consistent with the PCC participating in attentional disengagement from pain experiences during mind wandering (Kucyi et al. 2013). This argument relating PCC dysfunction to pain can be extended to relate PCC dysfunction to distressing paresthesia. Distressing paresthesia may in part result from impairment of the PCC participating in mind wandering which would make an individual less able to disengage from the experience of distressing paresthesia.

This study has several limitations. These include its cross-sectional design, which leaves us unable to explore possible cause and effect relationships between changes in regional brain volumes and paresthesia. Our cohort was a convenience sample of individuals enrolled in HIV care at academic clinics, rather than a random sample of HIV+ individuals in care. We also did not include an HIV negative control group which limits our ability to make conclusions relative to non-HIV populations. Since we did not collect skin biopsies, we cannot ascertain whether those with paresthesia but without signs of neuropathy may have had HIV small fiber peripheral neuropathy. Future studies should include skin biopsies to determine whether people with paresthesia without signs of neuropathy do not have HIV-related to small fiber neuropathy. Another limitation of this analysis is that we re-analyzed a previously used patient cohort and associated structural brain images. There is a critical need for replication of the pain structural brain changes previously published (Keltner et al. 2017b) as well as the paresthesia structural brain changes presented in this current manuscript. Finally, despite that we controlled for scanner as a covariate in the adjusted analysis to control for bias resulting from inter-scanner variability, using brain structural MRI images from different scanners at different academic research locations may introduce systematic bias.

Given that paresthesia is prevalent, additional research is warranted to investigate the mechanisms leading to smaller regional brain volumes in paresthesia. Future cross-sectional studies including functional and diffusion tensor MRI imaging may provide insight into alterations of functional and white matter brain circuit connectivity related to the posterior cingulate cortex, thalamus, and midbrain in participants with paresthesia. In particular,

similar to diabetic peripheral neuropathy spinal cord imaging studies (Casseb et al. 2016; Eaton et al. 2001; Selvarajah et al. 2006), future spinal cord imaging and spinal cord diffusion tensor studies may find smaller spinal cord cross-sectional area and spinal cord posterior column damage in HIV patients with paresthesia. Longitudinal multi-modal MRI studies may be suited to investigate if changes in regional brain volumes precede onset of paresthesia or vice versa. Such longitudinal studies may also permit examination of whether change in regional brain volumes over time may be related to variation in paresthesia over time. Future longitudinal studies may yield insight into mechanistic relationships between paresthesia and pain. Specifically, longitudinal multi-modal neuroimaging studies may be able to establish if HIV peripheral nerve damage contributes to ascending subcortical white matter atrophy and further investigate paresthesia preceding pain. If true, then individuals with paresthesias may be targeted with interventions designed to reduce the likelihood of progression to chronic neuropathic pain.

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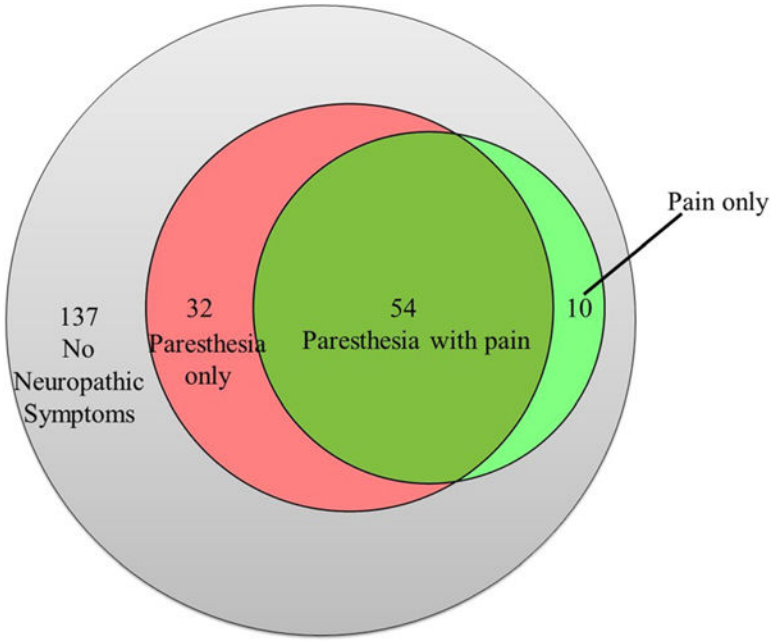

Fig. 1.

Venn diagram of non-decomposed paresthesia symptoms versus non-decomposed pain symptoms: 54 of the 64 patients with neuropathic pain also had paresthesia

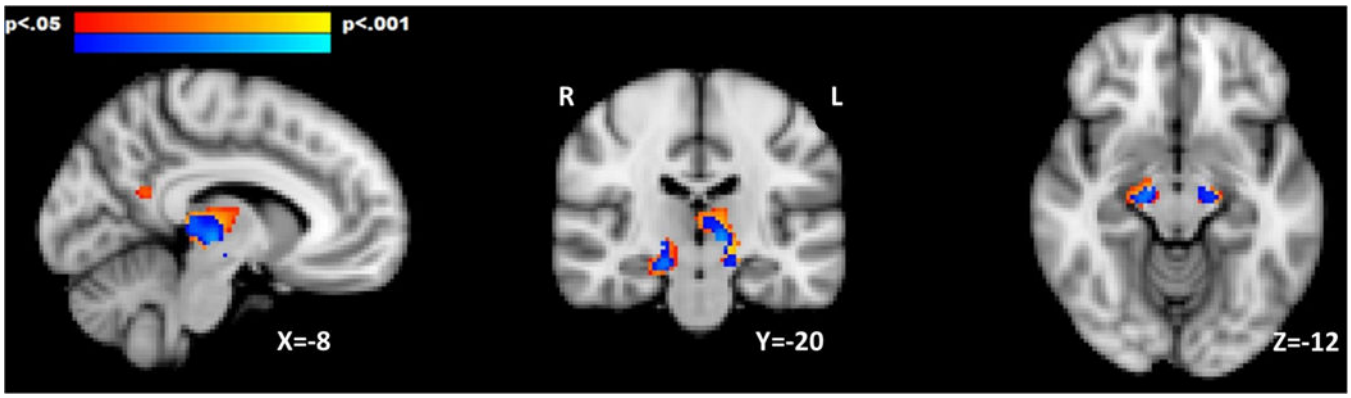

Fig. 2.

VBM results for non-decomposed and statistically decomposed paresthesia: colored regions are regional brain volumes that were negatively correlated with neuropathic paresthesia symptom severity ratings (*p* values thresholded at 0.05). Yellow-red regions are non-decomposed adjusted paresthesia results. Blue regions are statistically decomposed adjusted paresthesia results. Blue-colored regions for statistically decomposed adjusted paresthesia are overlaid over yellow-red-colored regions for non-decomposed adjusted paresthesia. Similar to non-decomposed adjusted neuropathic pain (Keltner et al. 2017b), more severe non-decomposed adjusted paresthesia was associated with smaller left PCC regional brain volumes. However, more severe decomposed adjusted paresthesia was not associated with smaller left PCC regional brain volumes. Distinct from non-decomposed adjusted pain, smaller bilateral regional midbrain volumes and left smaller regional thalamus volumes are associated with more severe non-decomposed adjusted paresthesia as well as more severe statistically decomposed adjusted paresthesia

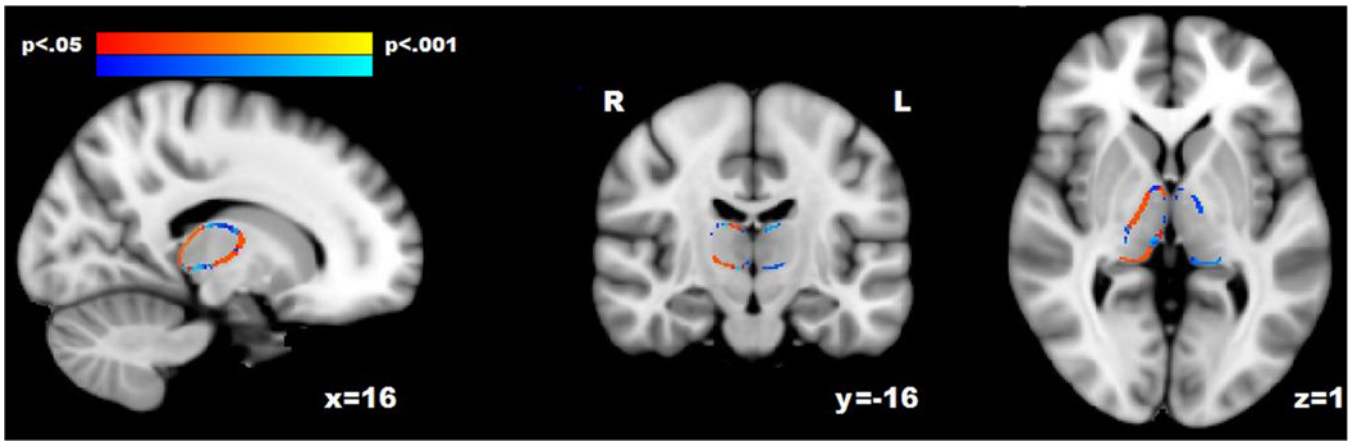

Fig. 3.

FIRST results for non-decomposed paresthesia: colored regions are thalamic surface regions displaced inward toward the center of the thalamus (consistent with smaller thalamic volume). The orange-red adjusted FIRST results (right thalamus) are overlaid over bilateral blue unadjusted FIRST results. These FIRST results indicate that the thalamus surface was displaced inward for those with more severe paresthesia compared those with less severe paresthesia (*p* values thresholded at 0.05)

Table 1

Demographic and clinical characteristics of the participants for the non-decomposed symptom of paresthesia. Column 5 lists the *p* value showing if the characteristic proportions or mean values are significantly different for individuals with paresthesia compared with individuals without paresthesia

	All individuals	Yes Non-decomposed paresthesia	No Non-decomposed paresthesia	*p* value Yes vs No
No. of individuals	233	86	147	
Male	187	67	120	0.491
Female	46	19	27	
Age				
Mean	43.7	46.47	42.08	< 0.0001 *
SD	7.81	7.20	7.67	
Race/ethnicity, No. (%)				
Caucasian	92	39	53	0.328
African American	110	39	71	
Hispanic	26	6	20	
Other	5	2	3	
CD4 nadir				
Mean	196.9	172.3	205.0	0.430
SD	202.5	183.2	218.5	
CD4 current				
Mean	475.0	515.2	451.6	0.100
SD	284.8	172.3	274.6	
LT Hx of D-drug				
Yes	136	50	76	0.511
No	107	36	71	
Global deficit score				
Mean	0.42	0.45	0.41	0.498
SD	0.44	0.39	0.47	
Global deficit score				
Yes deficit	70	31	39	0.126
No deficit	163	55	108	
Framingham CVD risk				

	All individuals	Yes Non-decomposed paresthesia	No Non-decomposed paresthesia	*p* value Yes vs No
Mean	8.56	10.9	7.2	0.663
SD	8.92	11.0	7.1	
Hepatitis C virus				
Yes	69	29	40	0.294
No	164	57	107	
LT Hx of inhalant abuse				
Yes	5	3	2	0.280
No	228	83	145	
LT Hx of methamphetamine abuse				
Yes	8	2	6	0.478
No	225	84	141	
LT HX alcohol dependence				
No	153	55	98	0.674
Yes	80	31	49	
Diabetes				
No	211	78	133	0.956
Yes	22	8	14	
Log_Skull_Vault				
Mean	14.0	14.0	14.0	0.731
SD	0.12	0.11	0.13	
Scanner				
University of Washington	30	11	19	0.663
University of Texas	45	21	24	
Johns Hopkins University	45	16	29	
Mount Sinai University scanner 1	36	15	21	
Mount Sinai University scanner 2	8	3	5	
UCSD scanner 1	20	6	14	
UCSD scanner 2	29	14	35	

*HIV distal sensory–predominant polyneuropathy patients with paresthesia and without paresthesia are statistically different. *D-drug,* dideoxynucleoside reverse transcriptase inhibitors; *LT Hx*, lifetime history; *CVD*, cardiovascular disease. CD4 refers to CD4 immune cells

Table 2

Relationship between non-decomposed paresthesia symptom and other symptoms and signs

	All individuals	No Non-decomposed paresthesia	Mild Non-decomposed paresthesia	Moderate Non-decomposed paresthesia	Severe Non-decomposed paresthesia	*p* value
No. of individuals	233	147	47	28	11	
Neuropathic pain severity						
None	169	137	24	8	0	< 0.001 *
Slight	18	5	12	1	0	
Mild	22	5	2	13	2	
Moderate	9	0	2	3	4	
Severe	15	0	7	3	5	
Loss of sensation severity						
None	166	139	18	6	3	< 0.001 *
Slight	22	5	13	2	2	
Mild	22	1	11	9	1	
Moderate	18	2	4	9	3	
Severe	5	0	1	2	2	
Vibration deficit						
Yes	60	25	14	14	7	< 0.001 *
No	173	122	33	14	4	
Sharp deficit						
Yes	60	22	19	14	5	< 0.001 *
No	173	125	28	14	6	
Reflex deficit						
Yes	99	53	22	16	8	0.024 *
No	134	94	25	12	3	

* Paresthesia has a significant statistical relationship to the variable

Table 3

List of clinical and imaging covariates that are and are not associated with changes in regional brain volumes. The definition for each covariate includes its type and range

Variable	Type	Range	Associated with changes in regional brain volumes and included in adjusted analysis
Age	Continuous	23–67 years old	Yes
Ethnicity	Nominal	Caucasian	Yes
		African American	
		Hispanic	
		Other	
Gender	Binary	Male and Female	Yes
Log-cerebral vault	Continuous	13.5–14.3	Yes
Scanner (No. of scanners at site)	Nominal	Univ Wash (1 scanner)	Yes
		Univ Texas (1 scanner)	
		Hopkins (1 scanner)	
		New York (2 scanners)	
		UCSD (2 scanners)	
History of hepatitis C	Binary	Yes or No	Yes
Methamphetamine abuse	Binary	Yes or No	Yes
Global deficit score	Continuous	0–3.47	Yes
History of diabetes	Binary	Yes or No	Yes
History of alcohol addiction	Binary	Yes or No	Yes
Risk for vascular disease **	Binary	Yes or No	Yes
HIV CD4 nadir	Continuous	0–1500	No
HIV CD4 current	Continuous	7–1803	No
History of D-Drug	Binary	Yes or No	No
History of inhalant abuse	Binary	Yes or No	No

** Framingham cardiovascular risk for vascular disease measured using age, systolic blood pressure, gender, history of smoking, total cholesterol, high-density lipoprotein cholesterol. *D-drug,* dideoxynucleoside reverse transcriptase inhibitors

Table 4

Adjusted VBM cluster characteristics: cluster characteristics for brain regions that are smaller for more severe HIV peripheral neuropathic paresthesia as shown in Fig. 2. The first line is for adjusted VBM cluster characteristics for the left PCC from our previous publication investigating smaller brain regions associated with presence of HIV neuropathic pain (Keltner et al. 2017b)

	Peak *p* value	*t*-value	MNI coord	No. of voxels
Left PCC (pain) Figure 1 from 2017 manuscript (Keltner et al. 2017b)	0.017	5.15	(− 6, − 54, 20)	65
Left PCC (non-decomposed) Fig. 2	0.033	4.15	(− 8, − 54, 20)	39
Right thalamus (non-decomposed) Fig. 2	0.014	3.38	(6, − 10, 4)	282
Left thalamus (non-decomposed) Fig. 2	0.004	4.368	(− 10, − 24, − 2)	567
Right midbrain (non-decomposed) Fig. 2	0.013	4.48	(18, − 18, − 14)	172
Left midbrain (non-decomposed) Fig. 2	0.009	3.93	(− 16, − 18, − 10)	61
Left putamen (non-decomposed) Fig. 2	0.032	3.887	(− 28, − 16, − 4)	63
Left thalamus (decomposed) Fig. 2	0.020	4.214	(− 10, − 24, − 2)	202
Right midbrain (decomposed) Fig. 2	0.027	4.241	(16, − 18, − 12)	67
Left midbrain (decomposed) Fig. 2	0.039	3.747	(− 16, − 18, − 12)	41

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