The effect of crack cocaine addiction on the microstructure and morphology of the human striatum and thalamus using novel shape analysis and fast diffusion kurtosis imaging.

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Abstract

The striatum and thalamus are subcortical structures intimately involved in addiction, and the morphology and microstructure of these has been studied in murine models of cocaine addiction. However, human studies using non-invasive MRI has shown inconsistencies in morphology using volumetric analysis. In our study, we used MRI-based volumetric and novel shape analysis, as well as a novel fast diffusion kurtosis imaging sequence to study the morphology and microstructure of striatum and thalamus in crack cocaine addiction (CA) compared to matched healthy controls (HC). We did not find significant differences in volume and mean kurtosis (MKT) between groups. However, we found significant contraction of nucleus accumbens in CA compared to HC. We also found significant age related changes in volume and MKT of CA in striatum and thalamus that are contrary to those seen in normal brain aging. Our findings suggest that the use of finer methods and sequences is needed to characterize morphological and microstructural changes in cocaine addiction, and that brain changes in cocaine addiction are related to age.

Introduction

The striatum and thalamus are subcortical structures greatly affected in the physiopathology of cocaine addiction in animal models and possibly in humans[1]. Studies in animal models show microstructural changes in striatal medium spiny neurons, as well as striatal indirect, direct, and thalamostriatal pathways[2]. Using neuroimaging in mice, Wheeler *et al.*[3] showed volumetric reduction in ventral and posterior striatum, and expansion in the dorsal striatum in a cocaine addiction model. However, non-invasive neuroimaging studies in human cocaine addicts have shown inconsistent and conflicting neuroanatomical abnormalities in striatum and thalamus[4].

A number of studies have observed lower volume in striatum[5,6], larger striatal and thalamic volumes[7], reduced volume in anterior and increase in posterior striatum[8], or no volumetric differences whatsoever[9]. These discrepancies may be explained by methodological factors (i.e. the use of volume as a metric, the segmentation method, small sample sizes), but also, polysubstance use and cocaine delivery (inhaled vs smoked) could play an important a role. Compared to inhaled cocaine, crack cocaine (smoked) is clinically related to stronger craving, addiction and deterioration in cognition[10]. Crack cocaine use and addiction is also most prevalent in the lower socioeconomic stratum and poses a great health risk to addicts both directly and indirectly, as well as being a great social problem and expense[11]. Diffusion kurtosis imaging is a novel imaging technique known to be very sensitive to tissue microstructure. However, it has not been used for the study of substance abuse and addiction.

To better understand the effects of cocaine as the main drug of use and the mechanism of addiction, there is a need for large-scale studies using more sophisticated computational neuroanatomical methods and novel neuroimaging sequences in human addicts, while focusing on one type of cocaine delivery separately. Also, it would be important to study brain morphology in a wider range of ages (young and older addicts), as it has been shown that brain changes related to cocaine abuse tend to worsen with age in young mice[3]. Because substance addiction is known to affect both the brain gross anatomy (volume and shape) and tissue composition (microstructure), our study employs an imaging protocol allowing both types of analysis. Volumetric and shape analysis are performed based on high-resolution T1-weighted magnetic resonance imaging data. For assessment of brain microstructure we employed fast diffusion kurtosis imaging (fDKI), which is a fast acquisition MRI sequence to obtain mean kurtosis (MKT), designed for a clinical setting and shown to give similar measures as DKI. In our study we compare the striatum and thalamus morphology and microstructure of active crack cocaine addicts with healthy controls, using novel analytic computational neuroanatomical methods and a recently introduced fast DKI sequence[12].

Materials and Methods

Participants

We recruited 54 cocaine addicts and 48 healthy controls (HC) from March to December of 2015. Healthy controls were matched by age (± 2y), sex and handedness. Education was matched as closely as possible. The recruitment criteria are shown in Supplementary Table 1. We decided to only study a subset of 36 (3F) crack cocaine addicts (CA) for three reasons: 1) The known difference in terms of effects and dependency between inhaled and smoked cocaine[10], 2) the small sample size of our inhaled cocaine addicts (n = 13), and 3) crack cocaine is a more important socio-economical issue in Mexico and the world due to the toxicity of it, the stronger craving and the low social stratum where it is mostly used. We excluded 9 participants, eliminated 1 participant due to claustrophobia and 3 due to excessive movement during image acquisition. Our final sample size for the morphological analysis was 36 CA (3F) / 40 HC (2F) with a median age of 30 (18 – 48) years old. For the DKI analysis, we had a final sample size of 17 CA / 18 HC as the DKI sequence was acquired in a smaller subset of participants and due to the outlier rejection using Thompson's Tau[13].

The study was approved by the ethics committee and performed at the Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz" in Mexico City, Mexico. The study was carried out according to the Declaration of Helsinki. All participants were invited through posters place in several centers for addiction

treatment. Healthy controls were recruited from the Institute (i.e. administrative workers) and using fliers around the city. Participants had the study fully explained to them and provided verbal and written informed consent. The participants underwent clinical and cognitive tests besides the MRI. Tobacco use in this population is unavoidable; therefore we determined years of tobacco use and tobacco dependency in CA and HC (details are in Supplementary Methods and Results). Participants were asked to abstain from crack cocaine as well as other drugs and alcohol, for at least 24 hours prior to the study and were urine-tested for the presence of the drugs before the MRI scan. The clinical and MRI sessions were done the same day minimum and 4 days apart as maximum.

MRI Acquisition

Brain images were acquired using a Phillips Ingenia 3T MR system (Phillips Healthcare, Best, Netherlands & Boston, MA, USA) with a 32-channel dS Head coil. We acquired structural T1-weighted data and DKI data using the fast kurtosis acquisition scheme. Specifically, the fast kurtosis protocol from Hansen *et al.*[14] was employed requiring a total of 19 diffusion weighted volumes: 1 b = 0 scan for normalization and 9 distinct directions at each of b = 1000 s/mm2 and b = 2500 s/mm2. The data was acquired using a spin-echo single-shot EPI, TR/TE = 11820/115 ms, flip-angle = 90° and inversion recovery for CSF suppression. A total of 50 consecutive axial slices were acquired with isotropic resolution of 2 mm, matrix = 112 x 112. T1-weighted images were acquired using a 3D FFE SENSE sequence, TR/TE = 7/3.5 ms, FOV = 240, matrix = 240

x 240 mm, 180 slices, gap = 0, plane = Sagittal, voxel = 1 x 1 x 1 mm (5 participants were acquired with a voxel size = .75 x .75 x 1 mm).

T1-weighted preprocessing and image processing

T1-weighted images were converted from DICOM format to MINC for preprocessing. T1 images were preprocessed using an in-house preprocessing pipeline with the software Bpipe (http://cobralab.ca/software/mincbeast_bpipe.html)[15], which makes use of the MINC Tool-Kit (http://www.bic.mni.mcgill.ca/ServicesSoftware/ServicesSoftwareMincToolKit) and ANTs[16]. Briefly, we performed N4 bias field correction[17], linear registration to MNI-space using ANTs, we cropped the region around the neck in order improve registration quality, followed by transformation back to native space.

The native space preprocessed files were input into the MAGeT-Brain morphological analysis pipeline (http://cobralab.ca/software/MAGeTbrain.html)[18]. MAGeT- Brain is modified multi-atlas segmentation technique designed to take advantage of hard-to-define atlases and uses a minimal number of atlases for input into the segmentation process (more details in Supplementary Methods and Results). We obtained segmentations and volumetric measures for whole striatum and thalamus, as well as their subdivisions. For shape analysis, indices of surface displacement[19,20] and surface area[21] for the striatum and thalamus were derived. Briefly, surface displacements were derived based on the average of

the nonlinear portions of the 21 transformations estimated using MAGeT-Brain as the dot product between the surface normal and the local nonlinear registration vector at each point. Native surface area was estimated using a median surface representation based on the 21 surfaces from the MAGeT-Brain pipeline in native space. Surface area was estimated by assigning one-third of the surface area of each triangle to each vertex within the triangle. Finally, surface area and displacement values were blurred with a surface based diffusion-smoothing kernel of 5 mm[22]. These measures were provided for the striatum (~6,300 vertices/hemisphere) and the thalamus (~3,000 vertices/hemisphere).

DKI preprocessing

DKI data was corrected for motion and eddy currents using FSL version 5.0.9 (Oxford Centre for Functional MRI of the Brain). Tensor-based mean kurtosis (MKT) was calculated as previously described in[14] using Matlab (MathWorks, Natick, Massachusetts). MKT was calculated on unsmoothed data as we aimed for ROI based statistics (it should be noted that motion and eddy current corrections introduce slight blurring due to resampling). T1-weighted images were skull-stripped[23] and linearly co-registered to the MKT images[24]. To extract ROI based MKT values, we used the labels derived individually from the MAGeT Brain pipeline, focusing on whole left and right striatum, thalamus and nucleus accumbens (NAcc). The labels were resampled in DKI space using the T1 to DKI linear transformation, and mean MKT values from each label and each participant were calculated and stored in a CSV file for statistical analysis.

Statistical Analysis

All data were analyzed using R Statistics and RStudio. All variables were tested for normality using the Shapiro-Wilks test. Participant data was analyzed using t-tests and chi-squared when appropriate. For striatum and thalamus, we tested for group differences and group×age interactions using ANCOVA at an alpha level of 0.05 and using total brain volume, age and sex as covariates. To avoid excessive tests, for the striatum and thalamus subdivisions we first visualized the data using scatter plots and analyzed only the nuclei that showed a possible group×age interaction, similar to the striatum. We chose bilateral postcommissural caudate nucleus (PostCau) and nucleus accumbens (NAcc). We tested for linear relationships between years of consumption of crack cocaine in CA participants and striatum and thalamus volumes using correlation analysis at two-tails with an alpha of 0.05. We then used scatter plots to find linear relationships between the thalamic subnuclei and years of consumption, testing correlation only for the bilateral pulvinar. Finally, we performed a linear regression of the right pulvinar (rPul) volume and years consuming cocaine, with total brain volume, age and sex as covariates. Effect sizes were determined using sums of squares (SS) and partial-eta-squared (*partial-eta-squared = SS(effect) / (SS(effect) + SS(error)).* Tests were corrected for multiple comparisons using false discovery rate (FDR)[25] at 10% threshold and adjusted p-values are shown. The FDR threshold was chosen due to the small sample size, the high variability of results in previous studies and has been

used for shape analysis successfully[20]. For visualization purposes only, we created corrected volume variables using the residuals of the linear model.

Vertex-wise GLM analyses of surface morphometric measures were performed using RMINC (https://github.com/mcvaneede/RMINC), a statistical image analysis software package built to work in the R environment. All vertex-wise results were also corrected for multiple comparisons using FDR at 10% threshold. For surface area and displacement we tested for group differences and group×age interactions using GLM with total surface area, age and sex as covariates in surface area and only age and sex for displacement. We superimposed the striatum and thalamus subdivision atlases to label the subnuclei location of the significant clusters. Finally we created plots using the values of surface area and displacement observed in the peak vertex of significant clusters. For the DKI data, we tested for group differences and group×age interactions (ANCOVA, $\alpha = 0.05$) using age and sex as covariates. Again, FDR at 10% was used. We performed parametric correlation between years of consumption of crack cocaine (CA only) and striatum/thalamus MKT.

Results

Participant data are shown in Table 1. There were no significant relationships between the morphological data and years of tobacco use in our data (see Supplementary Methods and Results for details on the analysis).

Insert Table 1

In volume we did not find group effects (HC > CA), though CA average volume was lower than HC in striatum and thalamus (Table 2). We found significant group×age interactions in striatum volume (left: $F(1,70) = 4.31$, pFDR = 0.08, es = 0.06; right: $F(1,70) = 5.18$, pFDR = 0.07, es = 0.07), in PostCau (left: $F(1, 70) = 10.25$, pFDR = 0.02, es = 0.13; right: $F(1, 70) = 6.04$, pFDR = 0.07, es = 0.08), but not in the NAcc or thalamus. The interaction shows that striatum and caudate volume increased with age in the CA group and decreased in the HC (Figure 1). There were no significant correlations between years consuming crack cocaine and whole striatum/thalamus volume. Analyzing the scatterplots, no striatum nuclei correlated with years consuming cocaine. In the thalamic subdivisions, we found a significant correlation between years consuming with right pulvinar volume ($r = -.52$, pFDR = 0.006). The linear regression analysis confirmed this relationship ($b = -0.11$, $t(29) = -2.17$, $p = 0.04$). Thus, the longer years of crack cocaine consumption the smaller pulvinar volume.

Insert Table 2

Insert Figure 1

In displacement, we found a significant group difference (HC > CA) in the left striatum (t = 3.14, pFDR < .10) localized in the ventral striatum/NAcc area (Figure 2). We also found a non-significant group×age interaction (t = 3.28, pFDR < .20) in the same area. The left striatum displacement cluster peak vertex was not significantly correlated with years consuming (r= .23, p = .19). In general, the CA group had more contraction than HC in the cluster peak. There were no significant clusters in the thalamus. The surface area did not show significant clusters in striatum and thalamus.

Insert Figure 2

The DKI analysis did not show a group effect. However, it showed significant group×age interactions in bilateral striatum (left: F (1, 30) = 4.49, p = 0.05, es = 0.13; right: (F (1, 30) = 3.81, p = 0.06, es = 0.11), and in bilateral thalamus (left: F (1, 30) = 6.12, p = 0.05, es = 0.17; right: F (1, 30) = 5.57, p = 0.05, es = 0.16), with a higher effect size on left thalamus (Figure 3). In the striatum and thalamus interaction, MKT decreased with age in CA while it increased in HC. We found significant negative correlations between years consuming with left thalamus MKT (r= -0.62, p = 0.03) and not significant with right thalamus MKT (r= -0.47, p = 0.1), meaning the longer years they consumed the lower MKT

values. Striatum MKT showed no significant correlations. We did not find significant correlations between striatum and thalamus MKT and volume.

Insert Figure 3

Discussion

These findings suggest that morphometric changes in active crack cocaine addiction are subtle, and that volumetric analysis is less sensitive than shape analysis and DKI to measure these changes. In our sample, striatum and thalamus volume was not different between healthy controls (HC) and crack cocaine addicts (CA). This agrees with the study by[8] where they also showed no significant volumetric differences in striatum using manual segmentation. In their study, they also admitted patients with active crack cocaine addiction and had a small sample size. Narayana *et al.* [9] did not find differences as well using whole-brain voxel-based morphometry (VBM) with a similar sample size, however without specifying the type of cocaine delivery. In studies that include the thalamus, polysubstance users had greater volume in the right thalamus compared to cocaine-users[26], and a study found that cocaine-dependent subjects have decreased volume in the left thalamus compared to healthy controls[27]. The lack of group difference could be the result of several factors: variability of cocaine consumption, quality of the cocaine used, polysubstance use, and type of healthy controls used for comparison. In our case, the HC were closely paired for age, sex, handedness and education. However, we found that striatum volume increased with age in our CA group, and the effect was more

prominent in the left postcommissural caudate. In healthy human population, striatum and thalamus volumes decrease with normal aging, suggesting age-related atrophy[28,29]. Bartzokis *et al.*[30] showed accelerated age-related decline in cortical volume in cocaine addicts, though they did not study striatum nor thalamus specifically. Gray matter volume decrease shown by MRI is related to a decrease in synaptic spine density in murine models[31]. The volume increase in our CA group could suggest an increase in dendritic spines, supporting changes in synaptic plasticity due to years of cocaine consumption[32]. However, volume could be affected by non-specific microstructural changes; hence, an increase in volume by itself does not necessarily suggest an increase in dendritic spines. Instead, it could also suggest reorganization in circuitry, scarring or inflammation[32-34].

Thalamus volume was not affected by age in the CA group as in striatum. A deeper investigation showed that longer years consuming crack cocaine were correlated to decreased right pulvinar volume. The pulvinar is a thalamic nucleus highly connected to the visual cortex and the superior colliculus, and recent studies suggest one of its main functions is visual attention and modulation[35]. It is highly connected to the striatum as well[36] and related to the addictive pathology[32]. In fact, striatal availability of dopamine D2 receptor predicts thalamic functional responses to reward in cocaine addicts[37]. This suggests cocaine abuse may be related to atrophy of the thalamus and could be part of the habit reinforcement stage of the addiction cycle theory[38]. If the volume decrease is related to a decrease in dendritic spines, it may also explain inhibition and attention issues seen in cocaine addiction due to the visual-motor

connectivity of the pulvinar[33]. However, at the moment this is only possible to investigate in murine models.

The shape analysis showed significant changes in striatum anatomy between the groups, as opposed to volume. We found a greater contraction in the CA group than HC in the ventral striatum/NAcc, an important part of the reward system and addiction. The NAcc seems to be involved in the intoxication and withdrawal stages of cocaine addiction, with the consequent drug seeking behavior[32,38]. A study in adults with prenatal exposure to cocaine also found displacement differences compared to healthy controls in striatum using shape analysis[39]. However, they only studied the caudate and putamen, and their results were not corrected for multiple comparisons, though they support our own findings. A murine model of adolescent cocaine exposure determined displacement differences in striatum, with significant expansion of the lateral surface and contraction of the medial surface after 30 days of abstinence[3]. We also described non-significant age-related shape interaction with group similar to the volume analysis, showing expansion of the ventral striatum/NAcc in the CA group. A study on schizophrenia suggests that the ventral striatum/NAcc contracts with age in healthy controls[19,21], and this seems to be true for thalamus as well[40]. Our HC group showed the same age-related contraction, while the CA group showed expansion. This evidence may suggest that, although the NAcc is contracted in crack cocaine addiction, there is a tendency to expand with age. Similarly to volume, this could be related to either an increase of dendritic spines or gliosis. However, there were no linear correlations with years of cocaine use. To our knowledge, this is the first shape

analysis study in cocaine-addicted humans; therefore bigger sample sizes and longitudinal studies are needed to corroborate these results.

The DKI analysis, as with the volume, did not show group differences in striatum and thalamus MKT. It did show an age-related group interaction in striatum and thalamus with low effect sizes. MKT decreased with age in the CA group, especially evident in thalamus, and increased with age in HC. The basis of DKI is that in tissue, microstructural components hinder free (i.e. Gaussian) diffusion of water[41]. The measured diffusion MRI signal yields this deviation from normal diffusion as a non-zero kurtosis[42], providing an indirect measure of the microstructural composition of the tissue. One typically reported DKI metric is the mean kurtosis (MK) which has been associated with microstructural changes in a host of diseases such as stroke[43], but has also been shown to be sensitive to more subtle brain alterations as seen in ailments as mild traumatic brain injury[44], mild chronic stress[45], and even the brain remodeling that is part of normal aging[46]. For this study we employed a fast DKI method allowing rapid acquisition of the data needed for estimation of the tensor-based mean kurtosis (MKT)[12,14].

The fast DKI method uses a tensor-based mean kurtosis definition (the MKT) that differs slightly from the traditional mean kurtosis (MK). The agreement between MK and the rapidly obtainable MKT is, however, well-established[47], so we compare our results with the recently introduced MKT directly to studies employing conventional MK. Falanfola *et al.*[46] found whole-brain MK to increase rapidly with age until age 18, followed by a less steep increase until age 47 after

which a decline in MK was observed. For gray matter (GM) the MK was seen to continue to increase through life, whereas for white matter (WM) MK was found to increase rapidly up to age 18 and then steadily decline. Our DKI analysis showed an age-related group interaction in striatum and thalamus with low effect sizes. In agreement with that study, MKT increased with age in HC, but decreased with aging in the CA group, especially evident in thalamus. Meaning that in our study, crack cocaine addicts show an abnormal MKT decline with age, as well as decrease in thalamic MKT with years of cocaine use. A decreased MKT compared to normal brain tissue would suggest a less complex tissue microstructure with fewer diffusion barriers causing the diffusion process to be less non-Gaussian. Specific causes for this could be loss of neurites, leading to fewer cell connections, decreased tissue integrity and increased extra-cellular space. This may be corroborated by the significant negative correlations with years of cocaine use that, when compared with the pulvinar volume correlation, could suggest a reflection of thalamic atrophy. To our knowledge, this is the first study to use diffusion kurtosis imaging in substance addiction, hence more studies are needed in this and other types of substance abuse.

There were several limitations of our study. With the low effect sizes in all the morphological contrasts, it seems higher samples sizes may be needed to find more significant differences in these areas. Nevertheless, we were able to obtain significant results with our limited sample sizes. The DKI analysis had the lowest sample size, and still it showed a similar effect size than the other analyses. And unlike the rest of the analyses, the DKI showed thalamic effects

as well as striatal. Tobacco use and dependency was prevalent in half of our CA group, and although we did not find any effects in striatum and thalamus, one study has shown striatal volume and shape relation to craving tobacco. Studies in murine models may help to model the nature of the effects of poly-substance abuse.

Our findings mostly show morphological and microstructural changes in crack cocaine addicts, some of which are age-related. Most importantly, we found abnormal MKT development with age in CA, highlighting the potential for MKT and DKI in general as a method for in vivo investigation of the effects of addiction on brain microstructure. The shape analysis showed differences compared to healthy controls. We show that volumetric analysis by itself provides incomplete information about morphology and suggest that shape analysis and/or diffusion kurtosis imaging should be used in addition to better characterize substance abuse brain pathology.

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Figure Legends

Figure 1. Striatum volume group×age interaction. Scatter plot of left and right striatum corrected volume with regression lines and shadowed confidence intervals at 0.95 per group. HC = healthy controls, CA = cocaine addicts.

Figure 2. Striatum displacement. Left: Caudal anterior view of the left striatum showing the significant group cluster on ventral striatum/NAcc. Right, a) boxplot of the significant (*) displacement difference between groups in the peak vertex location (pFDR 10%); b) scatter plot of the group*age interaction in displacement showing regression lines and shadowed confidence intervals at 0.95 per group. The color bar shows the t-values at pFDR threshold of 20%. Negative values = contraction, positive values = expansion, HC = healthy controls, CA = cocaine addicts.

Figure 3. Striatum and thalamus MKT group×age interaction. Scatter plot of (top) left striatum MKT and (bottom) left thalamus MKT with regression lines and shadowed confidence intervals at 0.95 per group. HC = healthy controls, CA = cocaine addicts, MKT = mean kurtosis.

Table 1. Participant data

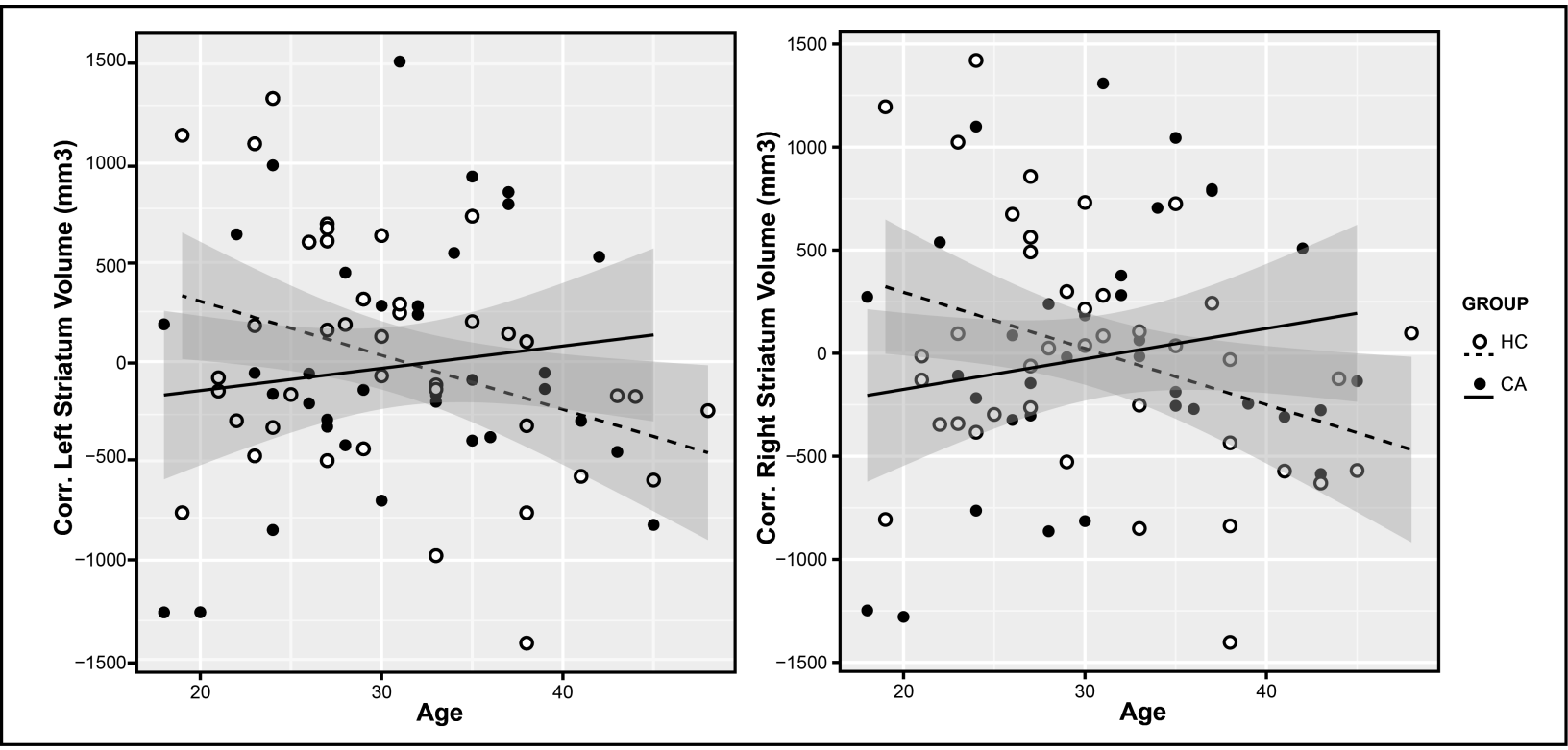
	CA (n=36)	HC (n=40)	Stats
Age	31.5 (18 – 45)	29.5 (19 – 48)	t = -0.43, p = 0.67
Education	Secondary	High school	χ^2 = 13.87, p = 0.02
Handedness **	(n = 36)	(n = 38)	χ^2 = 0.07, p = 0.96
Right	30	31	
Left	4	5	
Ambidextrous	2	2	
Onset age of consumption	(n = 35), 20 (13 – 41)	na	-
Years consuming	(n = 34), 9 (1 – 25)	na	-
Average consumption per intake **	(n = 33)	na	-
.8 gm	0	na	-
1.6 – 2.4 gm	1	na	-
3.2 – 5.6 gm	6	na	-
8 – 9 gm	16	na	-
9 – 10 gm	9	na	-
> 10 gm	1	na	-
Monthly expense in cocaine (USD)*	(n = 38), $145 (± $180)	na	-
Tobacco dependency **	(n = 33), 19	(n = 40), 3	χ^2 = 19.22, p < .001
Years of tobacco use	(n = 32), 14.03 (±8.81)	(n = 40), 5.88 (±7.94)	t = -4.08, p < 0.001

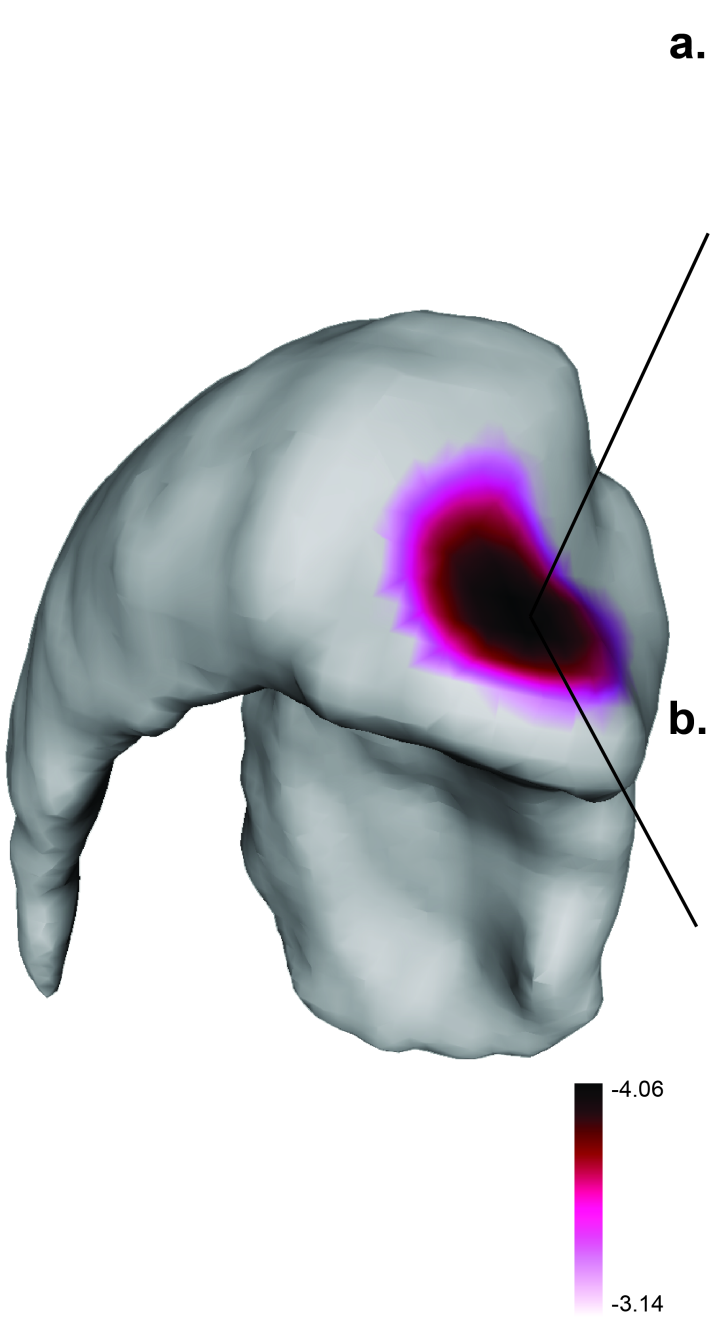
*Median (min – max) for all except: * = mean (sd), ** = count. CA = Crack cocaine addicts, HC = Healthy controls, n = due to absence of data we show each sample size per variable, na = not applicable, gm = grams, Stats = statistics, t = t-value, χ^2 = chi-squared.*

Table 2. Striatum and thalamus volumes (mm^3)

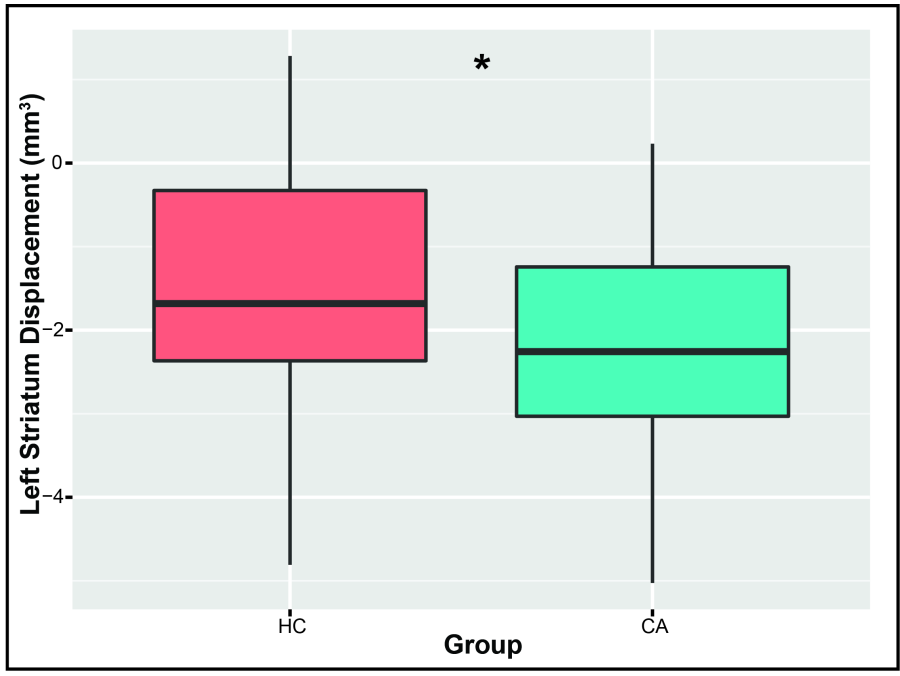
		CA	HC
Striatum			
	Left	9114 ± 708	9251 ± 1011
	Right	9130 ± 679	9248 ± 1003
Thalamus			
	Left	5641 ± 512	5752 ± 503
	Right	6024 ± 509	6124 ± 506

Mean ± standard deviation. CA = Crack cocaine addicts, HC = Healthy controls.





a.



b.