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Research report

Anterior and posterior thalamic volumes differentially correlate with memory, attention, and motor processes in HIV infection and alcohol use disorder comorbidity☆

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ABSTRACT

The thalamus, with its reciprocal connections to and from cortical, subcortical, and cerebellar regions, is a central active participant in multiple functional brain networks. Structural MRI studies measuring the entire thalamus without respect to its regional or nuclear divisions report volume shrinkage in diseases including HIV infection, alcohol use disorder (AUD), and their comorbidity (HIV+AUD). Here, we examined relations between thalamic subregions (anterior, ventral, medial, and posterior) and neuropsychological functions (attention/working memory, executive functioning, episodic memory, and motor skills). Volumes of thalamic subregions were derived from automatic segmentations of standard T1 weighted MRIs of 65 individuals with HIV, 189 with AUD, 80 with HIV+AUD comorbidity, and 141 healthy controls (CTRL). Total thalamic volume was smaller and cognitive and motor composite scores were lower in the three diagnostic groups relative to the CTRL group. The AUD and HIV+AUD groups had significantly smaller thalamic subregional volumes than the CTRL group. The HIV+AUD group had smaller anterior thalamic volume than the HIV-only group and smaller ventral thalamic volume than the AUD-only group. In the HIV+AUD group, memory scores correlated with anterior thalamic volumes, attention/working memory scores correlated with posterior and medial thalamic volumes, and motor skill scores correlated with posterior thalamic volumes. Exploratory analyses focused on the HIV+AUD group indicated that within the posterior thalamic region, the pulvinar and medial geniculate nuclei were related to attention/working memory scores, and the pulvinar was related to motor skills scores. This study is novel in locating volume deficits in specific thalamic subregions, in addition to the thalamus as a whole, in HIV, AUD, and their comorbidity and in identifying functional ramifications of these deficits. Taken together, this study highlights the relevance of thalamic subregional volume deficits to dissociable cognitive and motor processes.

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1. Introduction

The thalamus, with its reciprocal connections to and from cortical, subcortical, and cerebellar areas, is a central active participant in multiple functional brain networks. Consisting of upwards of 60 nuclei, the thalamus, once believed to be simply a relay station connecting subcortical and cortical regions, is now known to have a role in attention, working memory, executive functions, episodic memory, and psychomotor processes (Aggleton et al., 2016; Antonucci et al., 2021; Cassel and de Vasconcelos, 2022; Pergola et al., 2018; Pfefferbaum et al., 2023).

The relevance of the thalamus in attentional processes has long been documented in both animal and human studies (Kastner and Arcaro, 2022). The ability to attend selectively to pertinent stimuli while filtering out less relevant information is a cornerstone of higher-order cognitive processes including memory and decision making and is a thalamic function (Gottlieb and Balan, 2010; Luckmann et al., 2014). The interconnection between the thalamic pulvinar and frontal and parietal cortical sites, for example, serves as a critical network enabling attentional control (Schmahmann and Pandya, 1990; Yeterian and Pandya, 1985).

Regarding the thalamus as a substrate of mnemonic processes, neural connections between the thalamus and the hippocampus by way of the fornix have been highlighted in neuroanatomical studies in humans and animals (Sweeney-Reed et al., 2021), arguing for its place in the Papez circuit (Aggleton et al., 2016). Further, the severe memory impairment associated with localized thalamic strokes (Carlesimo et al., 2011; Exner et al., 2001; Kopelman, 1995; Van der Werf et al., 2000) and Korsakoff's syndrome (Kopelman, 1995; Segobin and Pitel, 2021) provides evidence for the thalamus as an integral part of an "extended hippocampal" mnemonic system (Aggleton and Brown, 2006; Aggleton and Saunders, 1997).

Structural MRI studies examining thalamic volume without respect to its nuclear divisions report shrinkage in a number of neuropsychiatric conditions, including HIV infection (Ortega et al., 2013; Pfefferbaum et al., 2012; Wade et al., 2015), alcohol use disorder (AUD) with and without Korsakoff syndrome (KS) (Cardenas et al., 2007; Chanraud et al., 2007; Pitel et al., 2015; Segobin and Pitel, 2021; Sullivan and Pfefferbaum, 2009) and their comorbidity (HIV infection and AUD); (Fama et al., 2014; Spies et al., 2022). In addition, FDG-PET imaging revealed significant hypometabolism of the thalamus in treated HIV infection compared with seronegative participants (Hammoud et al., 2018), lending evidence for thalamic dysfunction along with anomalous structure in people living with HIV (PLWH). In a quest to find mechanisms contributing to thalamic volume deficits in HIV infection using MR spectroscopy, metabolite abnormalities were identified; lower concentrations of frontal white matter N-acetylaspartate and lower basal ganglia glutamate/glutamine ratios correlated with smaller thalamic volumes in PLWH (Cohen et al., 2010).

In AUD and alcohol-related KS, episodic memory deficits, believed to be associated with thalamic dysfunction, notably the anterior thalamic region (Aggleton and O'Mara, 2022; Harding et al., 2000), have been linked to thiamine (B1) deficiency in the context of chronic heavy drinking (Kopelman, 1995; Pitel et al., 2015; Victor et al., 1971), notably the anterior thalamic region (Aggleton and O'Mara, 2022; Harding et al., 2000). Application of the Caine criteria (Caine et al., 1997) (i.e., ophthalmoplegia, ataxia, mental confusion, dietary insufficiency) used to diagnose alcohol-related Wernicke's encephalopathy (WE), the neurological syndrome often preceding KS, has been shown to be predictive of severity of cognitive deficits in HIV (Le Berre et al., 2019), which could implicate the thalamus in contributing to mnemonic deficits in HIV. Support for this speculation derives from observations that smaller thalamic volume has been consistently associated with more severe memory deficits in individuals with a history of excessive, heavy drinking, particularly those with alcohol-related KS (Pitel et al., 2015; Segobin and Pitel, 2021). In AUD without KS, smaller thalamic volume has also been associated with poorer executive function (Chanraud et al., 2010). Further, poorer performance on tests of immediate and delayed episodic memory was associated with smaller thalamic volume in individuals with HIV+AUD comorbidity, even after taking hippocampal volume into account (Fama et al., 2014).

Here we tested the hypothesis that smaller volumes of thalamic regions would be associated with poorer cognitive and motor function in HIV, AUD, and their comorbidity relative to unaffected controls. Based on previous studies, we hypothesized that in the diagnostic groups, poorer episodic memory would be related to smaller anterior thalamic volume whereas poorer psychomotor performance would be related to smaller posterior thalamic volume. We also expected, as has been demonstrated in our previous studies, that the comorbid HIV+AUD group would exhibit more severe deficits in thalamic volumes and functional scores and subsequently show more brain-behavior relations than the single diagnostic groups.

2. Methods

2.1. Participants

Participants included 65 individuals with HIV (28–78 years old; 18 F, 47 M), 189 with AUD (21–76 years old; 56 F, 133 M), 80 with HIV+AUD (22–79 years old; 28 F, 52 M), and 141 healthy controls (CTRL; 20–86 years old; 68 F, 73 M) (Table 1).

Participants with HIV were recruited by referral from community physicians and HIV treatment facilities. AUD participants were almost exclusively recruited from local substance abuse treatment programs and sobriety support groups and met DSM-IV-TR criteria for alcohol dependence or abuse and DSM-5 criteria for AUD. CTRL participants were recruited from the local community. Screening for exclusion was based on the Structured Clinical Interview for DSM-IV-TR (First et al., 1998) and DSM-5 (APA, 2013) and interviews on health status, administered by calibrated research clinicians. Participants were excluded if they had a significant history of medical (e.g., epilepsy, stroke, multiple sclerosis, uncontrolled diabetes, or loss of consciousness $>$ 30 minutes), psychiatric (i.e., schizophrenia or bipolar I disorder) or neurological (e.g., neurodegenerative disease) disorder. An additional exclusion criterion for the CTRL group was any DSM-IV-TR Axis I or DSM-5 disorder. Severity of depressive symptoms was assessed with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). All participants underwent a semi-structured timeline follow-back interview to quantify lifetime alcohol consumption (Skinner, 1982; Skinner and Sheu, 1982). All participants were administered a breathalyzer prior to testing to ensure absence of breath alcohol content. This research protocol was approved by the Institutional Review Boards of Stanford University (FWA0000935) and SRI International (FWA00007933) and written informed consent was obtained from all participants, none of whom was clinically demented or conserved.

The 3 clinical groups (HIV, AUD, HIV+AUD) had fewer years of education ($H=102.04$, $p<.0001$), scored lower on a screening test of overall current cognitive function (Dementia Rating Scale-2) (Jurica et al., 2004) ($H=61.48$, $p<.001$), and had a lower estimated IQ as assessed by the National Adult Reading Test (NART) (Nelson, 1982) ($H=29.46$, $p<.0001$) than the CRTL group (Table 1). Self-identified racial composition of the groups differed (Chi Square=104.51, $p<.0001$). The 3 clinical groups also endorsed a greater level of depressive symptoms (BDI-II) [$H=99.64$, $p<.0001$] and reported a lower level of socioeconomic status ($H=110.12$, $p<.0001$) than the CTRL group. Total amount of lifetime alcohol consumed differed among groups ($H=335.33$, $p<.0001$). As expected, the AUD and HIV+AUD groups consumed more alcohol over their lifetime than the HIV and CTRL groups, with the AUD group consuming even more alcohol over their lifetime than the HIV+AUD group.

The HIV and HIV+AUD groups did not differ on CD4+ T cell-count ($Z=0.60$, $p=.55$), duration of diagnosis ($Z=.75$, $p=.46$), or age at

diagnosis (Z=.30, p=.76). Of those with HIV infection, 85.7 % of HIV and 86.8 % of HIV+AUD reported being on an antiretroviral treatment (ART) regimen and 68.6 % of HIV and 60.5 % of HIV+AUD had undetectable viral loads (<50 copies per ml) at the time of testing.

In the HIV group, the median $CD4^+$ T-cell count was 559 cells/mm^3 (quartiles=408 cells/mm^3, 800 cells/mm^3); 36 (54.1 %) HIV participants had been diagnosed with AIDS (i.e., having had an AIDS-defining event or a $CD4^+$ T-cell count <200 cells/mm^3) at some time since their HIV diagnosis. The median age at HIV diagnosis was 34.1 years (quartiles 28.4, 43.9 years) and median years since HIV diagnosis was 19.8 (quartiles 11.8, 26.3 years).

In the HIV+AUD group the median $CD4^+$ T-cell count was 536 cells/mm^3 (quartiles=318 cells/mm^3, 814 cells/mm^3), 43 (56.6 %) HIV+AUD participants had been diagnosed with AIDS at some time since their HIV diagnosis. The median age at diagnosis was 34.7 years (quartiles 28.2, 40.5 years) and median years since HIV diagnosis was 18.1 (quartiles 11.0, 24.4 years).

A number of HIV, AUD, and HIV+AUD participants had a history of a drug-related use disorder(s). In the HIV group, 5 participants had a history of opiate abuse or dependence, 13 had a history of cocaine abuse or dependence, and 13 had a history of cannabis abuse or dependence. In addition, 23 HIV participants met criteria for nicotine dependence sometime in their life, and 1 HIV participant met criteria for a lifetime diagnosis of hallucinogen abuse. No HIV participant ever had a diagnosis of sedative abuse or dependence. At the time of testing, 2 HIV participants met criteria for current drug abuse/dependence: 1 for cocaine and 1 for cannabis.

In the AUD group, 27 participants had a history of opiate abuse or dependence, 13 had a history of cocaine abuse or dependence, 9 had a history of hallucinogenic abuse or dependence, and 11 had a history of sedative abuse or dependence. In addition, 67 AUD participants had a history of cannabis abuse or dependence, and 129 participants met criteria for nicotine dependence sometime in their life. At the time of testing, 3 AUD participants met criteria for current drug abuse/dependence: 2 for opiates and 1 for cannabis.

In the HIV+AUD group, 22 participants had a history of opiate dependence, 50 had a history of cocaine abuse or dependence, 9 had a history of hallucinogen abuse or dependence, 8 had a history of sedative abuse or dependence, and 36 had a history of cannabis abuse or dependence. In addition, 48 HIV+AUD participants met criteria for nicotine dependence sometime in their life. At the time of testing, 6 HIV+AUD participants met criteria for current drug abuse/dependence: 2 for amphetamine, 2 for cocaine, and 2 for cannabis.

2.2. MRI data acquisition and quantification

T1-weighted Inversion-Recovery Prepared SPGR images were acquired on 3 Tesla GE whole body MR systems (General Electric Healthcare, Waukesha, WI) using an 8-channel phased-array head coil. (TR=6.55/5.92 ms, TE=1.56/1.93 ms, TI=300/300 ms, matrix = 256×256, thick=1.25 mm, skip=0 mm, 124 slices). Drift was corrected by adjusting scanner calibration parameters when necessary to maintain spatial stability within manufacturer guidelines, and routine phantom data were used to evaluate spatial fidelity.

Preprocessing of the T1-weighted MRI data (Adeli et al., 2019) involved noise removal (Coupe et al., 2008), correcting field inhomogeneity via N4ITK (Tustison et al., 2011), and segmenting the brain mask by majority voting (Rohlfing et al., 2004). The voting was performed with respect to the maps generated by separately applying FSL BET (Smith, 2002), AFNI 3dSkullStrip (Cox, 1996), FreeSurfer mri_gcut (Sadananthan et al., 2010), and the Robust Brain Extraction (ROBEX) method (Iglesias et al., 2011) to the bias and non-bias corrected T1-weighted MRIs.

Four regional thalamic volumes (anterior, ventral, medial, and posterior) were quantified using a modified version of THalamus Optimized Multi-Atlas Segmentation (THOMAS) for parcellating and quantifying

Table 1
Demographic characteristics of participant groups: CTRL, HIV, AUD, HIV+AUD (median, quartiles).

Group	Sex	Age	RACE[a]	Education	NART[b]	CD4 count	Lifetime alcohol (kg)	BDI-II[c]	DRS-2[d]	SES[e]
CTRL (C, n=141)	68 F, 73 M	51.3 [37.1, 64.2]	81 / 28 / 22 / 0 / 1 / 7 / 2	16 [14,18]	113 [108,119]	na	12 [3,38]	1 [0,4]	140 [138.5, 142]	22 [18,33]
HIV (H, n=65)	18 F, 47 M	53.9 [47.5, 60.1]	32 / 24 / 0 / 0 / 1 / 7 / 1	14 [12,16]	105.5 [98.3, 113]	559 [408,800]	42 [11,103]	8 [3,16]	137 [133,140]	40 [29,53]
AUD (E, n=189)	56 F, 133 M	51.6 [44.2, 58.2]	83 / 76 / 5 / 1 / 5 / 9 / 10	13 [12,15]	107 [99, 114.3]	na	925 [522,1545]	8 [3,15]	137 [133,140]	41 [30,55]
HIV+AUD (HE, n=80)	28 F, 52 M	52.1 [47.7, 58.2]	14 / 49 / 0 / 2 / 1 / 12 / 2	13 [12,14]	105 [100,110]	536 [318,814]	694 [280,1266]	10 [2,16]	136 [131,139]	40.5 [34,54]
Group Differences	p=.003	ns	p<.0001	p<.0001 C>H=E=HE	p<.0001 C>H=E=HE	ns	p<.0001 C<H<HE<E	p<.0001 C>H=E=HE	p<.0001 C>H=E=HE	p<.0001 C<H=E=HE

NOTES:
[a] Self-identified racial background: white or Caucasion/ Black or African American/ Asian/ Native Hawaiian or Pacific Islander/ American Indian or Alaskan Native/ Multiracial/ Don't Know
[b] NART – National Adult Reading Test [C: n=79, H: n=36, E: n=62, HE: n=47]
[c] BDI-II – Beck Depression Inventory –Second Edition
[d] DRS-2 – Dementia Rating Scale – Second Edition. [C: n=117, H: n=62, E: n=130, HE: n=77]
[e] SES - lower scores reflect higher socioeconomic status

thalamic regions (Fig. 1). This multi-atlas segmentation method has been shown to provide reliable and valid quantification of thalamic regional volumes using standard white-matter nulled T1-weighted data (Su et al., 2019). In the current work, a recently proposed variant of THOMAS (HIPS-THOMAS) optimized for T1 data input was used (Vidal et al., in press). We did not pose any hypothesis regarding laterality in terms of potential volume differences or relation with neuropsychological test performance. Thus, the left and right hemisphere volumes were combined and expressed as bilateral volumes. Further, within these four identified thalamic subregions, ten individual thalamic nuclei volumes were estimated (anterior ventral (AV), ventral lateral posterior (VLp), ventral lateral anterior,(VLa) ventral anterior (VA), ventral posterior lateral (VPL), pulvinar (Pul), medial geniculate (MGN), lateral geniculate (LGN), mediodorsal (MD), and centromedian (CM)). All thalamic volumes were adjusted for age- and intracranial volume (ICV) based on linear regression functions derived from the CTRL participants and applied to all data; ICV adjustment attenuated volume differences due to sex. Data from the CTRL group presented here were used in an earlier study (Pfefferbaum et al., 2023).

2.3. Cognitive and motor functional domains

Five functional domains were assessed: (1) Attention/Working Memory, (2) Executive Functioning, (3) Immediate Episodic Memory (verbal and visual), (4) Delayed Episodic Memory (verbal and visual), and (5) Motor Skills. Inclusion of tests for each domain were hypotheses driven, having demonstrated utility in assessing specific cognitive processes in individuals with HIV and AUD. Test scores were computed as age, education, and sex corrected Z-scores based on scores from 102 healthy control participants from laboratory studies (47 women, 55 men; ages 47.9±14.9 years; 50 white, 25 Black, 27 other; 15.8±2.4 years of education; 90 right-handed). Z-scores allowed for direct comparison across individual test scores within and between groups and were averaged within each domain to yield a composite score. Although most participants had scores for most tests, domain scores were calculated if the participant had at least one score within a domain. Z-score for a domain was calculated as the average Z-score of the test variables that were available for that participant.

The *Attention/Working Memory* domain included scores derived from Trails A (Reitan, 1958) or Color Trails 1 (D'Elia et al., 1996) (time in seconds to complete) and Digit Span from either the Wechsler Memory Scale – Revised (Wechsler, 1987) or MicroCog (Powell et al., 2004) (raw score) both forward and backward trials.

The *Executive Functioning* domain included scores derived from Trails B (Reitan, 1958) or Color Trails 2 (D'Elia et al., 1996) (time in seconds to complete), Digit Symbol from the Wechsler Adult Intelligence Test – Revised (D'Elia et al., 1996) or Symbol Digit (Smith, 1982) (number correct), and Phonemic Fluency (F-A-S) (Borkowski et al., 1967) (number of correct words produced).

The *Immediate Memory* domain included scores derived from the Logical Memory I subtest from the Wechsler Memory Scale – Revised (immediate free recall) (Wechsler, 1987) or the Stories subtest from the MicroCog (Story 1 and Story 2) (immediate recognition) (Powell et al., 2004) and the Rey-Osterrieth Complex Figure Test (immediate recall directly after copy condition) (Rey, 1942).

The *Delayed Memory* domain included scores derived from the Logical Memory II subtest from the Wechsler Memory Scale -Revised (delayed free recall) (Wechsler, 1987) or the Stories from the MicroCog (delayed recognition) (Powell et al., 2004) and the Rey-Osterrieth Complex Figure Test (delayed recall) (Rey, 1942).

The *Motor Skills* domain included scores derived from Grooved Pegboard (time to completion) (Matthews and Klove, 1964), Fine Finger Movement (mean number of turns with each hand) (Corkin et al., 1986), and Finger Tapping (mean of unimanual trials) (Sullivan et al., 2002).

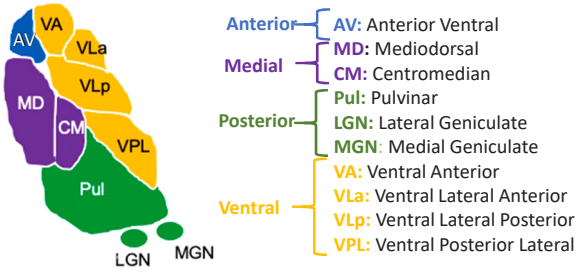


Fig. 1. Parcellation of thalamic regions and nuclei. Thalamic volumes were quantified using a modified version of THalamus Optimized Multi-Atlas Segmentation (THOMAS).

2.4. Statistical analysis

Nonparametric analyses (Kruskal-Wallis, Wilcoxon, Chi Square) were used to examine between- and within-group comparisons because several scores were not normally distributed and the number of participants in each group varied. Spearman's rho assessed the relations between cognitive and motor domain scores and thalamic regional volumes. A Bonferroni correction was employed for brain-behavior correlational analyses based on 5 comparisons (4 thalamic subregion volumes and total volume) and significance was set at $p<.01$. Secondary analyses were conducted to investigate smaller thalamic volumes (i.e., 10 thalamic nuclei).

3. Results

Statistics supporting statements about group differences and variable relations appear in Table 2 to 6 and Figs. 2 to 4 and Supplemental Figure 1.

3.1. Between-group analyses

3.1.1. Total thalamic and 4 subregional volumes

All 3 clinical groups had smaller total thalamic volume than the CTRL group. Initial 4 group comparisons revealed regional thalamic volume deficits as a function of diagnoses (Table 2; Fig. 2). Post-hoc analyses indicated that the AUD and comorbid HIV+AUD groups had significantly smaller thalamic volumes in all 4 subregions (anterior, ventral, posterior, and medial) relative to CTRLs, whereas the HIV group showed only modest thalamic regional volume deficits compared to CTRLs (all $p<.09$). No group differences among the clinical groups (HIV, AUD, HIV+AUD) reached significance for any regional thalamic volume.

3.2. Thalamic nuclei volumes

The AUD and HIV+AUD groups had smaller volumes than the CTRL group in 5 nuclei: anterior ventral (AV), ventral lateral posterior (VLp), ventral anterior (VA), pulvinar (Pul), and mediodorsal (MD) thalamic nuclei (Table 3; Supplemental Figure). The HIV group had smaller volumes than the CTRL group in only the ventral lateral posterior (VLp) thalamic nuclei. In addition, the HIV+AUD group had smaller ventral anterior (VA) thalamic nuclei volume than the CTRL, HIV, and AUD groups.

3.3. Cognitive and motor domains

Group differences were significant for all cognitive and motor composite scores (all $p<.0001$; Table 4, Fig. 3). All 3 clinical groups (HIV, AUD, HIV+AUD) scored lower than the CTRL group on all composite scores. Further, the comorbid HIV+AUD group had lower Immediate Memory scores than the HIV group and lower Executive Functioning and Motor Skills scores than the AUD group.

Table 2
Age- and head-size corrected regional thalamic volumes (median, quartiles) and group comparisons.

						2-group comparisons			
Volumes (mm3)	Control (C)	HIV	AUD	HIV+AUD	Kruskal-Wallis (H)	Wilcoxon Rank Sum	Z	p	Cohen's *d*
Anterior									
median	180	170	167	161	22.13	HIV = C	1.75	0.080	.25
quartiles	[157,208]	[143,202]	[134,195]	[133,183]	p<.0001	**AUD < C**	**3.80**	**0.0001**	**.43**
						HIV+AUD < C	**4.23**	**<0.0001**	**.60**
						HIV = AUD	1.19	0.233	.20
						HIV=HIV+AUD	1.83	0.068	.34
						AUD = HIV+AUD	1.04	0.300	.11
Ventral									
median	2808	2716	2702	2645	14.21	HIV = C	1.91	0.056	.25
quartiles	[2624,2941]	[2575,2852]	[2527,2886]	[2461,2836]	p=.003	**AUD < C**	**2.38**	**0.018**	**.24**
						HIV+AUD < C	**3.60**	**0.0003**	**.50**
						HIV = AUD	0.02	0.988	.01
						HIV = HIV+AUD	1.46	0.144	.26
						AUD = HIV+AUD	1.87	0.062	.28
Posterior									
median	2683	2621	2597	2586	14.12	HIV = C	1.72	0.086	.27
quartiles	[2518,2879]	[2399,2836]	[2380,2772]	[2315,2808]	p=.003	**AUD < C**	**3.30**	**0.001**	**.40**
						HIV+AUD < C	**3.07**	**0.002**	**.51**
						HIV = AUD	0.70	0.485	.13
						HIV = HIV+AUD	1.14	0.256	.23
						AUD = HIV+AUD	0.59	0.557	.12
Medial									
median	1367	1349	1315	1326	17.44	HIV = C	1.84	0.065	.26
quartiles	[1297,1453]	[1240,1411]	[1220,1410]	[1215,1381]	p=.001	**AUD < C**	**3.67**	**0.0002**	**.40**
						HIV+AUD < C	**3.40**	**0.0007**	**.49**
						HIV = AUD	1.00	0.315	.15
						HIV = HIV+AUD	1.32	0.186	.24
						AUD = HIV+AUD	0.51	0.609	.10
Overall Volume									
median	10296	9963	9940	9932	15.01	**HIV < C**	**2.35**	**0.019**	**.34**
quartiles	[9799,10841]	[9466,10490]	[9412,10568]	[9160,10589]	p=.002	**AUD < C**	**3.24**	**0.001**	**.35**
						HIV+AUD < C	**3.17**	**0.002**	**.48**
						HIV = AUD	0.03	0.978	.17
						HIV = HIV+AUD	0.71	0.478	.16
						AUD = HIV+AUD	0.89	0.371	.16

3.3.1. *HIV and HIV+AUD groups: detectable vs. nondetectable viral load*

Neither the subgroup of HIV participants without detectable viral load nor the subgroup of HIV participants with detectable viral load differed significantly from the control group for any regional thalamic volume (anterior, ventral, posterior, and medial). Nonetheless, the group differences between the control and HIV groups were significant for the total thalamic volume and were in the direction of deficit for each regional volume regardless of viral load.

By contrast, both the subgroup of HIV+AUD participants without detectable viral load and the subgroup of HIV+AUD participants with detectable viral load had smaller anterior [undetectable load Z=2.67, p=.0075; detectable load Z=3.95, p<.0001], ventral [undetectable load Z=2.95, p=.003; detectable load Z=2.28, p=.022], and medial [undetectable load Z=2.07, p=.038; detectable load Z=3.66, p=.0003] regional thalamic volumes than controls. In addition, the HIV+AUD subgroup with detectable viral loads had smaller posterior thalamic volume than the controls [Z=3.31, p=.0009]. Further, the subgroup of HIV+AUD participants with detectable viral loads had even smaller anterior [Z=2.27, p=.023], posterior [Z=1.99, p=.047], and medial [Z=2.28, p=.023] thalamic volumes than the subgroup of HIV+AUD participants with no detectable viral load.

3.4. *Within-group analyses*

3.4.1. *Relations between regional thalamic volumes and functional composite scores*

Spearman's rho (Bonferroni correction, p≤.01) assessed relations between thalamic regional volumes and functional composite scores within each group (Table 5, Fig. 4). No thalamic-neuropsychological test score relation reached significance in the HIV-only, AUD-only, or CTRL groups with Bonferroni correction for multiple comparisons. Only the comorbid HIV+AUD group showed significant relations between thalamic volumes and composite scores with (1) Attention/Working Memory score correlated with medial and posterior thalamic volumes, (2) Immediate Memory score correlated with anterior thalamic volume, and (3) Motor Skill score correlated with posterior thalamic volume. A multiple regression was conducted to test whether medial and posterior thalamic volumes were independent predictors of Attention/Working Memory score in the HIV+AUD group. The results indicated that posterior thalamic volume (p=.004) remained significant even after accounting for medial thalamic volume, but medial thalamic volume was not a significant independent predictor of Attention/Working Memory score after accounting for posterior thalamic volume (p=.64).

CD4+ cell count, age of HIV diagnosis, duration of HIV diagnosis, or current viral load were not significantly related with any thalamic regional volume or cognitive or motor domain scores at the Bonferroni corrected p≤.01 level in either HIV group (HIV, HIV+AUD).

Secondary analyses investigated the association and potential contribution of total lifetime alcohol consumption and a lifetime history of cocaine misuse to the prediction of regional thalamic volumes and behavioral scores (Attention/Working Memory, Immediate Memory, and Motor Skills) in the HIV+AUD group. Zero-order correlations indicated that greater lifetime alcohol consumption was associated with lower Delayed Memory composite score (rho=-.22, p=.048) and the HIV+AUD subgroup with a history of cocaine misuse had lower Immediate Memory composite scores than its counterparts without a

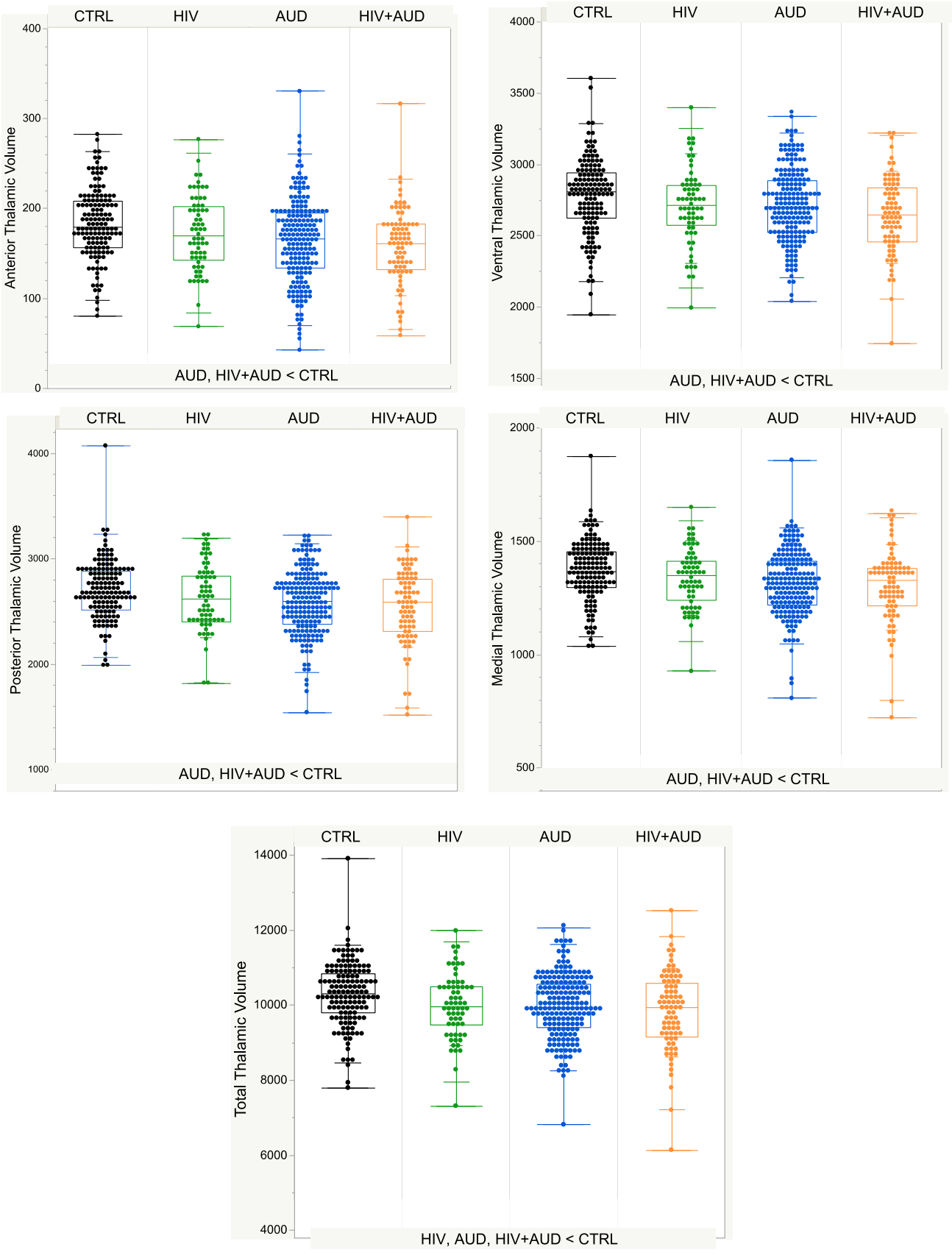


Fig. 2. Boxplots depicting volumes of the anterior, ventral, medial, and posterior thalamic regions and total thalamus in CTRL, HIV, AUD, and HIV+AUD groups.

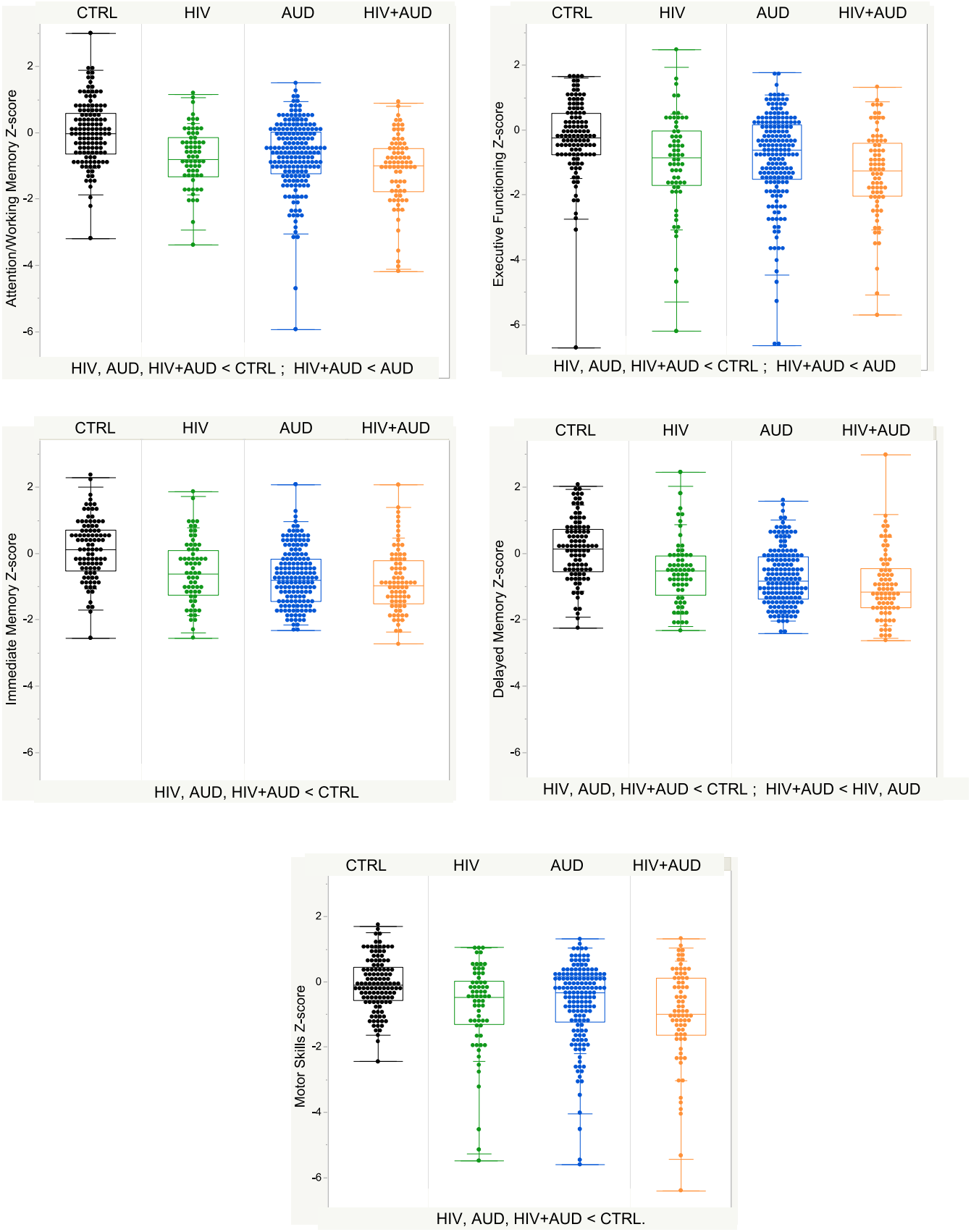
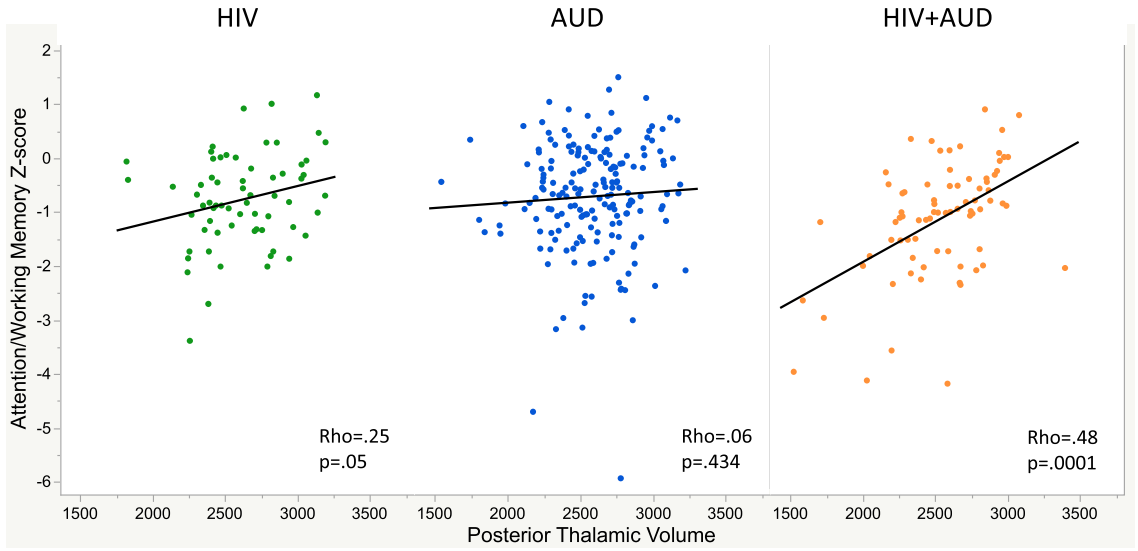
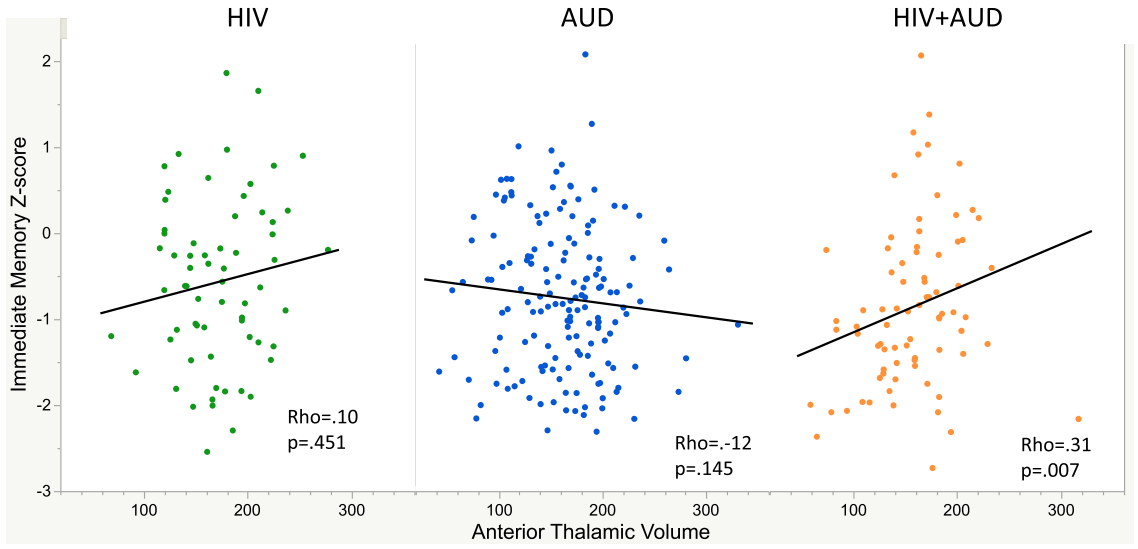


Fig. 3. Boxplots depicting age- and education-corrected Z-scores for theoretically-driven cognitive and motor composite scores in CTRL, HIV, AUD, and HIV+AUD groups.





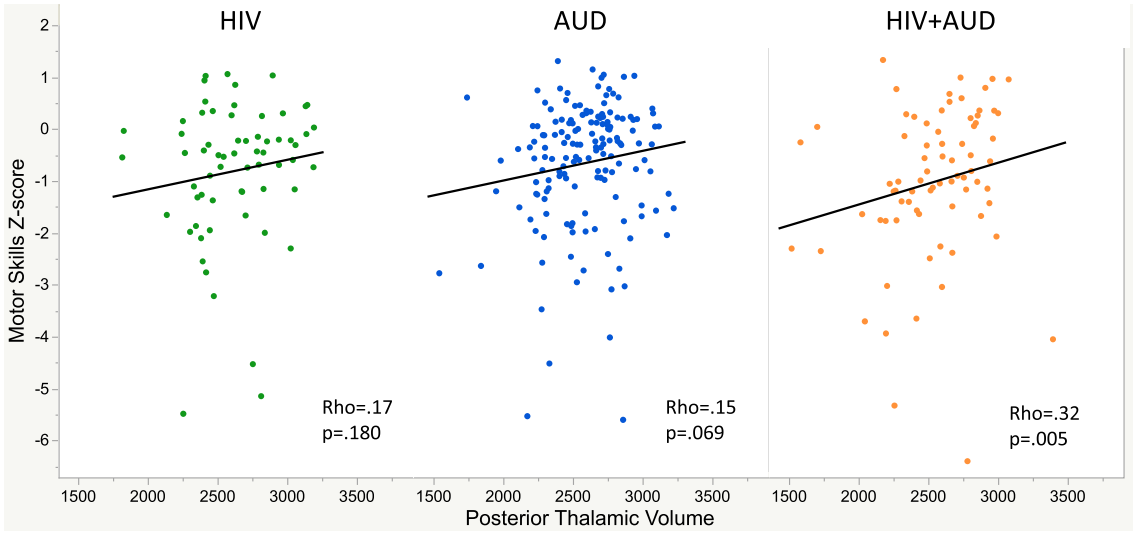


Fig. 4. Scatterplots depicting the significant relations between attention/working memory and motor skills composite scores and posterior thalamic volume and immediate memory composite score and anterior thalamic volume in the HIV+AUD group.

Table 3
Age- and head-size corrected thalamic nuclei volumes (median, quartiles) and group comparisons.

Nuclei Volumes (mm3)	Control (C)	HIV	AUD	HIV+AUD	Kruskal-Wallis (H)	2-group comparisons Wilcoxon Rank Sum	Z	p	Cohen's *d*
Anterior Ventral (AV)									
median	180	170	167	161	22.13	HIV = C	1.75	0.080	.252
quartiles	[157, 208]	[143, 202]	[134, 195]	[133, 183]	p<.0001	**AUD < C**	**3.80**	**0.0001**	**.434**
						HIV+AUD < C	**4.23**	**<0.0001**	**.598**
						HIV = AUD	1.19	0.233	.198
						HIV=HIV+AUD	1.83	0.068	.337
						AUD = HIV+AUD	1.04	0.300	.110
Mediodorsal (MD)									
median	1181	1153	1125	1116	21.64	HIV = C	1.79	0.073	.251
quartiles	[1115, 1260]	[1045, 1216]	[1043,1204]	[1042, 1186]	p<.0001	**AUD < C**	**4.04**	**<0.0001**	**.430**
						HIV+AUD < C	**3.83**	**0.0001**	**.537**
						HIV = AUD	1.30	0.193	.187
						HIV = HIV+AUD	1.65	0.099	.299
						AUD = HIV+AUD	0.74	0.461	.123
Centromedian (CM)									
median	189	189	188	192	0.59				
quartiles	[176, 199]	[166, 201]	[169, 207]	[170, 209]	ns; p=.898				
Pulvinar (Pul)									
median	2381	2331	2290	2246	14.74	HIV = C	1.70	0.090	.257
quartiles	[2212, 2540]	[2103, 2506]	[2077, 2438]	[2026, 2500]	p=.002	**AUD < C**	**3.36**	**0.0008**	**.400**
						HIV+AUD < C	**3.15**	**0.002**	**.511**
						HIV = AUD	0.78	0.435	.137
						HIV = HIV+AUD	1.19	0.232	.245
						AUD = HIV+AUD	0.65	0.513	.131
Lateral Geniculate (LGN)									
median	197	190	192	190	2.65				
quartiles	[174, 222]	[172, 213]	[165, 215]	[169, 212]	ns; p=.449				
Medial Geniculate (MGN)									
median	119	119	118	118	1.18				
quartiles	[111, 128]	[111, 129]	[108, 127]	[108, 129]	ns; p=.758				
Ventral Anterior (VA)									
median	551	531	525	509	13.27	HIV = C	0.99	0.321	.144
quartiles	[1499, 591]	[502, 574]	[490, 570]	[488, 546]	p=.004	AUD = C	1.93	0.053	.214
						HIV+AUD < C	**3.49**	**0.0005**	**.471**
						HIV = AUD	0.56	0.576	.069
						HIV+AUD < HIV	**2.39**	**0.017**	**.345**
						HIV+AUD < AUD	**2.15**	**0.031**	**.277**
Ventral Lateral Anterior (VLa)									
median	127	130	130	127	0.658				
quartiles	[107, 155]	[104, 157]	[110, 153]	[102, 159]	ns; p=.883				
Ventral Lateral Posterior (VLp)									
median	1560	1506	1510	1444	17.01	**HIV < C**	**2.31**	**0.021**	**.353**
quartiles	[1454, 1668]	[1423, 1587]	[1391, 1609]	[1357, 1591]	p=.0007	**AUD < C**	**2.91**	**0.004**	**.303**
						HIV+AUD < C	**3.79**	**0.0002**	**.523**
						HIV = AUD	0.08	0.935	.055
						HIV = HIV+AUD	1.35	0.178	.181
						AUD = HIV+AUD	1.64	0.102	.236
Ventral Posterior Lateral (VPL)									
median	547	555	543	531	4.88				
quartiles	[515, 583]	[503, 591]	[502, 588]	[494, 570]	ns; p=.181				

history of cocaine misuse (Chi Square=5.06, p=.025). No relation between lifetime alcohol consumption and regional thalamic volume was significant, and the HIV+AUD subgroup with a history of cocaine misuse had larger anterior thalamic volumes than those without a history of cocaine misuse (Chi Square=5.57, p=.02). Regression models within the HIV+AUD group predicting behavioral composite scores, taking into account a history of cocaine misuse and lifetime alcohol consumption, continued to show that (1) posterior thalamic volume was an independent predictor of Attention/Working Memory score (p<.0001, accounting for almost 25 % of the variance) and (2) anterior thalamic volume was an independent predictor of Immediate Memory score (p=.008) (Supplemental Table 1). Posterior thalamic volume was a modest predictor of Motor Skills score (p=.085) after accounting for lifetime diagnosis of cocaine misuse and lifetime alcohol consumption. Lifetime alcohol consumption was not an independent predictor of Attention/Working Memory, Immediate Memory, or Motor Skills score once thalamic volume and history of cocaine misuse was taken into account. By contrast, history of cocaine misuse was an independent predictor, alongside anterior thalamic volume, of Immediate Memory scores in the HIV+AUD group.

3.5. Relations between thalamic nuclei volumes and functional composite scores

To limit the number of comparisons, we focused our analyses on the HIV+AUD group, as this was the only clinical group to show significant

Table 4
Age- and education-corrected cognitive and motor domain composite Z-scores (median, quartiles) and group comparisons.

						2-group comparisons			
Composite	Control (C)	HIV	AUD	HIV+AUD	Kruskal-Wallis (H)	Wilcoxon Rank Sum	Z	p	Cohen's *d*
Attention/Working Memory	(n=129)	(n=65)	(n=185)	(n=77)					
median	−0.04	−0.81	−0.65	−1.00	61.97	**HIV < C**	**5.14**	**<0.0001**	**.83**
quartiles	[−0.65, 0.58]	[−1.33, −0.16]	[−1.23, 0.03]	[−1.77, −0.46]	p<.0001	**AUD < C**	**5.63**	**<0.0001**	**.70**
						HIV+AUD < C	**6.96**	**<0.0001**	**1.13**
						HIV = AUD	0.88	0.377	.06
						HIV = HIV+AUD	1.86	0.063	.37
						HIV+AUD < AUD	**3.07**	**0.002**	**.40**
Executive Functioning	(n=116)	(n=63)	(n=185)	(n=77)					
median	−0.24	−0.87	−0.62	−1.25	38.14	**HIV < C**	**3.93**	**<0.0001**	**.61**
quartiles	[−0.75, 0.51]	[−1.71, −0.02]	[−1.52, 0.16]	[−2.03, −0.40]	p<.0001	**AUD < C**	**4.06**	**<0.0001**	**.49**
						HIV+AUD < C	**5.85**	**<0.0001**	**.88**
						HIV = AUD	0.87	0.383	.09
						HIV = HIV+AUD	1.44	0.151	.21
						HIV+AUD < AUD	**2.71**	**0.007**	**.31**
Immediate Memory	(n=97)	(n=65)	(n=158)	(n=78)					
median	0.11	−0.61	−0.80	−0.98	56.31	**HIV < C**	**4.12**	**<0.0001**	**.70**
quartiles	[−0.53, 0.70]	[−1.25, 0.09]	[−1.45, −0.17]	[−1.52, −0.21]	p<.0001	**AUD < C**	**6.77**	**<0.0001**	**.81**
						HIV+AUD < C	**6.20**	**<0.0001**	**1.02**
						HIV = AUD	1.34	0.179	.14
						HIV = HIV+AUD	1.91	0.057	.30
						AUD = HIV+AUD	1.10	0.270	.15
Delayed Memory	(n=97)	(n=65)	(n=158)	(n=78)					
median	0.15	−0.53	−0.84	−1.16	62.66	**HIV < C**	**4.55**	**<0.0001**	**.73**
quartiles	[−0.54, 0.74]	[−1.27, −0.07]	[−1.39, −0.10]	[−1.64, −0.45]	p<.0001	**AUD < C**	**6.61**	**<0.0001**	**.94**
						HIV+AUD < C	**6.72**	**<0.0001**	**1.13**
						HIV = AUD	0.97	0.330	.16
						HIV+AUD < HIV	**2.75**	**0.006**	**.41**
						HIV+AUD < AUD	**2.34**	**0.020**	**.29**
Motor Skills	(n=120)	(n=64)	(n=156)	(n=75)					
median	−0.11	−0.49	−0.33	−0.99	26.89	**HIV < C**	**3.59**	**0.0003**	**.70**
quartiles	[−0.56, 0.43]	[−1.30, 0.01]	[−1.24, 0.16]	[−1.64, 0.11]	p<.0001	**AUD < C**	**3.52**	**0.0004**	**.54**
						HIV+AUD < C	**4.66**	**<0.0001**	**.84**
						HIV = AUD	0.78	0.438	.12
						HIV= HIV+AUD	1.02	0.308	.15
						AUD = HIV+AUD	1.90	0.058	.28

relations between regional thalamic volume and functional scores. We tested only those thalamic regions that yielded significant relations (i.e., anterior thalamic region which comprised the anterior ventral nucleus; posterior thalamic region which comprised the pulvinar, medial geniculate, and lateral geniculate nuclei) with functional scores (Attention/Working Memory, Immediate Memory, Motor Skills). Within the posterior thalamic region, the pulvinar (Pul) and medial geniculate nuclei (MGN) volumes were significantly correlated with the Attention/Working Memory score, whereas only the pulvinar (Pul) nucleus volume was correlated with Motor Skills score (Table 6). Anterior ventral (AV) nuclei volume (the only nuclei comprising the anterior thalamic region) was significantly correlated with Immediate Memory score.

4. Discussion

Consistent with previous reports, this study revealed thalamic volume deficits in HIV, AUD, and their comorbidity (Fama et al., 2014; Pfefferbaum et al., 2012). Critically, this study extends those reports by identifying volume deficits in specific thalamic regions (anterior, ventral, medial, and posterior) and select thalamic nuclei in AUD and HIV+AUD, with modest deficits observed in the HIV-only group compared with the CTRL group. Further, the HIV+AUD group had even smaller anterior thalamic volume than the HIV-only group and smaller ventral thalamic volume than the AUD-only group, indicating a compounded effect of diagnostic comorbidity on anterior and ventral thalamic regions.

As expected, deficits across cognitive (attention/working memory, executive functioning, memory) and motor domains were observed in the HIV, AUD, and HIV+AUD groups, with a compounded performance deficit in the comorbid HIV+AUD group in attention/working memory and delayed memory. These results are consistent with previous studies reporting cognitive and motor deficits in these diseases (Gongvatana et al., 2014), but herein possible neural mechanisms contributing to these deficits were identified in regional thalamic volumes.

Significant relations between thalamic regional and nuclei volumes and cognitive and motor functions in HIV+AUD comorbidity were identified in support of our hypotheses. Employing a correction for multiple comparisons, these relations reached significance in only the HIV+AUD group, which showed the greatest volume deficits and performance impairments of the 3 diagnostic groups. Specifically, attentional and working memory processes were related to regional posterior thalamic volume, particularly the pulvinar and medial geniculate nuclei volumes. This result comports with a recently published meta-analyses highlighting the relevance of the thalamus in attentional processes in HIV via the neural connections of the posterior thalamus (pulvinar) with frontal and parietal cortical areas post-ART (Antonucci et al., 2021).

Immediate memory processes were related to anterior thalamic volume. This finding comports with earlier human and animal studies

Table 5
Spearman Correlations: Functional domain composite scores and regional thalamic volumes.

	anterior		ventral		posterior		medial		total volume		
CTRL	rho	p	rho	p	rho	p	rho	p	rho	p	n
Attention/Working Memory	.053	.552	.115	.194	.138	.118	.094	.292	.092	.302	129
Executive Function	.045	.629	.101	.279	.150	.108	.088	.348	.105	.264	116
Immediate Memory	−.064	.535	.094	.358	−.065	.525	−.018	.864	−.013	.901	97
Delayed Memory	−.112	.276	.040	.700	−.096	.352	−.024	.814	−.027	.792	97
Motor Skills	.129	.159	.141	.124	.138	.134	.082	.376	.163	.075	120
HIV											
Attention/Working Memory	.289	.020	.235	.060	.250	.049	.215	.086	.238	.056	65
Executive Function	.123	.336	.184	.148	.104	.419	.141	.271	.113	.376	63
Immediate Memory	.095	.451	.092	.468	.168	.181	.031	.808	.162	.198	65
Delayed Memory	.001	.999	−.014	.909	.036	.776	−.061	.628	.034	.787	65
Motor Skills	.055	.665	.094	.461	.170	.180	.027	.835	.127	.318	64
AUD											
Attention/Working Memory	−.005	.950	.007	.927	.058	.434	−.041	.584	.017	.818	185
Executive Function	−.036	.629	−.124	.093	.002	.977	−.059	.423	−.104	.160	185
Immediate Memory	−.117	.145	−.060	.457	.046	.569	.0001	.998	.010	.905	158
Delayed Memory	−.099	.214	−.028	.725	.022	.780	.001	.993	−.002	.979	158
Motor Skills	.057	.478	.114	.157	.146	.069	.042	.600	.088	.275	156
HIV+AUD											
Attention/Working Memory	.229	.045	.225	.049	**.479**	**.0001**	**.291**	**.010**	**.353**	**.002**	77
Executive Function	.098	.399	.147	.120	.250	.029	.169	.141	.244	.033	77
Immediate Memory	**.305**	**.007**	.167	.145	.143	.213	.079	.491	.118	.305	78
Delayed Memory	.210	.015	.105	.361	.175	.126	.046	.691	.088	.442	78
Motor Skills	.151	.197	.122	.297	**.320**	**.005**	.086	.463	.200	.086	75

p≤.01 Bonferroni Correction

Table 6
Relations between anterior and posterior thalamic nuclei volume and select domain composite scores in the HIV+AUD group.

HIV+AUD	AV	Pul	LGN	MGN
Attention/Working Memory	.229	**.476**	.265	**.458**
Immediate Memory	**.305**	.148	.042	.118
Motor Skills	.151	**.345**	-.009	.164

Bold = p≤.01
Legend: AV = anterior ventral; Pul = Pulvinar; LGN = lateral geniculate nucleus; MGN = medial geniculate nucleus

highlighting the relevance of the anterior thalamus to mnemonic processes via connections with the hippocampus and medial temporal lobe via the fornix (Aggleton and Brown, 1999; Aggleton et al., 2010). Our results extend those findings to people comorbid for HIV+AUD.

Relations between posterior thalamus volume (i.e., pulvinar nuclei) and motor skills in the HIV+AUD group were also observed. This finding is consistent with and extends the finding of Pfefferbaum and colleagues (Pfefferbaum et al., 2023) who reported a relation between posterior thalamic volume and psychomotor function (i.e., grooved pegboard) in a group of healthy controls. Taken together, the relations observed lend support for the hypothesis that although the thalamus is relevant to a wide range of cognitive and motor processes subserved by thalamocortical and thalamocerebellar neural circuits, there is evidence for specificity of the functional roles of distinctive thalamic regions and nuclei to selective cognitive and motor processes.

Due to the number of clinical participants with a history of cocaine dependence, secondary analyses were conducted and indicated that within the HIV, AUD, and HIV+AUD groups, participants with a history of cocaine dependence did not have smaller volumes in any thalamic region and thus did not account for the primary diagnostic differences in thalamic volumes. Even after accounting for the contribution of lifetime alcohol consumption and a history of cocaine misuse, smaller anterior thalamic volume remained a significant predictor of lower immediate memory performance and smaller posterior thalamic volume remained a significant predictor of lower attention/working memory. Smaller posterior thalamic volume was a modest predictor of lower motor skills performance after accounting for lifetime alcohol consumption and a history of cocaine misuse. These findings lend support to previous reports (see meta-analyses by O'Connor et al., 2018) highlighting the importance of the association between substance-related and other comorbidities, beyond that of alcohol misuse to untoward effects of brain and behavior in people living with HIV infection.

As for our speculation of heightened deficits in individuals with HIV+AUD comorbidity, these results provide evidence for selective relations between thalamic regions and component processes of attention/working memory, immediate memory, and motor skills that were dependent on the compounded effects of HIV and AUD. We speculate that diagnostic comorbidity unmasked a pattern of brain-performance effects not detectable in the single diagnoses, which served as latent liabilities when combined.

Despite focus on the functional specificity of distinct thalamic regions, several studies have emphasized the overarching coordinating role of the thalamus based on functional MRI (fMRI) findings, highlighting the flexibility of thalamic subdivisions and their association with multiple dissociable processes considering their rich connections with numerous neural networks (Antonucci et al., 2021; Hwang et al., 2021). Emphasizing this position, a meta-analysis of 93 fMRI studies mapping co-activation thalamic-cortical/subcortical regions in relation to cognitive function identified thalamus-parietal cortex co-activation with attention/working memory processes and thalamic-inferior temporal gyrus co-activation with episodic memory processes (Antonucci et al., 2021). Appreciating the involvement of the thalamus in complex cognitive processes and the coordinating functions served through its interconnections with cortical, subcortical, and cerebellar regions, our results support the position that although the thalamus as a whole may be involved in many different cognitive processes, evidence indicates that "the function of certain nuclei appears more clearly tied to specific processes" (Antonucci et al., 2021).

Connections between the thalamus and hypothalamus, which is a critical node of the HPA axis (hypothalamic-pituitary-adrenal axis) that is central to the stress response and shown to affect cognitive processes, may also be relevant in understanding behavioral deficits. Disruption of

these connections or compromise of either structure may contribute to cognitive deficits occurring in HIV and AUD. In support of this possibility, rodent and nonhuman primate studies have reported associations among greater stress reaction, greater alcohol intake, and adverse neurobehavioral sequelae (Ben-Azu et al., 2024; Jimenez and Grant, 2017). Our data suggest that the comorbidity of HIV infection and AUD, with its concomitant stresses, could demonstrate an additive effect culminating in greater behavioral deficits and smaller ventral anterior thalamic volumes than having either disease alone. This pattern of compounded effects is consistent with animal studies reporting neurobehavioral deficits associated with AUD, infection, and psychosocial stress (Ben-Azu et al., 2024).

Limitations of this study include the disparate racial and ethnic composition of our participant groups. Although demographic variables such as education were statistically controlled for, it is not possible to account for associated life experiences that may also influence the outcome of behavioral measures. In addition, even with the heightened anatomical resolution and reliability of the THOMAS segmentation method, it remains impossible to use standard resolution T1-weighted MRI to parcellate the more than 60 thalamic nuclei, thereby necessitating delineation and quantification of clusters of thalamic regions based on a priori hypotheses highlighting specific thalamic areas and associated functions.

In summary, we identified thalamic regional and nuclei volume deficits in AUD and HIV+AUD comorbidity relative to unaffected controls, with modest deficits observed in the HIV-only group. Additionally, these clinical groups were impaired compared with controls on attention/working memory, executive functioning, memory, and motor skills. We demonstrated associations between distinct thalamic regions and nuclei and cognitive and motor processes in the HIV+AUD group, with smaller posterior thalamic volume associated with poorer attention/working memory (i.e., pulvinar and medial geniculate nuclei) and motor skills (pulvinar nuclei), whereas smaller anterior thalamic volume was associated with poorer immediate memory. Taken together, this study highlights the relevance of selective thalamic regions and nuclei to dissociable cognitive and motor processes that emerged with the compounded burden of disease comorbidity, in this case HIV+AUD.

Declaration of Competing Interest

None

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2024.111085.

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