




RESEARCH ARTICLE

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

Natalie M. Zahr^{1,2}  | Edith V. Sullivan²  | Kilian M. Pohl^{1,2} |
Adolf Pfefferbaum^{1,2} | Manojkumar Saranathan³ 

¹Neuroscience Program, SRI International, Menlo Park, California

²Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, California

³Department of Medical Imaging, University of Arizona College of Medicine, Tucson, Arizona

Correspondence

Natalie M. Zahr, Neuroscience Program, SRI International, 333 Ravenswood Ave., Menlo Park, CA 94025.
Email: natalie.zahr@sri.com

Funding information

National Institute of Mental Health, Grant/Award Number: R01 MH113406; National Institute on Alcohol Abuse and Alcoholism, Grant/Award Numbers: R01 AA005965, R21 AA023582, R37 AA010723, U01 AA017347

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

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. *Human Brain Mapping* published by Wiley Periodicals, Inc.

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, 200×200 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, 224×224 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, 200×200 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.

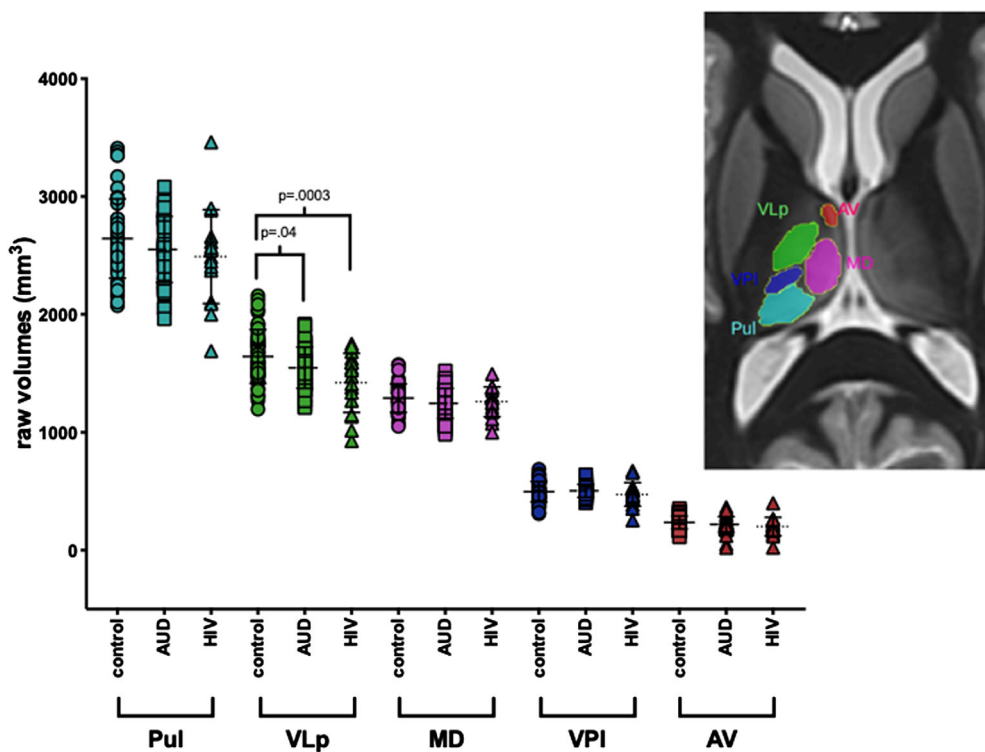


FIGURE 1 Raw volumes of the five thalamic nuclei in order of size: pulvinar (Pul), ventral lateral posterior (VLp), mediodorsal (MD), ventral posterior lateral (VPI), and anterior ventral (AV)

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

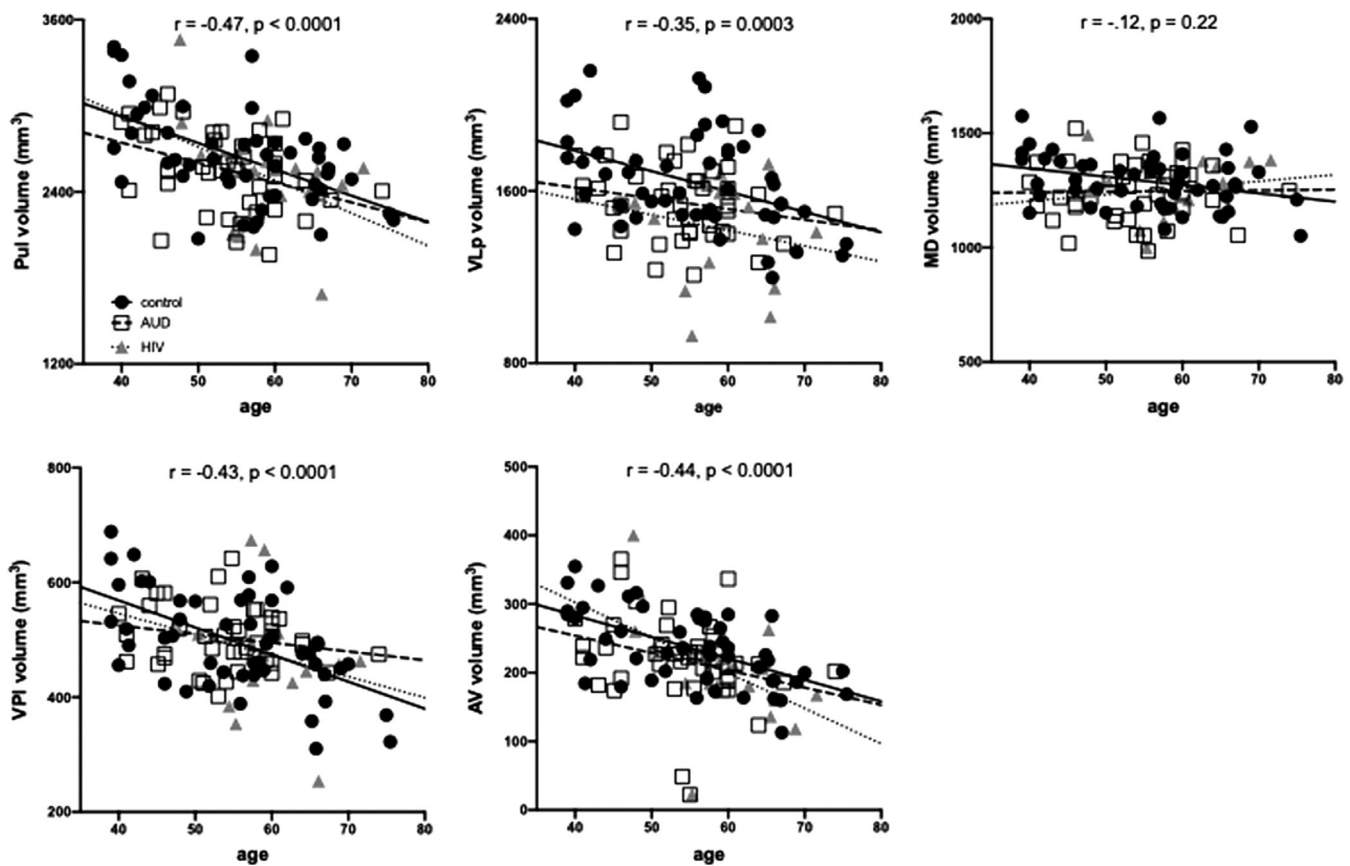


FIGURE 2 Volume decline as a function of age for each thalamic nucleus. Despite fit lines shown for each group separately, statistics are the results of simple regression collapsed across the three diagnostic groups. For individual diagnostic group Spearman's ρ nonparametric correlations, see the results 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 ($p = .35$).

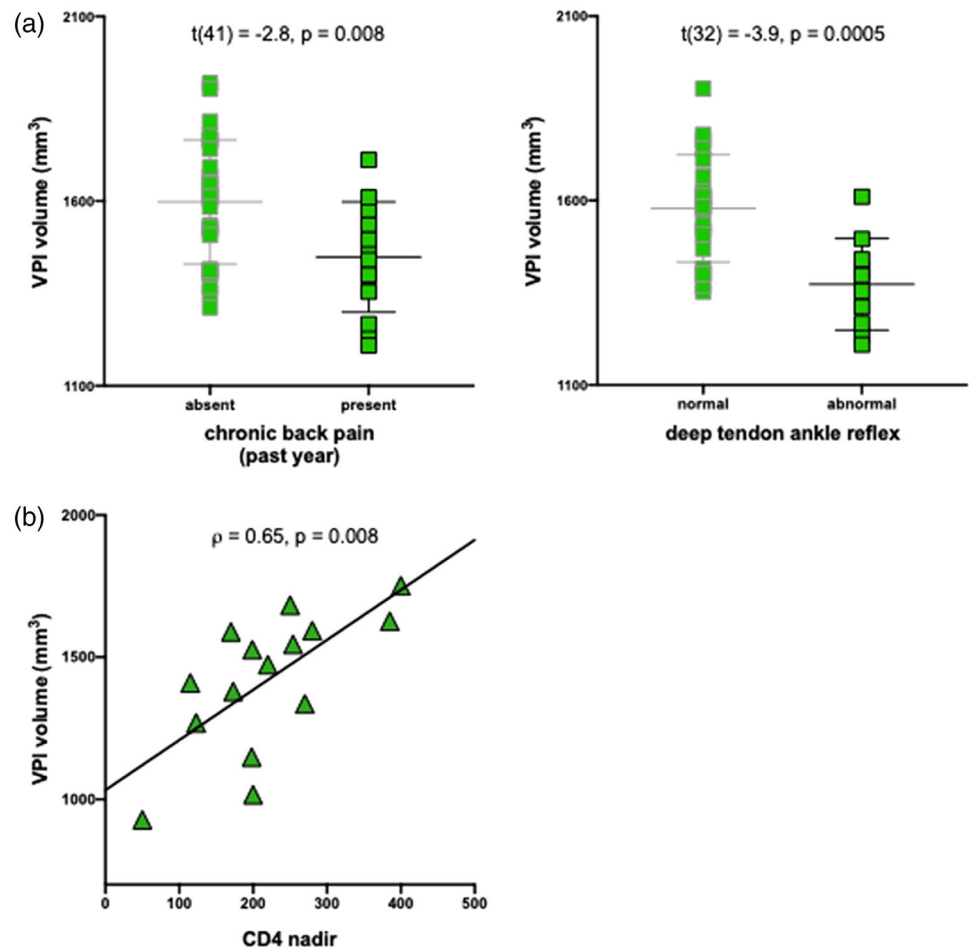
VLp volume in the AUD group was not associated with lifetime alcohol consumption ($p = .84$), months since last drink ($p = .12$), or scores on the CIWA for alcohol scale ($p = .42$). Similarly, VLp volume in the HIV group was not correlated with years infected ($p = .73$), viral load ($p = .25$), VACs 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.

ACKNOWLEDGMENTS

This study was supported with grant funding from the National Institute of Alcohol Abuse and Alcoholism (NIAAA): R21 AA023582, R01 AA005965, U01 AA017347, R37 AA010723, and National Institute of Mental Health: R01 MH113406.

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/>.

ORCID

Natalie M. Zahr  <https://orcid.org/0000-0002-3346-4894>

Edith V. Sullivan  <https://orcid.org/0000-0001-6739-3716>

Manojkumar Saranathan  <https://orcid.org/0000-0001-9020-9948>

REFERENCES

- Adalsteinsson, E., Sullivan, E.V., Mayer, D., Sailasuta, N., Hurd, R., & Pfefferbaum, A. (2005). *Proton MR spectroscopy for in vivo quantification of small animal brain alcohol kinetics*. Proceedings of the International Society for Magnetic Resonance in Medicine, May 8–14.
- Aggleton, J. P., Dumont, J. R., & Warburton, E. C. (2011). Unraveling the contributions of the diencephalon to recognition memory: A review. *Learning & Memory, 18*, 384–400.
- Alexander, G., DeLong, M., & Strick, P. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357–381.
- Ances, B. M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. *Journal of Acquired Immune Deficiency Syndromes, 59*, 469–477.
- Axford, D. W. E., & Williams, D. A. (1981). Flour enrichment around the world. *British Flour Milling and Baking Research Association, 4*, 156–163.
- Baker, L. M., Paul, R. H., Heaps-Woodruff, J. M., Chang, J. Y., Ortega, M., Margolin, Z., ... Ances, B. M. (2015). The effect of central nervous system penetration effectiveness of highly active antiretroviral therapy on neuropsychological performance and neuroimaging in HIV infected individuals. *Journal of Neuroimmune Pharmacology, 10*, 487–492.
- Bauerfeind, J. C. (1988). *Nutrition of food*. In: Modern Nutrition in Health and Disease, 7th Ed. Edited by M.E. Shils and V.E Young. Philadelphia: Lea and Febiger.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck depression inventory-II*. San Antonio, TX: Psychological Corporation.
- Belzungui, T., Insausti, R., Ibanez, J., & Gonzalo, L. M. (1995). Effect of chronic alcoholism on neuronal nuclear size and neuronal population in the mammillary body and the anterior thalamic complex of man. *Histology and Histopathology, 10*, 633–638.
- Butters, N. (1981). The Wernicke-Korsakoff syndrome: A review of psychological, neuropathological and etiological factors. *Currents in Alcoholism, 8*, 205–232.
- Byne, W., Tatusov, A., Yiannoulos, G., Vong, G. S., & Marcus, S. (2008). Effects of mental illness and aging in two thalamic nuclei. *Schizophrenia Research, 106*, 172–181.
- Canavan, A. G. M., Passingham, R. E., Marsden, C. D., Quinn, N., Wyke, M., & Polkey, C. E. (1989). Sequencing ability in Parkinsonians, patients with frontal lobe lesions and patients who have undergone unilateral temporal lobectomies. *Neuropsychologia, 27*, 787–798.
- Cermak, L. S. (1987). Models of memory loss in Korsakoff and alcoholic patients. In O. A. Parsons, N. Butters, & P. E. Nathan (Eds.), *Neuropsychology of alcoholism* (pp. 207–226). New York: Guilford Press.
- Cohen, R. A., Harezlak, J., Schifitto, G., Hana, G., Clark, U., Gongvatana, A., ... Navia, B. (2010). Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *Journal of Neurovirology, 16*, 25–32.
- Cornblath, D. R., Chaudhry, V., Carter, K., Lee, D., Seysedadr, M., Miernicki, M., & Joh, T. (1999). Total neuropathy score: Validation and reliability study. *Neurology, 53*, 1660–1664.
- Darian-Smith, C., Darian-Smith, I., & Cheema, S. S. (1990). Thalamic projections to sensorimotor cortex in the macaque monkey: Use of multiple retrograde fluorescent tracers. *The Journal of Comparative Neurology, 299*, 17–46.
- Davis, D. A., Ghantous, M. E., Farmer, M. A., Baria, A. T., & Apkarian, A. V. (2016). Identifying brain nociceptive information transmission in patients with chronic somatic pain. *Pain Reports, 1*, e575.
- Day, J. J., Grant, I., Atkinson, J. H., Brysk, L. T., McCutchan, J. A., Hesselink, J. R., ... Richman, D. D. (1992). Incidence of AIDS dementia in a two-year follow-up of AIDS and ARC patients on an initial phase II AZT placebo-controlled study: San Diego cohort. *The Journal of Neuro-psychiatry and Clinical Neurosciences, 4*, 15–20.
- Dejerine, J., & Roussy, G. (1906). Le syndrome thalamique. *Revue Neurologique, 14*, 521–532.
- Delis, D. C., Freeland, J., Kramer, J. H., & Kaplan, E. (1988). Integrating clinical assessment with cognitive neuroscience: Construct validation of the California verbal learning test. *Journal of Consulting and Clinical Psychology, 56*, 123–130.
- Delker, E., Brown, Q., & Hasin, D. S. (2016). Alcohol consumption in demographic subpopulations: An epidemiologic overview. *Alcohol Research: Current Reviews, 38*, 7–15.
- Demakis, G. J., Sawyer, T. P., Fritz, D., & Sweet, J. J. (2001). Incidental recall on WAIS-R digit symbol discriminates Alzheimer's and Parkinson's diseases. *Journal of Clinical Psychology, 57*, 387–394.
- Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. (1976). The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry, 33*, 766–771.
- Fama, R., Eisen, J. C., Rosenbloom, M. J., Sassoon, S. A., Kemper, C. A., Deresinski, S., ... Sullivan, E. V. (2007). Upper and lower limb motor impairments in alcoholism, HIV-infection, and their comorbidity. *Alcoholism: Clinical and Experimental Research, 31*, 1038–1044.
- Fama, R., Rosenbloom, M. J., Sassoon, S. A., Rohlfling, T., Pfefferbaum, A., & Sullivan, E. V. (2014). Thalamic volume deficit contributes to procedural and explicit memory impairment in HIV

- infection with primary alcoholism comorbidity. *Brain Imaging and Behavior*, 8, 611–620.
- Feuerlein, W. (1977). Neuropsychiatric disorders of alcoholism. *Nutrition and Metabolism*, 21, 163–174.
- First, M. (2000). *Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.
- Fregly, A. R. (1968). An ataxia battery not requiring rails. *Aerospace Medicine*, 39, 277–282.
- Garcia-Garcia, I., Michaud, A., Dadar, M., Zeighami, Y., Neseliler, S., Collins, D. L., ... Dagher, A. (2019). Neuroanatomical differences in obesity: Meta-analytic findings and their validation in an independent dataset. *International Journal of Obesity*, 43, 943–951.
- Garcin, R., & Lapresle, J. (1954). Sensory syndrome of the thalamic type and with hand-mouth topography due to localized lesions of the thalamus. *Revue Neurologique (Paris)*, 90, 124–129.
- Gates, T. M., & Cysique, L. A. (2016). The chronicity of HIV infection should drive the research strategy of NeuroHIV treatment studies: A critical review. *CNS Drugs*, 30, 53–69.
- Ge, S., Sanchez, M., Nolan, M., Liu, T., & Savage, C. L. (2018). Is alcohol use associated with increased risk of developing adverse health outcomes among adults living with human immunodeficiency virus: A systematic review. *Journal of Addictions Nursing*, 29, 96–118.
- Gebhardt, C. A., Naeser, M. A., & Butters, N. (1984). Computerized measures of CT scans of alcoholics: Thalamic region related to memory. *Alcohol*, 1, 133–140.
- Gold, J. J., & Squire, L. R. (2006). The anatomy of amnesia: Neurohistological analysis of three new cases. *Learning & Memory*, 13, 699–710.
- Groenewegen, H. J., & Berendse, H. W. (1994). The specificity of the 'non-specific' midline and intralaminar thalamic nuclei. *Trends in Neurosciences*, 17, 52–57.
- Haber, S., & McFarland, N. R. (2001). The place of the thalamus in frontal cortical-basal ganglia circuits. *The Neuroscientist*, 7, 315–324.
- Haber, S. N. (2003). The primate basal ganglia: Parallel and integrative networks. *Journal of Chemical Neuroanatomy*, 26, 317–330.
- Hammoud, D. A., Sinharay, S., Steinbach, S., Wakim, P. G., Geannopoulos, K., Traino, K., ... Nath, A. (2018). Global and regional brain hypometabolism on FDG-PET in treated HIV-infected individuals. *Neurology*, 91, e1591–e1601.
- Harding, A., Halliday, G., Caine, D., & Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain*, 123, 141–154.
- Harper, C. (1998). The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *Journal of Neuropathology and Experimental Neurology*, 57, 101–110.
- Harper, C., Fornes, P., Duyckaerts, C., Lecomte, D., & Hauw, J. J. (1995). An international perspective on the prevalence of the Wernicke-Korsakoff syndrome. *Metabolic Brain Disease*, 10, 17–24.
- Head, H., & Holmes, G. (1911). Sensory disturbances from cerebral lesions. *Brain*, 34, 102–254.
- Heaps, J. M., Joska, J., Hoare, J., Ortega, M., Agrawal, A., Seedat, S., ... Paul, R. (2012). Neuroimaging markers of human immunodeficiency virus infection in South Africa. *Journal of Neurovirology*, 18, 151–156.
- Heaps, J. M., Sithinamsuwan, P., Paul, R., Lerdlum, S., Pothirisi, M., Clifford, D., ... SEARCH 007/011 study groups. (2015). Association between brain volumes and HAND in cART-naive HIV+ individuals from Thailand. *Journal of Neurovirology*, 21, 105–112.
- Hillbom, M., Juvela, S., & Karttunen, V. (1998). Mechanisms of alcohol-related strokes. *Novartis Foundation Symposium*, 216, 193–204.
- Hollingshead, A. (1975). *Four-factor index of social status*. New Haven, CT: Yale University.
- Holz, N. E., Laucht, M., & Meyer-Lindenberg, A. (2015). Recent advances in understanding the neurobiology of childhood socioeconomic disadvantage. *Current Opinion in Psychiatry*, 28, 365–370.
- Janssen, M. A., Meulenbroek, O., Steens, S. C., Goraj, B., Bosch, M., Koopmans, P. P., & Kessels, R. P. (2015). Cognitive functioning, wellbeing and brain correlates in HIV-1 infected patients on long-term combination antiretroviral therapy. *AIDS*, 29, 2139–2148.
- Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, 17, 825–884.
- Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, 5, 143–156.
- Jones, A. M., & Pivik, R. T. (1985). Vestibular activation, smooth pursuit tracking, and psychosis. *Psychiatry Research*, 14, 291–308.
- Josseaux, T., Auffray Calvier, E., Dumas Duport, B., Lebouvier, T., Pouliquen Mathieu, G., de Kersaint Gilly, A., & Desal, H. (2007). Acute anterograde amnesia by infarction of the mamillothalamic tracts. *Journal of Neuroradiology*, 34, 59–62.
- Kaku, M., & Simpson, D. M. (2014). HIV neuropathy. *Current Opinion in HIV and AIDS*, 9, 521–526.
- Kelly, R. M., & Strick, P. L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *The Journal of Neuroscience*, 23, 8432–8444.
- Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: An investigation of the cognitive reserve hypothesis. *Applied Neuropsychology*, 10, 153–162.
- Kieburz, K., Ketonen, L., Cox, C., Grossman, H., Holloway, R., Booth, H., ... Caine, E. D. (1996). Cognitive performance and regional brain volume in human immunodeficiency virus type 1 infection. *Archives of Neurology*, 53, 155–158.
- Korbo, L., & West, M. (2000). No loss of hippocampal neurons in AIDS patients. *Acta Neuropathologica*, 99, 529–533.
- Kril, J. J., Halliday, G. M., Svoboda, M. D., & Cartwright, H. (1997). The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*, 79, 983–998.
- Lieber, C. S. (2004). Alcoholic fatty liver: Its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol*, 34, 9–19.
- Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., D'Elia, L., ... Schulte, G. (1994). WHO neuropsychiatric AIDS study, cross-sectional phase II. Neuropsychological and neurological findings. *Archives of General Psychiatry*, 51, 51–61.
- Malamud, N., & Skillicorn, S. A. (1956). Relationship between the Wernicke and the Korsakoff syndrome; a clinicopathologic study of seventy cases. *A.M.A. Archives of Neurology and Psychiatry*, 76, 585–596.
- Manji, H., Jager, H. R., & Winston, A. (2013). HIV, dementia and antiretroviral drugs: 30 years of an epidemic. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84, 1126–1137.
- Markowitsch, H. J., Irl, E., & Streicher, M. (1982). The thalamic mediodorsal nucleus receives input from thalamic and cortical regions related to vision. *Neuroscience Letters*, 32, 131–136.
- Martin, R. C., Loring, D. W., Meador, K. J., & Lee, G. P. (1990). The effects of lateralized temporal lobe dysfunction on formal and semantic word fluency. *Neuropsychologia*, 28, 823–829.
- Nakazato, A., Tominaga, D., Tasato, D., Miyagi, K., Nakamura, H., Haranaga, S., ... Fujita, J. (2014). Are MMSE and HDS-R neuropsychological tests adequate for screening HIV-associated neurocognitive disorders? *Journal of Infection and Chemotherapy: Official Journal of the Japan Society of Chemotherapy*, 20, 217–219.
- Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow, H. (2005). The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53, 695–699.
- Osterrieth, P., & Rey, A. (1944). Le test de copie d'une figure complex. *Archives de Psychologie*, 30, 205–221.

- Parsons, O., & Nixon, S. (1998). Cognitive-functioning in sober social drinkers: A review of the research since 1986. *Journal of Studies on Alcohol*, 59, 180–190.
- Pergola, G., Danet, L., Pitel, A. L., Carlesimo, G. A., Segobin, S., Pariente, J., ... Barbeau, E. J. (2018). The regulatory role of the human mediodorsal thalamus. *Trends in Cognitive Sciences*, 22, 1011–1025.
- Pergola, G., Gunturkun, O., Koch, B., Schwarz, M., Daum, I., & Suchan, B. (2012). Recall deficits in stroke patients with thalamic lesions covary with damage to the parvocellular mediodorsal nucleus of the thalamus. *Neuropsychologia*, 50, 2477–2491.
- Periyasamy, R., Manivannan, M., & Narayanamurthy, V. B. (2008). Changes in two point discrimination and the law of mobility in diabetes mellitus patients. *Journal of Brachial Plexus and Peripheral Nerve Injury*, 3, 3.
- Pfefferbaum, A., Rogosa, D. A., Rosenbloom, M. J., Chu, W., Sassoon, S. A., Kemper, C. A., ... Sullivan, E. V. (2014). Accelerated aging of selective brain structures in human immunodeficiency virus infection: A controlled, longitudinal magnetic resonance imaging study. *Neurobiology of Aging*, 35, 1755–1768.
- Pfefferbaum, A., Rosenbloom, M. J., Sassoon, S. A., Kemper, C. A., Deresinski, S., Rohlfing, T., & Sullivan, E. V. (2012). Regional brain structural dysmorphology in human immunodeficiency virus infection: Effects of acquired immune deficiency syndrome, alcoholism, and age. *Biological Psychiatry*, 72, 361–370.
- Pfefferbaum, A., Zahr, N. M., Sassoon, S. A., Kwon, D., Pohl, K. M., & Sullivan, E. V. (2018). Accelerated and premature aging characterizing regional cortical volume loss in human immunodeficiency virus infection: Contributions from alcohol, substance use, and hepatitis C coinfection. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, 3, 844–859.
- Planche, V., Su, J. H., Mournet, S., Saranathan, M., Dousset, V., Han, M., ... Tourdias, T. (2019). White-matter-nulled MPRAGE at 7T reveals thalamic lesions and atrophy of specific thalamic nuclei in multiple sclerosis. *Multiple Sclerosis Journal*, 1352458519828297. doi: 10.1177/1352458519828297. [Epub ahead of print]
- Poppenk, J., & Moscovitch, M. (2011). A hippocampal marker of recollection memory ability among healthy young adults: Contributions of posterior and anterior segments. *Neuron*, 72, 931–937.
- Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271–276.
- Robertson, K., Kumwenda, J., Supparatpinyo, K., Jiang, J. H., Evans, S., Campbell, T. B., ... Group, A.C.T. (2011). A multinational study of neurological performance in antiretroviral therapy-naive HIV-1-infected persons in diverse resource-constrained settings. *Journal of Neurovirology*, 17, 438–447.
- Ruff, R. (1988). *Ruff figural fluence test: Administration manual*. San Diego, CA: Neuropsychological Resources.
- Sakai, S. T., Stepniewska, I., Qi, H. X., & Kaas, J. H. (2000). Pallidal and cerebellar afferents to pre-supplementary motor area thalamocortical neurons in the owl monkey: A multiple labeling study. *The Journal of Comparative Neurology*, 417, 164–180.
- Sanford, R., Ances, B. M., Meyerhoff, D. J., Price, R. W., Fuchs, D., Zetterberg, H., ... Collins, D. L. (2018). Longitudinal trajectories of brain volume and cortical thickness in treated and untreated primary human immunodeficiency virus infection. *Clinical Infectious Diseases*, 67, 1697–1704.
- Saranathan, M., Tourdias, T., Bayram, E., Ghanouni, P., & Rutt, B. K. (2015). Optimization of white-matter-nulled magnetization prepared rapid gradient echo (MP-RAGE) imaging. *Magnetic Resonance in Medicine*, 73, 1786–1794.
- Sassoon, S. A., Rosenbloom, M. J., Fama, R., O'Reilly, A., Pfefferbaum, A., & Sullivan, E. V. (2007). Component cognitive and motor processes contributing to speeded visuomotor abilities in alcoholism, HIV infection and their comorbidity. *Alcoholism: Clinical and Experimental Research*, 31(8), 1315–1324.
- Schmaal, L., Goudriaan, A. E., Joos, L., Kruse, A. M., Dom, G., van den Brink, W., & Veltman, D. J. (2013). Modafinil modulates resting-state functional network connectivity and cognitive control in alcohol-dependent patients. *Biological Psychiatry*, 73, 789–795.
- Schuster, P. (1937). Beitrage zur Pathologie des Thalamus opticus. *Mitteilung Archiv Fu'r Psychiatrie Und Nervenkrankheiten*, 106, 13–53.
- Segobin, S., Laniece, A., Ritz, L., Lannuzel, C., Boudehent, C., Cabe, N., ... Pitel, A. L. (2019). Dissociating thalamic alterations in alcohol use disorder defines specificity of Korsakoff's syndrome. *Brain*, 142, 1458–1470.
- Shu, S. Y., Wu, Y. M., Bao, X. M., & Leonard, B. (2003). Interactions among memory-related centers in the brain. *Journal of Neuroscience Research*, 71, 609–616.
- Skinner, H. A. (1982). *Development and validation of a lifetime alcohol consumption assessment procedure*. Toronto: Canada. Addiction Research Foundation.
- Skinner, H. A., & Allen, B. A. (1982). Alcohol dependence syndrome: Measurement and validation. *Journal of Abnormal Psychology*, 91, 199–209.
- Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews. Neuroscience*, 12, 585–601.
- Spreen, O., & Benton, A. L. (1977). *Neurosensory center comprehensive examination for aphasia*. Victoria, BC: University of Victoria Neuropsychology Laboratory.
- Squire, L. R., Amaral, D. G., & Press, G. A. (1990). Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. *The Journal of Neuroscience*, 10, 3106–3117.
- Squire, L. R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory. *Annual Review of Psychology*, 44, 453–495.
- Stepniewska, I., Preuss, T. M., & Kaas, J. H. (1994). Thalamic connections of the primary motor cortex (M1) of owl monkeys. *The Journal of Comparative Neurology*, 349, 558–582.
- Su, J., Tourdias, T., Saranathan, M., Ghanouni, P., & Rutt, B. K. (2016). THOMAS: Thalamus optimized multi-atlas segmentation at 3T (p. 4328). Singapore: ISMRM.
- Su, J. H., Thomas, F. T., Kasoff, W. S., Tourdias, T., Choi, E. Y., Rutt, B. K., & Saranathan, M. (2019). Fast, fully automated segmentation of thalamic nuclei from structural MRI. *NeuroImage*, 194, 272–282.
- Sullivan, E. V., Lane, B., Deshmukh, A., Rosenbloom, M. J., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (1999). In vivo mammillary body volume deficits in amnesic and nonamnesic alcoholics. *Alcoholism, Clinical and Experimental Research*, 23, 1629–1636.
- Sullivan, E. V., Zahr, N. M., Sassoon, S. A., Thompson, W. K., Kwon, D., Pohl, K. M., & Pfefferbaum, A. (2018). The role of aging, drug dependence, and hepatitis C comorbidity in alcoholism cortical compromise. *JAMA Psychiatry*, 75, 474–483.
- Tate, J. P., Justice, A. C., Hughes, M. D., Bonnet, F., Reiss, P., Mocroft, A., ... Sterne, J. A. (2013). An internationally generalizable risk index for mortality after one year of antiretroviral therapy. *AIDS*, 27, 563–572.
- Thomas, F. T., Su, J., Rutt, B. K., & Saranathan, M. (2017). A method for near realtime automated segmentation of thalamic nuclei. Honolulu, HI; ISMRM. p 4736.
- Torvik, A. (1987). Brain lesions in alcoholics: Neuropathological observations. *Acta Medica Scandinavica*, 717, 47–54.
- Tourdias, T., Saranathan, M., Levesque, I. R., Su, J., & Rutt, B. K. (2014). Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. *NeuroImage*, 84, 534–545.
- Trites, R. L. (1977). *The grooved pegboard test. Neuropsychological test manual*. Ontario, Canada: Royal Ottawa Hospital.
- Underwood, J., De Francesco, D., Post, F. A., Vera, J. H., Williams, I., Boffito, M., ... Pharmacokinetic, Clinical Observations in People Over Fifty study, g. (2017, 18). Associations between cognitive impairment

- and patient-reported measures of physical/mental functioning in older people living with HIV. *HIV Medicine*, 18(5), 363–369.
- Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B., & Jolles, J. (2003). Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia*, 41, 1330–1344.
- van Donkelaar, P., Stein, J. F., Passingham, R. E., & Miall, R. C. (2000). Temporary inactivation in the primate motor thalamus during visually triggered and internally generated limb movements. *Journal of Neurophysiology*, 83, 2780–2790.
- van Holst, R. J., de Ruiter, M. B., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2012). A voxel-based morphometry study comparing problem gamblers, alcohol abusers, and healthy controls. *Drug and Alcohol Dependence*, 124, 142–148.
- Victor, M., Adams, R. D., & Collins, G. H. (1971). *The Wernicke-Korsakoff syndrome*. Philadelphia: F.A. Davis Co.
- Victor, M., Adams, R. D., & Collins, G. H. (1989). *The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition* (2nd ed.). Philadelphia: F.A. Davis Co.
- Vivithanaporn, P., Heo, G., Gamble, J., Krentz, H. B., Hoke, A., Gill, M. J., & Power, C. (2010). Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study. *Neurology*, 75, 1150–1158.
- Wang, H., Suh, J. W., Das, S. R., Pluta, J. B., Craige, C., & Yushkevich, P. A. (2013). Multi-atlas segmentation with joint label fusion. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 35, 611–623.
- Wechsler, D. (1987). *Wechsler memory scale - revised*. San Antonio, TX: The Psychological Corporation.
- Yildiz, A., & Tufan, F. (2015). Lower creatinine as a marker of malnutrition and lower muscle mass in hemodialysis patients. *Clinical Interventions in Aging*, 10, 1593.
- Yoneoka, Y., Takeda, N., Inoue, A., Ibuchi, Y., Kumagai, T., Sugai, T., ... Ueda, K. (2004). Acute Korsakoff syndrome following mammillothalamic tract infarction. *American Journal of Neuroradiology*, 25, 964–968.

How to cite this article: Zahr NM, Sullivan EV, Pohl KM, Pfefferbaum A, Saranathan M. Sensitivity of ventrolateral posterior thalamic nucleus to back pain in alcoholism and CD4 nadir in HIV. *Hum Brain Mapp*. 2020;41:1351–1361. <https://doi.org/10.1002/hbm.24880>