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Sensitivity of ventrolateral posterior thalamic nucleus to back pain in alcoholism and CD4 nadir in HIV

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Abstract

Volumes of thalamic nuclei are differentially affected by disease-related processes including alcoholism and human immunodeficiency virus (HIV) infection. This MRI study included 41 individuals diagnosed with alcohol use disorders (AUD, 12 women), 17 individuals infected with HIV (eight women), and 49 healthy controls (24 women) aged 39 to 75 years. A specialized, high-resolution acquisition protocol enabled parcellation of five thalamic nuclei: anterior [*anterior ventral (AV)*], posterior [*pulvinar (Pul)*], medial [*mediodorsal (MD)*], and ventral [*including ventral lateral posterior (VLp)* and *ventral posterior lateral (VPL)*]. An omnibus mixed-model approach solving for volume considered the “fixed effects” of nuclei, diagnosis, and their interaction while covarying for hemisphere, sex, age, and supratentorial volume (svol). The volume by diagnosis interaction term was significant; the effects of hemisphere and sex were negligible. Follow-up mixed-model tests thus evaluated the combined (left + right) volume of each nucleus separately for effects of diagnosis while controlling for age and svol. Only the VLp showed diagnoses effects and was smaller in the AUD ($p = .04$) and HIV ($p = .0003$) groups relative to the control group. In the AUD group, chronic back pain ($p = .008$) and impaired deep tendon ankle reflex ($p = .0005$) were associated with smaller VLp volume. In the HIV group, lower CD4 nadir ($p = .008$) was associated with smaller VLp volume. These results suggest that the VLp is differentially sensitive to disease processes associated with AUD and HIV.

KEYWORDS

alcoholism, in vivo, pain, sensorimotor, thalamic nuclei

1 | INTRODUCTION

Alcohol use disorder (AUD) affects ~20 million individuals in the United States. Frequent concomitants of alcoholism are liver disease (steatosis, hepatitis, cirrhosis) (Lieber, 2004), cardiovascular disease (Hillbom, Juvola, & Karttunen, 1998), and malnutrition (Feuerlein, 1977). One of the best studied alcohol-related nutritional deficiency is

Korsakoff's syndrome (KS, Victor, Adams, & Collins, 1989), commonly heralded by Wernicke's encephalopathy (WE), caused by a deficiency in the B vitamin, thiamine (Butters, 1981), and characterized by severe and relatively circumscribed deficits in recall of new information (Cermak, 1987; Squire, Knowlton, & Musen, 1993). KS dementia has traditionally been attributed to lesions of the thalamus and mammillary bodies (Squire, Amaral, & Press, 1990). In seeking a specific neural

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substrate for the amnesia associated with KS, histological examination has highlighted anterior ventral (AV) (Harding, Halliday, Caine, & Kril, 2000) and mediodorsal (MD) (Malamud & Skillicorn, 1956; Victor, Adams, & Collins, 1971) thalamic nuclei (Aggleton, Dumont, & Warburton, 2011; Gold & Squire, 2006; Markowitsch, Irlle, & Streicher, 1982). A primary role for the anterior thalamus is supported by reports that structural lesions (i.e., infarcts) to bilateral mammillothalamic tracts can result in KS-like dementia (Josseume et al., 2007; Yoneoka et al., 2004).

Individuals with AUD, even without WE or KS typically exhibit cognitive and motor deficits and degradation of specific cortical and subcortical brain regions (Adalsteinsson et al., 2005, May 8-14; Harper, 1998; Parsons & Nixon, 1998). The thalamus is sensitive to uncomplicated (i.e., absent diagnosable neurological complications) alcoholism as manifested by overall volume reduction determined histologically (Kril, Halliday, Svoboda, & Cartwright, 1997). A number of MR imaging studies have confirmed thalamic volume shrinkage in alcoholism (Sullivan et al., 1999; van Holst, de Ruiter, van den Brink, Veltman, & Goudriaan, 2012). An early computerized tomography study in alcoholics suggested that performance on a verbal learning task was associated with reduced density in the region of thalamic MD (Gebhardt, Naeser, & Butters, 1984). By contrast, post-mortem histology of the alcoholic brain showed abnormally small neuronal size and reduced neuronal number in anterior thalamic nucleus (Belzunegui, Insausti, Ibanez, & Gonzalo, 1995; Harding et al., 2000).

Another disorder that can result in cognitive compromise and dementia is HIV. HIV-associated neurocognitive disorder (HAND) ranges from asymptomatic to HIV-associated dementia (HAD) (Day et al., 1992; Maj et al., 1994; Nakazato et al., 2014; Robertson et al., 2011). The prevalence of HAD on the severe end of the spectrum has declined with antiretroviral therapy (ART) (Baker et al., 2015; Gates & Cysique, 2016), but mild to moderate cognitive deficits in HIV remain an issue (Manji, Jager, & Winston, 2013; Underwood et al., 2017; Vivithanaporn et al., 2010). Accelerated loss of brain tissue, specifically, in frontal and sensorimotor neocortices, thalamus, and hippocampus—related to disease duration and CD4 nadir (Cohen et al., 2010; Pfefferbaum et al., 2014)—may represent a risk factor for premature cognitive compromise if not dementia (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Pfefferbaum et al., 2014; Pfefferbaum et al., 2018; Sanford et al., 2018). In seeking a neural substrate for HAD, an early imaging study in HIV-infected individuals found no relation between neuropsychological test performance and hippocampal volume (Kiebertz et al., 1996); a later stereological study found no statistically significant differences in hippocampal neuronal number between nine HIV/AIDS patients and 10 controls (Korbo & West, 2000). By contrast, in HIV and alcoholism comorbidity, poor performance on tests of explicit (immediate and delayed) and implicit (visuomotor procedural) memory are associated with smaller thalamic volumes (Fama et al., 2014). Indeed, the thalamus has often been highlighted as a specific target of HIV [volume deficits: (Heaps et al., 2012; Janssen et al., 2015; Pfefferbaum et al., 2012; Pfefferbaum et al., 2014; Pfefferbaum et al., 2018); reduced

glucose metabolism: (Hammoud et al., 2018)], possibly related to CD4 count (Heaps et al., 2015).

A lack of consensus regarding memory substrates in AUD and HIV may be due to limitations related to measuring gross volumes of brain structures. This is exacerbated by lack of reliable and quantitative MRI-based thalamic segmentation schemes. Thalamic nuclei have unique cellular and molecular compositions and distinct connectivity profiles (Poppenk & Moscovitch, 2011) that mirror functional diversity (e.g., Groenewegen & Berendse, 1994; Haber, 2003; Shu, Wu, Bao, & Leonard, 2003) and may account for differential sensitivity to pathological conditions (Byne, Tatusov, Yiannoulos, Vong, & Marcus, 2008; Small, Schobel, Buxton, Witter, & Barnes, 2011). Recently, a method for segmentation of the thalamic nuclei from structural MRI has been proposed that was validated against manual segmentation guided by the Morel atlas (Su et al., 2019). Based on the extant literature, we hypothesized that thalamic nuclei AV and MD would be smaller in AUD and HIV relative to control individuals and relate to performance on tasks of explicit memory (e.g., Pergola et al., 2012; Van der Werf et al., 2003).

2 | METHODS

2.1 | Participants

The Institutional Review Boards of Stanford University and SRI International approved this study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki by the signing of consent documents in the presence of staff. Subjects were 41 HIV-negative individuals diagnosed with AUD (12 women), 17 individuals infected with HIV (eight women), and 49 controls (24 women) ages 39 to 75 years (control 55.3 ± 10.1 , AUD 53.9 ± 7.5 , HIV 59.6 ± 7.0). AUD and HIV participants were referred from local outpatient or treatment centers or recruited during presentations in clinics by project staff and by distribution of flyers at community events. Healthy, control participants were recruited from the local community by referrals and flyers. Table 1 presents demographic characteristics of the three groups.

All participants were screened with the Structured Clinical Interview for DSM-IV (First, 2000), structured health questionnaires, a semi-structured timeline follow-back interview to quantify lifetime alcohol consumption (Skinner, 1982; Skinner & Allen, 1982), and were given the Clinical Institute Withdrawal Assessment for Alcohol (CIWA). Upon initial assessment, subjects were excluded if they had a significant history of medical (e.g., epilepsy, stroke, multiple sclerosis, uncontrolled diabetes, or loss of consciousness >30 min), psychiatric (i.e., schizophrenia or bipolar I disorder), or neurological disorders (e.g., neurodegenerative disease).

Blood samples (~40 cc) were collected and analyzed by Quest Diagnostics for complete blood count with differential, comprehensive metabolic panel, HIV and HCV screening.

The neuropsychological battery administered included Trail Making Test (A and B) (Reitan, 1958), the Wechsler Adult Intelligence Scale

TABLE 1 Characteristics of the study groups: mean \pm SD/frequency count

	Control (n = 49)	AUD (n = 41)	HIV (n = 17)	p-value ^a
N (men/women)	25/24	29/12	9/8	n.s.
Age (years)	55.3 \pm 10.1	53.9 \pm 7.5	59.6 \pm 7.0	n.s.
Handedness (right/left)	46/3	35/6	15/2	n.s.
Ethnicity ^b	29/10/10	23/17/1	9/7/1	.02
Body mass index	25.4 \pm 4.4	28.6 \pm 5.4	24.6 \pm 4.9	.007
Education (years)	16.0 \pm 2.6	13.4 \pm 2.6	14.2 \pm 2.5	<.0001
Socioeconomic status ^d	27.2 \pm 14.0	41.3 \pm 15.9	37.3 \pm 15.8	<.0001
WTAR IQ (predicted full scale)	104.7 \pm 12.1	97.1 \pm 11.2	100.4 \pm 15.0	.03
Beck depression index (BDI)	4.4 \pm 5.7	12.6 \pm 10.1	7.9 \pm 8.8	<.0001
Smoker (never/past/current)	44/1/4	10/10/20	7/5/5	<.0001
Nicotine (daily)	1.5 \pm 4.8	3.9 \pm 4.2	2.3 \pm 3.8	n.s.
Global assessment of functioning (GAF)	85.0 \pm 6.1	66.6 \pm 9.1	73.8 \pm 11.5	<.0001
VACS index	18.3 \pm 13.0	19.2 \pm 12.4	37.3 \pm 19.4	<.0001
Hepatitis C virus (HCV, positive/negative)	2/47	7/34	4/13	.05
Lifetime alcohol consumption (kg)	51.2 \pm 76.7	1,432.1 \pm 1,343.2	97.8 \pm 91.0	<.0001
AUD onset age	—	24.9 \pm 9.2	—	n.a.
Months since last drink	—	3.9 \pm 9.8	—	n.a.
CIWA ^c score	—	28.7 \pm 14.4	—	n.a.
HIV onset age (years)	—	—	35.8 \pm 9.4	n.a.
HIV duration (years)	—	—	22.9 \pm 9.2	n.a.
Viral load (log copies/ml)	—	—	1.6 \pm 0.9	n.a.
CD4 cell count (100/mm ³)	—	—	761.4 \pm 321.4	n.a.
CD4 cell count nadir (100/mm ³)	—	—	219.1 \pm 93.8	n.a.
AIDS-defining event (yes/no)	—	—	2/15	n.a.

Note: Values in bold are statistically significant.

^at tests used on continuous variables (e.g., age); χ^2 used on nominal variables (e.g., handedness).

^bSelf-defined: Caucasian/African American/Other (Asian, Native American, Islander).

^cLower score = higher status.

^dClinical Institute Withdrawal Assessment for Alcohol Scale.

(WAIS), Digit Symbol test (Sassoon et al., 2007), and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Performance on tests of explicit memory included the Wechsler Memory Scale-Revised (WMS-R) Digit and Block Forward and Backward spans (Wechsler, 1987), and the California Verbal Learning Test-II (CVLT-II) (Delis, Freeland, Kramer, & Kaplan, 1988). Performance on phonological fluency (letters F, A, and S) (Spreen & Benton, 1977), semantic fluency (inanimate objects, animals, birds/colors) (Martin, Loring, Meador, & Lee, 1990), figural fluency (i.e., RUFF) (Ruff, 1988), and the Rey-Osterrieth complex figure test (Osterrieth & Rey, 1944) were also examined.

Motor functions evaluated included balance using an ataxia battery (stand heel to toe, walk 10 steps on line, balance on one leg in eyes open and eyes closed conditions) (Fregly, 1968) and upper limb motor function using Grooved Pegboard (Trites, 1977) and Fine Finger Movement (Fama et al., 2007). Objective signs of neuropathy (Cornblath et al., 1999; Kaku & Simpson, 2014) comprised perception of vibration [right or left great toe; normal = 0, impaired (<10 s unilaterally or

bilaterally) = 1], deep tendon ankle reflexes [right or left ankle; normal = 0, impaired (absent or hypoactive at least unilaterally or bilaterally) = 1], and 2-point discrimination (performed on right or left soles of feet) (Periyasamy, Manivannan, & Narayanamurthy, 2008).

2.2 | MRI acquisition and analysis

Scanning was performed on a 3.0 Tesla GE MRI scanner (MR750, General Electric Healthcare, Waukesha, WI) with either an 8-channel or a 32-channel receive array head coil. Conventional T1- and T2-weighted structural scans were collected. The T1-weighted scans were cerebral spinal fluid (CSF)-nulled magnetization-prepared rapid gradient echo (MPRAGE) with prospective motion correction (PROMO). Scan parameters: repetition time (TR)/echo time (TE)/inversion time (TI)/time between inversions (TS) = 8 ms/3.5 ms/1,100 ms/3.0 s, flip angle = 9°, field of view (FOV) = 18 cm, 200 \times 200 matrix, 1 mm thickness, 210 slices. The T2-weighted scans were 3D fast spin echo with

variable refocusing flip angle (T2 Cube) and PROMO (TR/TE: 3500 ms/62 ms, echo train length 84, FOV = 18 cm, 224x224 matrix, 1 mm thickness, 210 slices). In addition, a white-matter-nulled (WMn) MPRAGE sequence (Saranathan, Tourdias, Bayram, Ghanouni, & Rutt, 2015) was acquired for segmentation of thalamic nuclei [scan parameters: TR/TE/TI/TS = 11 ms/5 ms/500 ms/4.5 s, flip angle = 7, FOV = 18 cm, 200x200 matrix, 1 mm thickness, 210 slices].

T1- and T2-weighted images from each subject were first processed via an established pipeline (Pfefferbaum et al., 2018). The pipeline affinely aligned T2-weighted to the T1-weighted images via FLIRT epi_reg (FSL V5.0.6) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) and then denoised, corrected for image inhomogeneity, performed skull stripping, and segmented both scans. An estimate of supratentorial brain volume was computed using the SRI24 atlas {Rohlfing, 2010 #5683} in the same pipeline.

The WMn-MPRAGE sequence was used to segment thalamic nuclei using a recently proposed technique called Thalamus Optimized Multi Atlas Segmentation (THOMAS) (Planche et al., 2019; Su et al., 2019; Thomas, Su, Rutt, & Saranathan, 2017). Briefly, an atlas comprising WMn-MPRAGE data from 20 individuals with manual delineations of thalamic nuclei performed by a neuroradiologist guided by the Morel atlas was created (Tourdias, Saranathan, Levesque, Su, & Rutt, 2014). Thalamic nuclear labels were then nonlinearly warped from the atlas space to the input WMn-MPRAGE space and the labels combined using an intelligent joint fusion algorithm to generate one set of thalamic nuclei (Wang et al., 2013).

Previous work compared the THOMAS segmentation method on data acquired from the same subjects with two different coils (8 vs. 32 channel) (Su, Tourdias, Saranathan, Ghanouni, & Rutt, 2016) and

reported comparable performance with no statistical significance in the resulting Dice coefficients relative to manual segmentation. Thus, 8-channel and 32-channel data were combined.

The THOMAS segmentation method, based on data collected at a 7-T field strength, divides the thalamus into 12 nuclei including small structures such as the lateral and medial geniculate nuclei and the centromedian nuclei (Su et al., 2019). Due to lower signal-to-noise and lower contrast at a field strength of 3 T, only the major thalamic nuclear groups— anterior [AV], posterior [pulvinar (Pul)], medial [MD], and ventral [including ventral lateral posterior (VLp) and ventral posterior lateral (VPI)]—were considered in the current study (Figure 1).

2.3 | Statistical analysis

JMP Pro 14.1.0 (SAS Institute Inc. 2016) was used for all statistical analysis. Three-group ANOVAS or χ^2 tests (for nominal variables) evaluated differences in demographics, medical history, blood analytes, and behavior (e.g., Table 1).

Using a mixed-model approach in JMP, volume was predicted using the “fixed effects” nuclei, diagnosis, and their interaction, while “random effects” included side (i.e., hemisphere), the interaction of side and diagnosis, sex, age, and supratentorial volume (svol). Because a nucleus-by-diagnosis interaction term emerged as significant for this omnibus analysis, follow-up tests considered for each nuclei volume (left + right) the effects of diagnosis while controlling for age and svol.

In the diagnostic groups only, *t* tests or nonparametric Spearman's ρ evaluated relations between bilateral thalamic nuclei volumes and demographic, clinical, and performance measures.

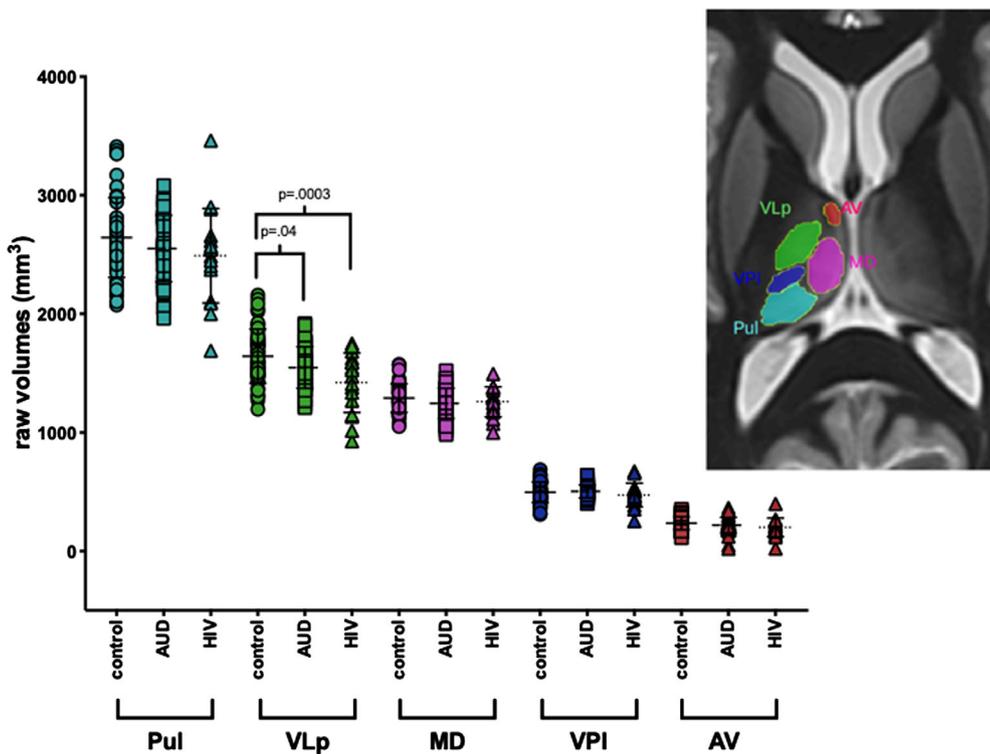


FIGURE 1 Raw volumes of the five thalamic nuclei in order of size: pulvinar (Pul), ventral lateral posterior (VLp), mediodorsal (MD), ventral posterior lateral (VPI), and anterior ventral (AV)

3 | RESULTS

3.1 | Demographics

Although the three groups were well-matched with respect to age, sex, and handedness (Table 1), the two diagnostic groups had lower education, socioeconomic status (SES) (Hollingshead, 1975), estimated premorbid IQ [as per the Wechsler Test of Adult Reading (WTAR), full-scale] (Demakis, Sawyer, Fritz, & Sweet, 2001), and global assessment of functioning (GAF) (Endicott, Spitzer, Fleiss, & Cohen, 1976) than the controls. Individuals in the AUD and HIV groups relative to those in the control group were more likely to be African-American, smoke, and have depressive symptoms [as assessed with the Beck Depression Inventory-II (BDI-II) Beck, Steer, & Brown, 1996]. The AUD relative to the other two groups had a greater lifetime consumption of alcohol and greater body mass index (BMI); the HIV relative to the other two groups had a higher VACS index [Veterans Aging Cohort Study index (Tate et al., 2013)], a measure of medical and psychiatric health where lower scores are in the direction of better health.

DSM-IV-diagnosed past substance abuse or dependence among the AUD group included 2 women and 17 men for cannabis, 3 women and 19 men for cocaine, 2 women and 10 men for amphetamines, 1 woman and 6 men for opiates, 3 men for sedatives, and 3 men for hallucinogens; among the HIV group, past substance abuse or dependence included 1 woman and 4 men for cannabis, 4 women and 2 men for cocaine, 1 man for amphetamines, and 1 woman for opiates.

Laboratory evaluation identified two controls, seven AUD, and four HIV subjects to be seropositive for hepatitis C virus (HCV). General markers of nutrition were not compromised. ANOVAs gave the following results: Blood urea nitrogen (BUN) $F(2,92) = 3.3, p = .04$; creatinine $F(2,92) = 14.9, p < .0001$; albumin $F(2,92) = 0.6, p = .53$; prealbumin $F(2,92) = 1.1, p = .35$; folate $F(2,92) = 0.1, p = .90$; vitamin B1 $F(2,92) = 1.1, p = .34$; and vitamin B12 $F(2,92) = 3.0, p = .06$. BUN levels were higher in the HIV relative to the control ($p = .02$) and AUD groups ($p = .02$). Similarly, creatinine levels were higher in the HIV group relative to the control ($p = .004$) and AUD groups ($p = .004$). Estimated glomerular filtration rate ($p < .0001$) and albumin to globulin ratio lower ($p = .002$) were lower in the HIV relative to the control group, indicating compromise of kidney function.

From data collected using structured health questionnaires, a three-group χ^2 test was significant for chronic back pain in the past year ($\chi^2 = 6.8, p = .03$): relative to the control group, the AUD ($p = .03$) and the HIV ($p = .02$) groups more frequently reported presence of chronic back pain in the past year.

Neuropsychological assessment showed deficits in explicit memory: The AUD performed worse than the control group on CVLT-II (free recall short delay: $p = .02$; free recall long delay: $p = .0001$); the HIV performed worse than the control group on semantic fluency for inanimate objects ($p = .009$). Both patient groups performed worse than the control group on ataxia with eyes open (control vs. AUD $p = .001$; control vs. HIV $p = .02$).

3.2 | Thalamic nuclei volumes

The mixed model with volume predicted using the “fixed effects” nuclei, diagnosis, and their interaction and the “random effects” side, side \times diagnosis, sex, age, and svol showed that nuclei-by-diagnosis interaction ($F[8,8] = 4.9, p < .0001$) was significant. Covariate Wald p -value were as follows: side $p = .72$, side \times diagnosis $p = .88$, sex $p = .55$, age $p < .0001$, svol $p = .004$.

Because a nucleus-by-diagnosis interaction emerged for the omnibus analysis, and because hemisphere and sex effects were negligible, follow-up tests considered each nuclear volume (right + left sum) by diagnosis while controlling for the significant covariates age and svol. After covarying for age and svol, the only nucleus that showed a diagnosis effect was the VLp ($F[2,2] = 5.7, p = .005$). For MD and VPI the model was not significant. For the remaining two nuclei, only the covariate age was significant: Pul ($p = .02$); AV ($p = .06$). The volumes (right + left) of each nucleus by diagnosis group are presented in Figure 1.

When simple regression statistics—collapsed across diagnostic groups—were evaluated for the effects of age on individual nuclei volume, correlations between smaller volumes and older age were observed for four of the five thalamic nuclei: Pul $r = -.47, p < .0001$; VLp $r = -.35, p = .0003$; VPI $r = -.43, p < .0001$; AV $r = -.44, p < .0001$ (Figure 2). The relation between older age and smaller volume was most consistent in the control group and emerged for the MD when the control group was considered independently of the two diagnostic groups: Pul (control: $\rho = -.51, p = .0002$; AUD: $\rho = -.36, p = .02$; HIV: $\rho = -.32, p = .21$), VLp (control: $\rho = -.39, p = .005$; AUD: $\rho = -.19, p = .22$; HIV: $\rho = -.23, p = .37$), MD (control: $\rho = -.32, p = .03$; AUD: $\rho = -.08, p = .61$; HIV: $\rho = .23, p = .37$), VPI (control: $\rho = -.49, p = .0004$; AUD: $\rho = -.16, p = .31$; HIV: $\rho = -.34, p = .19$), AV (control: $\rho = -.58, p < .0001$; AUD: $\rho = -.37, p = .02$; HIV: $\rho = -.51, p = .04$).

Finally, a three-group ANOVA of VLp volume by diagnosis was significant ($F[2, 106] = 7.3, p = .001$). Follow-up t tests demonstrate that relative to the control group, the VLp was smaller in the AUD ($p = .04$) and HIV ($p = .0003$) groups (Figure 1). Nonparametric Wilcoxon values approached statistical significance for the AUD to control comparison ($Z = -1.9, p = .06$) and were significant for the control to HIV comparison ($Z = -2.7, p = .007$).

3.3 | Thalamic VLp relations

As the VLp was the only nucleus showing effects of diagnoses, only VLp volume was evaluated for relations with relevant variables in the two diagnostic groups. For the AUD and HIV groups separately, relations were explored between VLp volume and demographic, clinical, blood, cognitive, motor, and neuropathy measures, including variables showing group differences in Table 1. Among all potential relations, the only ones that emerged in the AUD group were smaller VLp volume correlating with self-report of chronic back pain the past year ($t[41] = -2.8, p = .008$) and impaired deep tendon ankle reflex

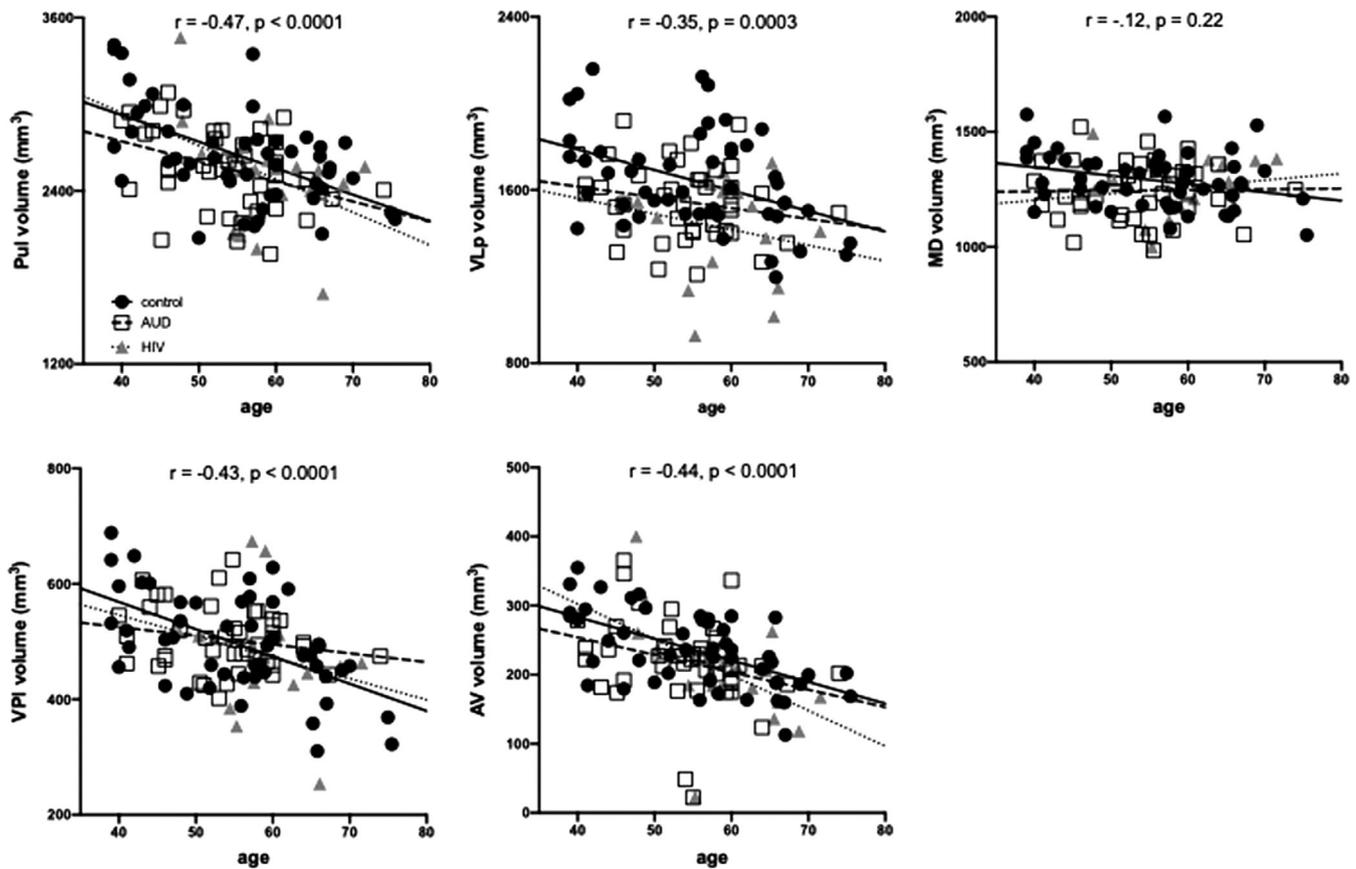


FIGURE 2 Volume decline as a function of age for each thalamic nucleus. Despite fit lines shown for each group separately, statistics are the results of simple regression collapsed across the three diagnostic groups. For individual diagnostic group Spearman's ρ nonparametric correlations, see the results section

($t[32] = -4.1, p = .0005$) (Figure 3a). AUD individuals with self-report of pain in the past year were more likely to have impaired ankle reflex [$\chi^2 = 8.1, p = .005$; of 18 individuals in the no pain group, only two had impaired ankle reflex; of 14 individuals with chronic back pain, eight had impaired ankle reflex]. VLp volume was not associated with opiate dependence or abuse ($t[41] = 1.3, p = .30$).

In the HIV group, among all potential variables evaluated, VLp volume correlated with only CD4 nadir ($r = .65, p = .008$). VLp volume in the HIV group was not associated with self-report of chronic back pain the past year ($p = .23$) or with impaired ankle reflex ($p = .35$).

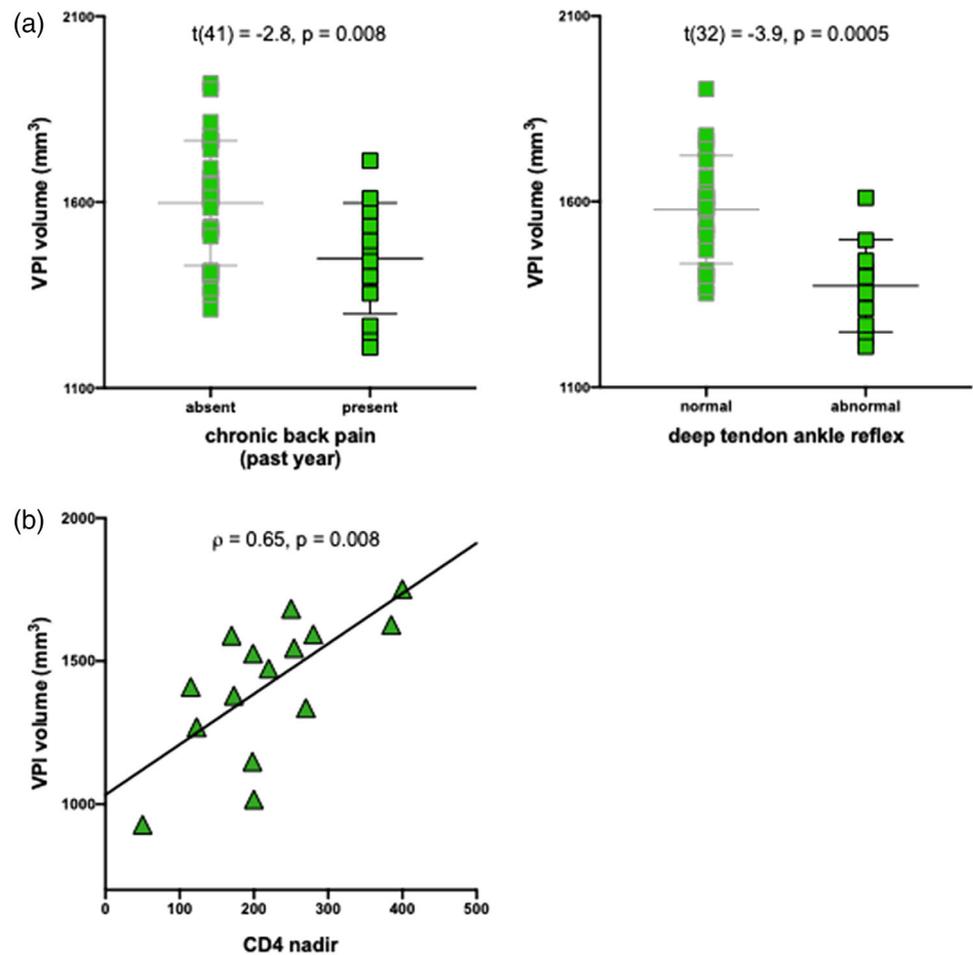
VLp volume in the AUD group was not associated with lifetime alcohol consumption ($p = .84$), months since last drink ($p = .12$), or scores on the CIWA for alcohol scale ($p = .42$). Similarly, VLp volume in the HIV group was not correlated with years infected ($p = .73$), viral load ($p = .25$), VACs scores ($p = .11$), BUN ($p = .97$), or creatinine ($p = .39$) levels. Indeed, VLp volume in the two diagnostic groups was not related to any other variable measured in the current study.

4 | DISCUSSION

Postmortem histology indicates neuronal loss in AV and MD nuclei of brains chronically exposed to alcohol (Belzunegui et al., 1995; Harding

et al., 2000). A recent diffusion tensor imaging (DTI) study partially supports these histological findings: probabilistic tractography used to segment the thalamus showed that the MD, which preferentially connects to the prefrontal cortex, is affected by both chronic alcoholism and KS (i.e., untreated thiamine deficiency) while the anterior thalamus, preferentially connected to the hippocampus, is principally affected in KS but not alcoholism per se (Segobin et al., 2019). The current assessment of MR images using semi-automated parcellation of thalamic nuclei did not demonstrate sensitivity of either AV or MD to AUD. Instead, in both AUD and HIV, the thalamic nucleus sensitive to disease was the VLp. That neither AV nor MD was affected may be due to the fact that the alcoholics included in the current study do not suffer from nutritional deficiencies. Inasmuch as acute cross-sectional blood markers can be used to estimate nutrition (e.g., Yildiz & Tufan, 2015), neither the AUD group nor the HIV group was malnourished. Indeed, the introduction of thiamine enrichment of rice and flour (Axford & Williams, 1981; Bauerfeind, 1988) has significantly reduced the incidence of WE and KS, as reported in Australia (Harper, Fornes, Duyckaerts, Lecomte, & Hauw, 1995). This comports with earlier studies suggesting that only alcoholics with thiamine deficiency have diencephalic damage (Krill et al., 1997; Torvik, 1987; Victor et al., 1989) specific to MD with additional damage to AV in KS (Harding et al., 2000; but see Pergola et al., 2018). Further, neither the AUD

FIGURE 3 VLP relations. (a) In the AUD group, smaller VLP volume correlated with self-report of chronic back pain the past year and impaired deep tendon ankle reflex. (b) In the HIV group, smaller VLP volume correlated with lower CD4 nadir



nor HIV groups in the current study had significant mnemonic deficits. Adequate nutrition in the AUD and HIV groups may have contributed to preservation of mnemonic function and volumes of the AV and MD thalamic nuclei.

The VLP is an integral part of cerebello-thalamocortical (Jones & Pivik, 1985; Kelly & Strick, 2003) and basal ganglia-thalamocortical (Alexander, DeLong, & Strick, 1986; Haber & McFarland, 2001) circuits. In the cerebello-thalamocortical circuit, the VLP receives significant cerebellar afferents (Sakai, Stepniewska, Qi, & Kaas, 2000) and is reciprocally connected with the primary motor area (Stepniewska, Preuss, & Kaas, 1994), the premotor area (Darian-Smith, Darian-Smith, & Cheema, 1990), and the supplementary motor area (SMA) (Sakai et al., 2000). In the basal ganglia-thalamocortical circuit, the VLP is strongly interconnected to the striatum and corresponding cortical areas (Haber & McFarland, 2001; Sakai et al., 2000). In monkeys, VL lesions lead to severe motor dysfunction (Canavan et al., 1989; van Donkelaar, Stein, Passingham, & Miall, 2000). In keeping with evidence that the VL thalamus is a sensorimotor structure also involved in nociception (Dejerine & Roussy, 1906; Garcin & Lapresle, 1954; Head & Holmes, 1911; Schuster, 1937), the current study reports relations between VLP volume, chronic back pain, and impaired ankle reflex in AUD. The relation between chronic back pain and VLP comports with a recent fMRI study suggesting that the magnitude of chronic pain maps to the ventral lateral thalamus (Davis, Ghantous,

Farmer, Baria, & Apkarian, 2016). A volume deficit of the VLP may affect sensitivity to pain perception. There is also a precedent for the involvement of the VL thalamus in AUD: Modafinil treatment of AUD patients resulted in improved response inhibition and modulation of brain activity in the VL (Schmaal et al., 2013). Thus, the current results align and contribute to literature supporting VLP as a sensorimotor structure.

In the HIV group, VLP volume selectively correlated with CD4 nadir. Sensitivity of total thalamic volume to CD4 nadir has previously been reported (Heaps et al., 2015).

A limitation of this study is that three groups were not matched with respect to factors listed in Table 1 including race, body mass index, education, socioeconomic status, premorbid IQ, depressive symptoms, smoking status, and global assessment of functioning. The directionality of these group differences, however, is expected based on the typical epidemiology of the patient groups (e.g., Delker, Brown, & Hasin, 2016; Ge, Sanchez, Nolan, Liu, & Savage, 2018). While some brain volumetric studies reported significant contributions of such factors to brain integrity (e.g., Garcia-Garcia et al., 2019; Holz, Laucht, & Meyer-Lindenberg, 2015; Kesler, Adams, Blasey, & Bigler, 2003), the current study did not find relations between variables differing among the three groups listed in Table 1 and VLP volume. Similarly, extensive analyses performed in large, longitudinal data sets of AUD (Sullivan et al., 2018) and HIV (Pfefferbaum et al.,

2018) groups relative to healthy controls did not find significant contributions of such factors to global brain integrity.

To our knowledge, this is the first volumetric study of thalamic nuclei volumes in AUD or HIV. It was expected that AUD and HIV would differentially affect volumes of unique thalamic nuclei (cf., Byne et al., 2008; Small et al., 2011); instead, both conditions were associated with smaller VLp volume. This finding is in contrast to results in multiple sclerosis that appears to specifically target AV and Pul thalamic nuclei (Planche et al., 2019). Whether AUD or HIV directly or indirectly contribute to VLp volume compromise cannot be determined by the current study. While unlikely that nutritional factors contributed to volume decline in either condition, a low CD4 cell count may selectively target the thalamus in HIV (Heaps et al., 2015). In conclusion, the current report indicates that VLp volume is sensitive to both AUD and HIV and is related to chronic back pain in AUD and to CD4 nadir in HIV.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be openly available at an online data repository such as <https://datadryad.org/>.

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