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Interactive effects of age and recent substance use on striatal shape morphology at substance use disorder treatment entry

Marc L. Copersino, Ph.D.^{1,2,†,*}, Raihaan Patel, Ph.D.^{3,5,*}, Jenessa S. Price, Ph.D.^{6,7}, Katherine Frost Visser, M.S.¹, Gordana Vitaliano, M.D., Ph.D.^{1,2}, Eric Plitman, Ph.D.³, Scott E. Lukas, Ph.D.^{1,2}, Roger D. Weiss, M.D.^{1,2}, Amy C. Janes, Ph.D.^{1,2,*}, M. Mallar Chakravarty, Ph.D.^{3,4,5,*}

¹Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA

²Harvard Medical School, Boston, MA, USA

³Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada;

[†]Corresponding author: Marc L. Copersino, Ph.D., McLean Hospital, 115 Mill Street, Mail Stop #103, Belmont, MA 02478, Phone: (617) 855-2853, Fax: (617) 855-4055, mcopersino@mclean.harvard.edu.

Marc L. Copersino, PhD, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA, McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA USA, Address: McLean Hospital, 115 Mill Street, MS #103, Belmont, MA 02478

Raihaan Patel, PhD, Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada; Department of Psychiatry, McGill University, Montreal, QC, Canada, Department of Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada, Address: Centre d'imagerie cérébrale Pavilion, Room GH-2112. 6875, boulevard LaSalle, Montreal (Quebec), H4H 1R3

Jenessa S. Price, PhD, Division of Transplant Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, Address: 9200 W. Wisconsin Ave., Suite E5700, Milwaukee, WI 53226

Katherine Frost Visser, MS, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, Address: Clinical Affective Neuroscience Laboratory, Department of Clinical Psychology, University of Georgia, 125 Baldwin Street, Athens, GA 30602

Gordana Vitaliano, MD, PhD, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA, McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA USA, Address: McLean Hospital, 115 Mill Street, Belmont, MA 02478

Eric Plitman, PhD, Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada; Department of Psychiatry, McGill University, Montreal, QC, Canada, Address: Centre d'imagerie cérébrale Pavilion, Room GH-2112. 6875, boulevard LaSalle, Montreal (Quebec), H4H 1R3

Scott E. Lukas, PhD, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA, McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA USA, Address: McLean Hospital, 115 Mill Street, Belmont, MA 02478

Roger D. Weiss, MD, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA USA, Address: McLean Hospital, 115 Mill Street, Belmont, MA 02478

Amy C. Janes, PhD, Division of Alcohol and Drug Abuse, McLean Hospital, 115 Mill St., Belmont, MA, 02478, McLean Imaging Center, McLean Hospital, 115 Mill St., Belmont, MA, 02478, Department of Psychiatry, Harvard Medical School, 25 Shattuck St, Boston, MA 02115

M. Mallar Chakravarty, PhD, Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada; Department of Psychiatry, McGill University, Montreal, QC, Canada, Department of Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada, Address: Centre d'imagerie cérébrale Pavilion, Room GH-2112. 6875, boulevard LaSalle, Montreal (Quebec), H4H 1R3

Contributors

All authors (MLC, RP, JSP, KJV, GV, EP, SEL, RDW, ACJ and MMC) contributed to the conceptualization, design, execution, and/or interpretation of the research study, as well as to the drafting, reviewing and revising of the manuscript. All authors have read and approved the final manuscript.

*Denotes equal contributions for first and last two authors

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Conflict of interest

The authors have no conflicts of interest to declare

⁴Department of Psychiatry, McGill University, Montreal, QC, Canada

⁵Department of Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada

⁶Division of Transplant Surgery, Dept of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

⁷Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Abstract

Background: Striatal neuroadaptations are regarded to play an important role in the progression from voluntary to compulsive use of addictive substances and provide a promising target for the identification of neuroimaging biomarkers. Recent advances in surface-based computational analysis enable morphological assessment linking variations in global and local striatal shape to duration and magnitude of substance use with a degree of sensitivity that exceeds standard volumetric analysis.

Methods: This study used a new segmentation methodology coupled with local surface-based indices of surface area and displacement to provide a comprehensive structural characterization of the striatum in 34 patients entering treatment for substance use disorder (SUD) and 49 controls, and to examine the influence of recent substance use on abnormal age-related striatal deformation in SUD patients.

Results: Patients showed a small reduction in striatal volume and no difference in surface area or shape in comparison to controls. Between-group differences in shape were likely neutralized by the bidirectional influence of recent substance use on striatal shape in SUD patients. Specifically, there was an interaction between age and substance such that among older patients more drug use was associated with greater inward striatal contraction but more alcohol use was associated with greater outward expansion.

Conclusions: This study builds on previous work and advances our understanding of the nature of striatal neuroadaptations as a potential biomarker of disease progression in addiction.

Keywords

striatum; morphology; MRI; plasticity; alcohol; polydrug

1. Introduction

The identification of biomarkers (i.e., measurable indices) of disease progression or chronicity of drug exposure in addiction would benefit research efforts aimed at improving the diagnosis and treatment of substance use disorders (SUD), among other ways, by enhancing patient classification and clinical subgroup detection (see Volkow et al., 2015 for review). Neuroadaptations in the striatum and its neural circuitry are regarded to play an important role in the progression from voluntary to compulsive use of addictive substances (see Everitt and Robbins, 2013, 2016; Volkow and Morales, 2015 for reviews) and provide a promising target for the identification of neuroimaging biomarkers. Accordingly, a growing body of literature links variations in global and local striatal morphology to duration and

magnitude of substance use. For example, chronic drinkers in one study had significantly smaller dorsal striatal (i.e., caudate and putamen) volume in comparison to controls that persisted for a year or more of abstinence; and, furthermore, longer duration of alcohol abstinence was associated with larger volume in the nucleus accumbens (Sullivan et al., 2005). In a study of tobacco smokers, striatal volume did not differ from controls; but lifetime smoking duration was associated with decreased volume in the nucleus accumbens and an increased volume in the putamen (Das et al., 2012). Studies of cocaine users have found striatal volumes to be smaller (Barrós-Loscertales et al., 2011), larger (Ersche et al., 2011; Jacobsen et al., 2001) or not different (Narayana et al., 2010) than that of controls; and, in one study, a negative association between lifetime duration of cocaine use and caudate volume (Ersche et al., 2011). Inconsistencies between cocaine patient versus control group findings may reflect methodological or other differences (e.g., route of cocaine administration, polysubstance use).

Variations in global and local striatal morphology have also been associated with individual neurocognitive differences relevant to addiction progression and severity. For example, one study identified a positive association between dorsal striatal volume and surface area and measures of tobacco cigarette craving (Janes et al., 2015). In a study of patients receiving treatment for stimulant use disorder, left caudate volume was positively correlated with impulsivity and executive dyscontrol (Ersche et al., 2011). In another sample of patients being treated for stimulant use disorder, cognitive performance deficits associated with striatal volume were greater in polysubstance versus individual substance users (Churchwell et al., 2012).

The patterns of findings across volumetric studies indicate that variations in global and local striatal morphology appear to be drug specific, and associated with chronicity of exposure and the number of substances used (i.e., single versus polysubstance use). The finding that patients with shorter versus longer durations of alcohol abstinence can be differentiated on the basis of striatal volume (Ersche et al., 2011) suggests that striatal morphology may also provide a measurable indicator of more recent drug exposure.

An important limitation of volumetric analyses is that averaging measurements over gross and subcomponent structures may neutralize group differences. Furthermore, measurement of volume alone does not provide a comprehensive structural characterization. Recent advances in surface-based computational analysis enable morphological assessment of subcortical structures with a degree of sensitivity that exceeds standard volumetric analysis (Garza-Villarreal et al., 2017; Kälin et al., 2017; Schuetze et al., 2016). A computational shape-analytic method developed by a member of our group (MMC) uses a segmentation methodology coupled with local surface-based shape indices (Chakravarty et al., 2013, 2015; Pipitone et al., 2014) of surface area and surface displacement (Raznahan et al., 2014) (<https://github.com/CobraLab/MAGeTbrain>). The magnitude of surface displacement provides a local measure of inward contraction or outward expansion reflecting differences in the local cell assembly, which may be due to an increase in the number of neurons, glia, or the local density of these regions. The directionality of displacement (inward or outward) is likely to be multicausal due to the interconnectivity of corticostriatal circuitry. In other words, the striatum integrates complex afferent and efferent corticostriatal pathways, and

shape deformations may be attributable to local or downstream cell loss, or neurogenesis in response to local or downstream cell loss.

Surface area and displacement are orthogonal measures that capture different dimensions of variation that are both independent of traditional volume measures and characterize the morphometry of subcortical structures more fully. Based on work done in our group examining other patient populations, surface area and displacement appear to be homologous to cortical surface area and thickness measures. Like cortical surface area, we have observed that these measures characterize neurodevelopmental phenotypes (for example see: Nadig et al., 2018; Raznahan et al., 2017; Shaw et al., 2015). However, surface displacement appears to be more sensitive to medication/environmental effects in neurodevelopmental disorders (see: Chakravarty et al., 2015; Schuetze et al., 2016). Like surface area and cortical thickness, these measures may be inter-related, but as they are, by definition, mathematically orthogonal to one another, we treat them as separate measures that can be used to better characterize structures implicated in addiction.

In a previous study using this shape-analytic method to examine differences in subcortical structure between active crack cocaine users and controls, between-group differences were identified on the basis of striatal shape but not volume (Garza-Villarreal et al., 2017). Furthermore, there was a group $\times$ age interaction such that increased age was associated with more striatal contraction (i.e., negative displacement) in controls but more striatal expansion (i.e., positive displacement) in crack cocaine users. The atypical age-related change in striatal shape among cocaine users is interesting but difficult to interpret due to the ineludible correlation between age and years of consumption. Results of that study may also have been influenced by unaccounted for amounts of recent cocaine use. The goal of the present study was to build on this previous work by using the same surface-based computational methods to examine the interactive effects of age and recent substance use on striatal shape to determine if substance use exerts an environmental influence on abnormal age-related changes in patients entering SUD treatment. We hypothesize that this shape-analytic method will be sensitive to shape deformations indicating an interaction between atypical age-related changes and patterns of recent substance use in chronic substance users. The principal significance of this study is that it uses a computational shape-analytic method that enables morphological assessment of subcortical structures with a degree of sensitivity that exceeds standard volumetric analysis, and advances our understanding of the nature of striatal neuroadaptations as a potential biomarker of disease progression in addiction that could in turn benefit research efforts aimed at improving the diagnosis and treatment of SUD.

2. Methods

2.2. Participants

Data were collected on 40 SUD patients and 51 controls, but data for 8 of the participants were excluded due to issues related to data and quality control. Study participants providing complete and useable data sets examined in the present study included 34 patients entering the Alcohol and Drug Abuse Treatment Partial Hospital Program at McLean Hospital, and 49 controls from the local community without a current or past SUD (except for nicotine in

the form of tobacco cigarettes). All study subjects underwent brain imaging at the McLean Imaging Center in Belmont, Massachusetts, USA. Controls were required to have a negative urine drug screen on the day of their brain scan.

Participant recruitment exclusion criteria included neurologic illness or injury, MRI contraindications, any psychiatric condition that would interfere with provision of consent or valid self-report, acute intoxication, pregnancy, or safety concerns. Participants could not be in withdrawal based on subjective report, observation of clinical signs, or the determination of high blood pressure or tachycardia at the time of MRI scanning. The McLean Hospital IRB approved this study. Written informed consent was obtained from all participants.

2.3. Interviewer-administered assessments

Participants were administered a clinical assessment battery on the day of their MRI scan by a trained rater to collect demographic, self-reported substance use and diagnostic data. Self-reported past 30-day and lifetime substance use data were collected using the Addiction Severity Index (ASI; McLellan, et al., 1992). Data regarding DSM-IV substance use and co-occurring disorders were collected using the Structured Clinical Interview for DSM-IV Research Version (First, et al., 1996).

2.4. Magnetic resonance imaging data acquisition

Participants underwent a high-resolution structural MRI brain scan via Siemens Trio 3 Tesla scanner (Erlangen, Germany) with a 32-channel head coil. Multi-planar rapidly acquired gradient echo-structural images (MPRAGE), were acquired with the following parameters: resolution = $1.0 \times 1.0 \times 1.33$ mm, repetition time (TR) = 2.1 s, echo time (TE) = 3.3 ms, slices = 128, matrix = 256×256 , flip angle = 7 degrees. Functional MRI data were collected subsequent to structural image acquisition with different aims and are not reported here.

2.5. Image processing and analyses

All T1-weighted MRI data were converted to the MINC file format (<http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC>) and underwent preprocessing using the bpipe tools from the CoBrA Laboratory (<https://github.com/CobraLab/minc-bpipe-library>). This process includes cropping of the neck region to improve downstream image processing, N4 correction of bias field intensity inhomogeneity (Tustison et al., 2010), and brain extraction using BEaST (Eskildsen et al., 2012). Output brain masks from BeAST were used to compute total brain volume of each participant.

Striatum volume and morphometry were measured using the Multiple Automatically Generated Templates (MAGeT) Brain pipeline (<http://cobralab.ca/software/MAGeTbrain/>) (Pipitone et al., 2014; Chakravarty et al., 2013). In brief, this pipeline uses a single atlas of the basal ganglia and thalamus derived from the detailed analysis of serial histological data (Chakravarty et al., 2006) to segment images in a subject dataset. MAGeT Brain bootstraps the segmentation by using an intermediate template library of 21 participants sampled from the entire population under study chosen to represent that variability with respect to age and sample distributions (i.e., case vs. control status). Non-linear registration of the single atlas to 21 templates allows the templates to act as a population specific atlas set. Further,

warping of each template to participant results in growing the number of possible candidate segmentations to 21, which are then fused using a majority-vote to generate the final segmentation. These methods have been validated and show high correspondence with manual segmentations (Chakravarty et al., 2013). Other studies showed strong criterion-related validity of this striatal segmentation method in comparison to manually-defined labels (Pearson $r=0.92$; Makowski et al., 2018), and strong reliability of striatal segmentation and atlas-to-template warping in comparison to serial histologically-derived atlases (Dice's Kappa=0.884; Tullo et al., 2018).

Surface-based representations of the striatum were generated using a similar methodology as previously described (Voineskos et al., 2015; Raznahan et al., 2014). Here, surfaced-based representations are warped from atlas to participant, and coordinates for developing the final surface were generated based on the median location of possible 21 surface generated. Vertex-wise measures of surface area were generated via averaging of the three polygons at the intersection of each vertex. Surface area measures were then blurred with a 5 mm surface-based blurring kernel (Kim et al., 2005).

Measures of inward and outward surface displacement (in millimeters) were measured using methods previously described (Chakravarty et al., 2015; Janes et al., 2015). Briefly, all transformation paths from each participant to the original atlas are concatenated, yielding 21 unique transformations mapping each participant through a template and further to the atlas. These 21 transformations are then averaged and inverted and any residual global linear effects were explicitly removed from the averaged transformation; the dot product between the surface normal at each vertex in the striatum and the three-dimensional displacement defined in the transformation is then estimated (Lerch et al., 2008) to compute the nonlinear change along the surface normal of each vertex. Positive and negative displacement values indicate outward and inward displacement of the participant relative to the model. Deformation signals along the tangent plane of each surface normal displacement are tested for significance using the same statistical models.

2.6. MRI volumetric and morphometric statistics

Volumetric analyses of the striatum were performed in the R statistical environment using a general linear model that included age, sex, and total brain volume (TBV) in the model to compare patient versus control striatum volume. Effect sizes for between group comparisons are reported using Hedges' g (Hedges and Olkin, 1985) and following Cohen's (1988) convention for describing small (0.2), medium (0.5) and large (0.8) effect sizes. To determine the specific effects of recent drug use, we performed a within patient analysis where we examined the drug use $\times$ age interaction while including age, sex, TBV, and nicotine and alcohol use in the last 30 days in the linear model. Attribute assignment based on days of substance use in the past 30 days with a cutoff score of 15 (i.e., ≥ 15 days of use in the past 30 was characterized as "higher" and < 15 days was characterized as "lower" use) were made post analysis to facilitate visual inspection of interactions. This cut score was chosen because it equates to substance use that was "less than half of the time" versus "equal to or more than half of the time." To further determine the effects of the possible confounds of concomitant alcohol use, we similarly examined alcohol use $\times$ age interactions and

included age, sex, TBV, and nicotine and drug use in the last 30 days in the linear model. Effect sizes for interaction analyses are reported using partial eta squared (Olejnik and Algina, 2003) and following Cohen's convention for describing small (.01), medium (.09) and large (.25) effect sizes for the coefficient of determination (Cohen, 1988).

Secondary planned analyses examined the age-related trajectories of striatal volume in SUD patients relative to controls to determine how normative aging may be influenced by substances of abuse. We also examined the association between striatal morphology and age in the control group to characterize normative age-related changes in striatal morphology in our sample.

Vertex-wise morphometry (surface area and displacement) were analyzed using the same statistical models; however, since overall volume and residual linear portions of the transformation were explicitly modelled and removed from the deformation fields TBV was not included in these models. Vertex-wise surface area and displacement measures were analyzed using the RMINC statistical package (<https://github.com/Mouse-Imaging-Centre/RMINC>) using a general linear model that included age $\times$ frequency of use in the past 30 days, sex and nicotine consumption. All vertex-wise surface area values were divided by total striatal surface area to account for global structure-wise difference in total size. Vertex-wise measures of surface area and displacement were corrected for multiple comparisons using a 10% false discovery rate (FDR) (Genovese et al., 2002; Nichols and Hayasaka, 2003) as in previous work (Garza-Villarreal et al., 2017; Janes et al., 2015). In brief, FDR controls the expected proportion of false positives among suprathreshold voxels, with the threshold being determined from the observed p-value distribution. It is computed in a within structure and within model fashion – i.e., for a given model and structure, a linear model is run at every vertex, and FDR is computed with number of comparisons set to the number of vertices in the structure. Interaction effect sizes using partial eta squared were computed on a per vertex basis where appropriate.

3. Results

3.1. Subject demographic and substance use characteristics

Patient and control groups did not differ in age, sex, education, or nicotine use, but were disproportionate with respect to race (see Table 1). Substance use disorder patients reported using the following substances in the past 30 days: alcohol (79%), cannabis (56%), opioids (55%), sedatives (53%), and stimulants (32%); 82% of patients reported using multiple substances (see Table 2). Days of alcohol use was strongly negatively correlated ($r = -.64$, $p < .001$) with days of any drug use (opioid, sedative, stimulant, cannabis) in the past 30 days. Days of any drug use was positively correlated with use of opioids ($r = .60$, $p < .001$), cannabis ($r = .55$, $p = .001$), sedatives ($r = .46$, $p < .01$), and stimulants ($r = .44$, $p = .01$) in the past 30 days. Given these two distinct patterns of use in the past 30-days, quantity of substance use among the 34 SUD patients was examined as both (1) days of any drug use (opioid, cannabis, sedative, stimulant) controlling for days of alcohol use, and (2) days of alcohol use controlling for days of any drug use. These are referred to as 'alcohol' and 'any drug use.' Across all SUD patients, 21 patients reported both alcohol and drug use in the past 30 days, 8 patients reported drug use only, and 5 patients reported alcohol use only.

With respect to associations between age and lifetime substance use, SUD patient age was correlated with years of regular alcohol use ($r=.78$, $p<.001$) and years of multiple drug use ($r=.36$, $p=.039$). For individual substances, SUD patient age was correlated with years of lifetime use of opioids ($r=.44$, $p=.009$) and stimulants ($r=.41$, $p=.017$), but not sedatives ($r=.27$, $p=.110$) or cannabis ($r=.12$, $p=.516$).

3.2. MRI volumetry and morphometry results

3.2.1. Patient versus control group analyses—In comparison to controls, SUD patients exhibited smaller striata bilaterally (left: $t=-2.3$, $p=0.02$; right: $t=-2.1$, $p=0.04$; see Fig 1A, 1B). P-values adjusted for 10% FDR (left: $p=0.04$; right: $p=0.05$) retain significance in the left striatum and fall at the cut-off for statistical significance in the right striatum. However, the magnitude of the difference in volume is small (Left: Hedge's $g = 0.25$, 95% CI: $-0.19 - 0.7$; Right: Hedge's $g = 0.21$, 95% CI: $-0.24 - 0.65$). Morphometry results demonstrate no striatal surface area or shape differences between SUD patients and controls.

3.2.2. Within patient group analyses—Any drug use $\times$ age interaction revealed a close to significant effect in the right striatum ($t=2.4$, FDR adjusted $p=0.08$, magnitude of age dependent effect of drug use = 0.02 , 95% CI: $-0.09 - 0.06$) and close to significant effect in the left striatum ($t=2.0$, FDR adjusted $p=0.09$, magnitude of age dependent effect of drug use = 0.02 , 95% CI: $-0.09 - 0.04$), such that increased drug use in the past 30 days among older patients was associated with smaller volumes; see Fig 1C, 1D.

However, analysis of vertex-wise displacement revealed a statistically significant 'any drug use $\times$ age' interaction effect bilaterally across the head of the caudate nucleus and ventral striatum that extends laterally to the ventral putamen (see Fig 2). There were no statistically significant 'any drug use $\times$ age' effects on the surface along the tangent plane of displacement. When examining the interaction effects, we observe that in older SUD patients, increased drug use over the past 30 days corresponded to larger inward displacements (reflecting greater concavity), while in younger SUD patients this effect was reversed (see Fig 2). Partial eta squared of the interaction effect at a selected peak vertex in the left striatum was 0.45 (95% CI: $0.14 - 0.75$), which may be characterized as a "very large" effect size. In the right striatum, partial eta squared at a selected peak vertex was 0.45 (95% CI: $0.17 - 0.72$), which may also be characterized as a "very large" effect size. Supplementary Figure 1A plots the partial eta squared of the drug use and age interaction for each vertex. There were no significant 'any drug use $\times$ age' interactions found when analyzing vertex-wise surface area.

The analysis of displacement in relation to the alcohol use $\times$ age interaction was statistically significant in a similar location – i.e., across the head of the caudate nucleus and ventral striatum, extending laterally to the ventral putamen (see Fig 3). Also similar was that the interaction revealed displacement differences that were more apparent and reversed in older SUD patients. Unlike the interaction effect associated with any drug use, greater alcohol use was associated with higher outward facing displacement (convexity) and lower alcohol use was associated with more inward facing displacement in older SUD patients (concavity; see Fig 3). Partial eta squared of the interaction effect at a selected peak vertex in the left

striatum was 0.38, (95% CI: 0.07 – 0.68), which may be characterized as a “very large” effect size. In the right striatum, partial eta squared at a selected peak vertex was 0.33 (95% CI: 0.07 – 0.55), which may also be characterized as a “very large” effect size. Supplementary Figure 1B plots the partial eta squared of the alcohol use and age interaction for each vertex. There were no significant ‘alcohol $\times$ age’ interactions found when analyzing vertex-wise surface area.

Analyses examining single drug (non-alcohol) use $\times$ age interactions that included age, sex, TBV, and nicotine and alcohol in the linear model were conducted *post hoc* in an exploratory manner to facilitate interpretation of our findings. For example, examining the influence of individual substances on striatal shape could help inform us if our ‘any drug use’ $\times$ age interaction was influenced by any drug in particular, or if the pattern of findings was based on a combination of substances. The analysis of displacement in relation to opioid use revealed a significant opioid use $\times$ age interaction effect bilaterally across the anterior putamen (medial-lateral plane) and extending laterally to the posterior putamen. Similar to the results for ‘any drug use’ and ‘alcohol use’, the interaction revealed displacement differences were more apparent in older SUD patients. However, unlike the interaction effect associated with any drug use, greater opioid use was associated with higher outward facing displacement (convexity) and lower opioid use was associated with more inward facing displacement (concavity). There was no ‘opioid use $\times$ age’ interaction effect along the tangent plane of displacement. Neither analysis of displacement in relation to cannabis or sedative use revealed an influence on striatal shape. Stimulant data lacked sufficient cell sizes to examine their interaction effects in isolation of other substances. Although our study was not powered for analyses examining single drug (non-alcohol) use $\times$ age interactions, the pattern of findings seems to support that the observed ‘any drug use’ $\times$ age interaction was not influenced by any drug in particular, but rather was based on a combination of substances.

3.2.3. Within control group analyses—Analyses of the association between striatal morphology and age in the control group were performed to characterize normative age-related changes in striatal morphology in our sample. Controlling for sex and smoking status, a linear model showed left and right striatum volume had a significant decrease with age in controls ($p < 0.05$). Neither surface area nor displacement was significantly associated with age in the control group. Furthermore, there were no interactive effects of age $\times$ smoking status on striatal volume, surface area or displacement.

4. Discussion

This study identified differences in striatal morphology according to age and recent substance use in patients entering SUD treatment and in comparison to controls using a new segmentation methodology (Pipitone et al., 2014; Chakravarty et al., 2013) coupled with local surface-based indices of surface area and displacement that provided a comprehensive structural characterization of the striatum. In comparison to controls, SUD patients exhibited smaller striata bilaterally, but the magnitude of the difference in volume was small. There were no between group differences in striatal surface area or shape.

Within the patient group, there was a significant interaction between age and substance use in the past 30 days such that older persons showed significantly greater bilateral shape deformation (striatal displacement) in comparison to younger adults. However, patients had two distinctly different patterns of substance use in the past 30 days such that alcohol use was strongly negatively correlated with any drug use (opioid, sedative, stimulant, or cannabis); and drug use was highly intercorrelated. Furthermore, these two distinct substance use patterns were differentially associated with striatal displacement directionality. In other words, greater alcohol use was associated with higher outward pointing displacement (reflecting greater convexity), and greater polydrug use was associated with larger inward pointing displacements (concavity). The combination of inward and outward regional striatal displacements across SUD patients likely accounts for the absence of shape differences between SUD patients and controls. Finally, there were no within patient group interactions between age and substance use on striatal volume or surface area.

Analyses examining single drug (non-alcohol) use $\times$ age interactions were conducted post hoc in an exploratory manner to facilitate interpretation of our findings. Specifically, after finding opposite deformation patterns in alcohol versus any drug use, we conducted the single drug (non-alcohol) analyses to explore whether the 'any drug use' $\times$ age interaction might have been influenced by any single drug in particular. Results of the single drug analyses appear to support the idea that the observed 'any drug use' $\times$ age interaction was not influenced by any drug in particular, but rather was based on a combination of substances.

Relatively little is known about the causes and consequences of striatal morphometric changes. One study identified rapid and reversible changes to striatal gray matter (GM) density following administration of haloperidol to neuroleptic-naïve healthy male subjects that authors attributed to rapid D2 receptor blockade (Tost et al., 2010). Non-striatal structural changes (specifically volume loss) in GM density have also been attributed in clinical studies to loss of dendrites and their synapses (Kassem et al., 2013), and to changes in interstitial (Reiss et al., 2004) and cerebrospinal (Naegel et al., 2017) fluid. Increases in GM volume are also theorized to result from non-specific microstructural changes associated with circuitual reorganization and tissue inflammation or scarring (Everitt and Robbins, 2005; Volkow and Morales, 2015; Zatorre et al., 2012).

Different lines of research support striatal abnormality as both a phenotype for (Ersche et al., 2012), and consequence of (Wheeler et al., 2013) substance use disorder. The present findings preclude drawing conclusions about causality but do suggest that magnitude and directionality of striatal displacement are associated with cumulative lifetime and recent patterns of substance use. Koikkalainen and colleagues (2007) identified age-related changes in healthy subjects that differ from the present findings, including bilateral inward displacement at the juncture of the caudate nucleus head and body, inward displacement of the left anterior putamen, and outward displacement of the left globus pallidus. Similar to the present study, Garza-Villarreal and colleagues (2017) identified age-related changes in striatal morphology associated with chronic cocaine use that are contrary to those seen in normal brain aging.

Although our single-time-point data do not permit assessment of the latency of striatal shape changes, Tost and colleagues (2010) provide evidence of rapid-onset short-latency volumetric changes in striatal gray matter following haloperidol administration. That study did not, however, incorporate measures of striatal shape deformation. In the present study, older SUD patients showed significantly greater bilateral shape deformation in comparison to younger SUD patients. But displacement directionality was associated with the amount of recent substance use. Specifically, among older SUD patients, high alcohol consumption was associated with greater outward pointing displacement, but low alcohol consumption was associated with greater *inward* pointing displacement. Similarly, greater polydrug use was associated with larger inward pointing displacement, but low polydrug use was associated with larger *outward* pointing displacement.

For a complete interpretation of the results, some study limitations should be noted. One limitation of the present study is our inability to separate aging effects from the cumulative effects of lifetime substance use. In a previous study that used the same surface-based computational methods to analyze striatal morphology in substance users (Garza-Villarreal et al., 2017), investigators had difficulty differentiating atypical age-related change in striatal shape from the cumulative effects of a single substance (crack cocaine). Patients in the present study used notably more substances; and age was correlated with both years of regular alcohol and years of multiple drug use, which limited our ability to differentiate the effects of aging from cumulative lifetime exposure to substances. The pattern of bilateral shape deformation identified in older SUD patients in the present study is, however, contrary to what has been observed in normal brain aging (see Koikkalainen et al., 2007). Furthermore, within our control subjects, although our results showed age-related decline in striatal volume consistent with Koikkalainen et al. (2007), our results showed no age-related shape deformation. This discrepancy may be attributable to our subjects being younger (i.e., 18–41 vs. 19–55 years) or methodological differences in data analysis.

Another limitation of the present study is the unknown effect of tobacco smoking on striatal morphology outcomes. Our results should not reflect the effects of cigarette smoking because there were no between-group differences with regard to current or lifetime nicotine use, and statistical analyses controlled for past-30 day nicotine use. However, given the uniquely different effects of multiple substance use on striatal morphology, tobacco smoking may have had unknown effects.

A third limitation of the present study is the absence of longitudinal data, which makes us unable to comment on potential striatal shape changes associated with abstinence duration. Those data would have been helpful in understanding the persistence or reversibility of shape changes. For example, one mouse imaging study suggests that striatal shape alteration induced by chronic cocaine exposure persists following one month of abstinence and may be associated with continued drug-seeking behaviors (Wheeler et al., 2013). The absence of longitudinal data also precludes examining the test-retest reliability of our findings within the control group and change associated with enrollment in the treatment program.

A fourth limitation of the present study is the absence of accompanying data to associate shape changes with other sequelae of SUD disease progression. Because the striatum is

functionally heterogeneous and topographically organized, the functional relevance of specific deformations requires consideration of the surface location in combination with accompanying clinical measures. A structural-functional association in striatal shape deformation was observed in one previous study examining the relationship between cigarette craving and striatal morphology (Janes et al., 2015). In that study, cue-induced tobacco cigarette craving was associated with shape deformations for both local contractions and expansions in the right striatum, suggesting that striatal morphology and behavioral aspects of addiction may be linked (Janes et al., 2015). In the present study, shape deformations associated with cumulative lifetime and recent patterns of substance use were prominent in the ventral striatum. Future studies linking striatal shape deformation to functional changes, such as those reflecting disengagement of the ventral striatum in mediating behavioral control of drug-seeking behavior (Everitt and Robbins, 2013) would further strengthen evidence for these neuroadaptations as a potential biomarker of disease progression in addiction.

A final limitation of our study is the sample size. Particularly in the within patient analyses, we are limited to 34 substance users. In an effort to increase the robustness of our results, we employ a standard false discover rate correction. We also use the regression coefficients as unstandardized effect sizes in order to convey the magnitude of the reported effects, in addition to statistical significance. These analyses show that our results have large magnitudes in comparison to the observed normal deviations of the morphometric variables in this sample. Nonetheless, with a lower sample size we can only confidently describe results of the given sample, and caution must be used when generalizing to larger populations.

The strength of this study is its use of a segmentation methodology coupled with local surface-based shape indices (Chakravarty et al., 2013, 2015) of surface area and surface displacement (Raznahan et al., 2014). These three complementary indices provide a comprehensive structural characterization that is more sensitive to anatomical changes than typical measures of regional volume or surface area alone.

Another strength of this study is that the effect sizes of the primary outcomes are notably large. We hypothesized that the shape-analytic method used in the present study would be sensitive to shape deformations indicating interactions between atypical age-related changes and the two predominant patterns of recent substance use in our SUD patient sample. Consistent with our hypothesis, our results showed significant ‘any drug use $\times$ age’ and ‘alcohol use $\times$ age’ interactions with effect sizes that can be characterized as “very large.”

5. Conclusions

The search for biomarkers of disease progression or chronicity of drug exposure that would benefit research efforts aimed at improving the diagnosis and treatment of SUD has been elusive (Volkow et al., 2015). New shape analytic methods suggest that striatal morphology may provide a biomarker in neurodegenerative disease progression, linking structural abnormalities to complex corticostriatal disease mechanisms (see Looi and Walterfang, 2013). Similarly, striatal neuroadaptations are regarded to play an important role in the

progression from voluntary to compulsive use of addictive substances and may provide a target for the identification of neuroimaging biomarkers. Accordingly, a growing body of literature links variations in global and local striatal morphology to duration and magnitude of substance use. Clinical biomarkers of addiction associated with neuroanatomical variations of the striatum would, for example, be beneficial in examining the effectiveness of novel pharmacotherapies such as memantine, which has been shown to have neuro-protective effects against striatal plasticity and attenuate addictive behaviors in animal models (Mancini et al., 2015). The present study identified anatomical variations associated with age and acute exposure in SUD patients that advance our understanding of the nature of striatal neuroadaptations as a potential neuroimaging biomarker of disease progression that could be helpful in developing and refining new SUD treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Effects of cumulative and recent substance use on striatal shape are examined
- Striatal shape deformity was measured as inward and outward surface displacement
- Surface displacement was associated with days of past-month use in older patients
- Cumulative and acute exposure may affect disease progression-related plasticity

Figure 1.

A and 1B show significant volumetric differences between SUD patients and controls found in both the left and right striatum (left: $t=-2.3$, $p=0.02$; right: $t=-2.1$, $p=0.04$). P-values adjusted for 10% FDR (left: $p=0.04$; right: $p=0.05$) retain significance in the left striatum and fall at the cut-off for statistical significance in the right striatum. Figure 1C and 1D plot the results of the significant drug use $\times$ age interaction for both left ($t=2.0$, $p=0.09$) and right ($t=2.4$, $p=0.04$) striatum volume, which only trend to significance after p-values are adjusted based on 10% FDR (right: $p=0.08$; left: $p=0.09$).

Figure 2. shows displacement differences in high drug users in comparison to low drug users. Superior, inferior, left sagittal and right sagittal views of the striatum are shown in the left and right panels. In the center, the left and right striatum are placed within the cortex for further orientation. Plots A and B display the displacement measurements at a peak vertex denoted by the yellow markers, where results were strong (A: left striatum, B: right striatum). This is done simply to visualize the trend of the significant interaction found. High drug users showed decreased displacement in comparison to low drug users in both the left and right striatum. All results are corrected to 10% FDR.

Figure 3. shows displacement differences in high alcohol users in comparison to low alcohol users. Superior, inferior, left sagittal and right sagittal views of the striatum are shown in the left and right panels. In the center, the left and right striatum are placed within the cortex for further orientation. Plots A and B display the displacement measurements at a peak vertex denoted by the yellow markers, where results were strong (A: left striatum, B: right striatum). This is done simply to visualize the trend of the significant interaction found. High alcohol users showed increased displacement in comparison to low alcohol users in both the left and right striatum. All results are corrected to 10% FDR.

Table 1.

Demographic and Smoking Characteristics of 34 Patients Receiving Treatment for a Substance Use Disorder, and 49 Control Subjects

Variable	Patients (n=34)	Controls (n=49)	p
Sex [% (n) Female]	41 (14)	53 (26)	.37
Race [% (n) Caucasian]	91 (31)	63 (31)	.01
Age [Mean (SD) years]	30 (10)	28 (6)	.23
Age (Min-Max)	18–51	18–41	--
Education [Mean (SD) years]	14 (2)	15 (2)	.43
Tobacco smoker? [% (n)Yes]	68 (23)	75 (37)	.46
Years Smoking [Mean (SD) years]	9 (8)	11 (6)	.38

Table 2.

Alcohol and Drug Use Characteristics and Diagnoses of 34 Patients Receiving Treatment for a Substance Use Disorder

	Mean (SD) or % (n)	Min-Max
Alcohol Severity Composite (ASI)	.304 (.334)	0.0–.91
Drug Severity Composite (ASI)	.197 (.144)	0.0–.42
Alcohol		
Days out of Past 30	8 (9)	0–26
Lifetime Years	9 (0)	0–31
Use Disorder	50% (17)	--
Opioid		
Days out of Past 30	8 (10)	0–30
Lifetime Years	2 (3)	0–17
Use Disorder	53% (18)	--
Sedative		
Days out of Past 30	4 (7)	0–28
Lifetime Years	1 (2)	0–6
Use Disorder	26% (9)	--
Stimulant		
Days out of Past 30	3 (6)	0–21
Lifetime Years	2 (4)	0–20
Use Disorder	23% (8)	--
Cannabis		
Days out of Past 30	6 (9)	0–28
Lifetime Years	6 (5)	0–20
Use Disorder	44% (15)	--