Cannabis-Related Working Memory Deficits and Associated Subcortical Morphological Differences in Healthy Individuals and Schizophrenia Subjects

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Cannabis use is associated with working memory (WM) impairments; however, the relationship between cannabis use and WM neural circuitry is unclear. We examined whether a cannabis use disorder (CUD) was associated with differences in brain morphology between control subjects with and without a CUD and between schizophrenia subjects with and without a CUD, and whether these differences related to WM and CUD history. Subjects group-matched on demographics included 44 healthy controls, 10 subjects with a CUD history, 28 schizophrenia subjects with no history of substance use disorders, and 15 schizophrenia subjects with a CUD history. Large-deformation high-dimensional brain mapping with magnetic resonance imaging was used to obtain surface-based representations of the striatum, globus pallidus, and thalamus, compared across groups, and correlated with WM and CUD history. Surface maps were generated to visualize morphological differences. There were significant cannabis-related parametric decreases in WM across groups. Similar cannabis-related shape differences were observed in the striatum, globus pallidus, and thalamus in controls and schizophrenia subjects. Cannabis-related striatal and thalamic shape differences correlated with poorer WM and younger age of CUD onset in both groups. Schizophrenia subjects demonstrated cannabis-related neuroanatomical differences that were consistent and exaggerated compared with cannabis-related differences found in controls. The cross-sectional results suggest that both CUD groups were characterized by WM deficits and subcortical neuroanatomical differences. Future longitudinal studies could help determine whether cannabis use contributes to these observed shape differences or whether they are biomarkers of a vulnerability to the effects of cannabis that predate its misuse.

Key words: cannabis/marijuana/schizophrenia/working memory/structural neuroimaging

Introduction

In the United States, cannabis is used more commonly than other illicit drugs, per the 2010 National Survey on Drug Use and Health.[1] Young adults have a higher and increasing prevalence of cannabis use than other age groups.[2] Given that decriminalization of cannabis may lead to more widespread cannabis use and that persistent cannabis use beginning in adolescence is associated with cognitive decline,[3,4] it is timely to examine the association between cannabis use and the morphology of neural circuitry supporting specific cognitive functions (especially in clinical populations that may be vulnerable to the effects of cannabis). Cannabis use and the administration of delta-9-tetrahydrocannabinol (Δ_9-THC) have been associated with both acute and long-term deficits in working memory (WM)[3,5,6] (ie, holding and manipulating information over brief time periods).[7] These effects appear to be related to disruption of synaptic synchrony[8–10] within the cortico-basalganglio-thalamic circuits that are part of a broader network subserving WM.[11]

This circuitry includes the striatum, globus pallidus, and thalamus and their reciprocal connections to the dorsolateral prefrontal cortex,[11,12] and densely expresses cannabis type 1 (CB1) receptors.[13] To date, multiple studies evaluated the effects of cannabis on the cortex, but studies examining the effects of cannabis on the subcortical components of WM circuitry have been minimal.[14,15] Accordingly, we sought to determine whether a remote

cannabis use disorder (CUD) was associated with morphological differences in the basalganglio-thalamic circuit, and whether such differences were associated with WM deficits and a history of cannabis use.

This question can be approached in at least 2 ways: (1) evaluating basalganglio-thalamic morphology and WM in controls and matched subjects with a CUD and (2) evaluating basalganglio-thalamic morphology and WM in clinical subjects with known WM deficits, along with a subset of this clinical group with a CUD. Evaluation of these 2 groupings would allow a parametric assessment of cannabis and illness associations with WM, along with testing if common cannabis associations were observed with controls and clinical subjects.

One clinical group with core WM deficits[16,17] and morphological differences in WM-related subcortical structures[18–21] are schizophrenia subjects. They also demonstrate transient WM deficits related to acute administration of Δ_9-THC,[22] although long-term cannabis effects on WM have been mixed.[23] Schizophrenia subjects may be particularly vulnerable to the effects of cannabis[24,25] given the potential overlap in their neurobiological substrates.[26–28] However, studies of chronic cannabis use influencing WM-related subcortical brain regions in schizophrenia subjects are sparse compared with other regions.[29,30] A recent study found chronic cannabis use was associated with exacerbated morphological abnormalities of the hippocampus in schizophrenia subjects,[31] which suggests that existing schizophrenia-related morphological abnormalities in subcortical regions may be susceptible to the effects of cannabis.

The goal of this study was to assess the association of CUDs with subcortical structures implicated in WM processing using structural neuroimaging methods. Because the combination of shape with volumetric assessments can improve detection of subtle differences in morphology,[32–34] we used both methods to test the following hypotheses: (1) healthy subjects with remote CUDs (ie, history of cannabis abuse or dependence, but not during the past 6 months) (CON-CUD) would demonstrate morphological differences in WM-related subcortical regions compared with clean healthy controls (ie, healthy subjects with no history of any substance use disorder) (CON-Clean); (2) schizophrenia subjects with a remote CUD and no history of other substance use disorders (SCZ-CUD) would be characterized by (a) morphological differences that are consistent with the morphology observed in CON-CUD, (b) morphological differences in regions implicated in schizophrenia, but not in CON-CUD, and (c) exaggerated morphological differences in regions that have been linked to both schizophrenia and CON-CUD; (3) schizophrenia subjects with no history of a substance use disorder (SCZ-Clean) would be characterized by morphological differences that are consistent with prior studies; (4) CON-CUD and SCZ-CUD would have lower WM than CON-Clean and SCZ-Clean, respectively; and (5) morphological differences characterizing the CUD groups would correlate with WM and CUD history.

Materials and Methods

Participants

Subjects included a sample of 44 CON-Clean, 10 CON-CUD, 28 SCZ-Clean, and 15 SCZ-CUD that were group-matched on age, gender, handedness,[35] and parental socioeconomic status[36] and were in a large cross-sectional neurobiological study of schizophrenia. Subjects were recruited from the community by advertising in local psychiatric clinics and surrounding neighborhoods. The institutional review boards at Washington University in St Louis and Northwestern University Feinberg School of Medicine approved the study protocol and all subjects provided informed consent.

Clinical Measures

Subjects were assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID),[37] and a psychiatrist evaluation, familial report, and current medical records informed a diagnosis of schizophrenia, duration of illness, and the lifetime history of abuse or dependence for cannabis, alcohol, cocaine, opioids, hallucinogens, stimulants, and sedatives. Inclusion criteria included not having substance abuse or dependence during the 6 months prior to study participation. "Remote" substance use disorders were defined as meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for abuse or dependence prior to the past 6 months. SCID data also included age of CUD onset, frequency of cannabis use (daily or weekly), duration of CUD (total mean years), duration of remission since CUD (total mean years), which can be reliably collected from clinical populations.[38] However, quantity and biological markers of cannabis use were not collected and subjects did not report pharmacological treatment targeting addiction. Self-reported treatment with first- and second-generation antipsychotic medications (FGA, SGA, respectively) was computed into chlorpromazine dose-years using a standard method,[39] while nicotine use (past year) was estimated using a semi-structured interview detailed here.[40]

Subjects completed a series of neuropsychological tests assessing WM. We computed a domain score by averaging standardized scores across 4 WM tasks[41] (ie, scaled scores from Letter-Numbering Sequencing, Spatial Span, and Digit Span subtests from the Wechsler Memory Scales-third edition,[42] and the 4-item d-prime score from a continuous performance task).[43] Scores from individual tests were converted into z scores using the mean and SD across all groups. Three subjects did not complete

the WM assessments (1 CON-CUD, 1 SCZ-Clean, and 1 SCZ-CUD). Two subjects completed only 2 subtests and were not included when computing the WM domain score (1 SCZ-Clean and 1 SCZ-CUD). Twelve subjects missed a single WM item, and a group-level mean imputation replaced the missing item.[44]

Psychopathology was assessed using global ratings from the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms.[45]

Imaging Acquisition

Magnetic resonance imaging scans were collected with a standard head coil on a Siemens Magnetom 1.5-T scanner using a Fast Low-Angle Shot sequence (repetition time = 20 ms, echo time = 5.4 ms, flip angle = 30°, 180 slices, field-of-view = 256 mm, matrix = 356 × 256, time = 13.5 min) that acquired a 1 mm³ isotropic whole-head image.[46] Total brain volume was estimated using an atlas scaling factor.[47] The atlas scaling factor is the reciprocal of the determinant of the alignment matrix to Talairach atlas space and signifies the extent that brain volume contracts or expands during alignment.

Surface Mapping

Striatal, globus pallidal, and thalamic surfaces were derived through application of large-deformation high-dimensional brain mapping.[32] This is an atlas-based transformation technique where a template image of the structure is first aligned with the target regions in each subject via anatomical landmarks and then warped onto the target via diffeomorphic mapping of voxel intensities. Finally, surfaces were generated by superimposing a tessellated graph over each subject's image.[32] An atlas of the human brain was consulted to associate shape patterns to specific subcortical regions.[48]

To assess localized shapes differences, a principal components analysis was first utilized for dimensionality reduction. Resulting eigenvectors were then used to calculate individual subject scores that represented unique variation in the shape of the left and right hemispheres. In each structure, 10 eigenvectors per hemisphere accounted for more than 80% of their total shape variance and were used in subsequent statistical analyses. Volumes were calculated as the space enclosed within the transformed surface of each structure.

Data Analysis

We conducted repeated measures ANOVA models (RM-ANOVA) with hemisphere and eigenvector as within-group effects and group membership as a between-subject factor to assess shape differences across groups. The atlas scaling factor (ie, total brain volume) was examined as a covariate. Post hoc RM-ANOVAs were conducted to test for significant between-group differences in shape.

Analyses comparing SCZ-CUD to SCZ-Clean included duration of illness as a covariate because schizophrenia subjects may have progressive shape change in subcortical regions.[49] We reference shape differences characterizing the contrasts between CON-CUD and CON-Clean and between SCZ-CUD and SCZ-Clean as "cannabis-related."

We compared volumes for each structure across groups using RM-ANOVA with group and hemisphere as fixed effects. We examined demographic, clinical, and WM variables across all subjects with ANOVAs. If the group effect was significant, we conducted post hoc ANOVAs to determine the significance of between-group differences using P values and Cohen's d effect sizes.

To correlate structural shape differences with WM and cannabis use history, a maximum likelihood estimate of the linear predictor (ie, xBeta) was generated for each structure from a logistic regression. xBetas were created to examine the shape differences between (1) CON-CUD and CON-Clean, (2) SCZ-Clean and CON-Clean, and (3) SCZ-Clean and SCZ-CUD using the 10 eigenvectors per hemisphere for each structure. xBeta is a single score representing shape differences between 2 groups where low scores reflect CON-Clean and SCZ-Clean shape and high scores represent deviations from that shape toward the respective comparison group (eg, CON-CUD, SCZ-Clean, or SCZ-CUD). We included nicotine use and SGA dose-years as covariates in partial correlations between WM and shape given their association with WM.[50,51]

Results

Participant Characteristics

Groups did not differ with respect to age, gender, handedness, and parental socioeconomic status (all $P ≥ .10$). CON-CUD did not differ from SCZ-CUD with respect to age of CUD onset, duration of CUD, or duration since CUD remission (all $P ≥ .10$). Sixty percent of CON-CUD and 66.7% of SCZ-CUD met criteria for cannabis dependence, while 80% of CON-CUD and 92.3% of SCZ-CUD used cannabis daily while remaining subjects used weekly. Also, 86.7% of SCZ-CUD met diagnostic criteria for CUD prior to the onset of schizophrenia. Nicotine use differed across all groups ($F_{3,93} = 3.7$, $P ≤ .05$), while FGA and SGA treatment did not differ between SCZ-Clean and SCZ-CUD ($F_{1,41} = 0.3$, $P ≥ .10$ and $F_{1,41} = 2.6$, $P ≥ .10$, respectively) (table 1). We examined nicotine as a covariate in our analyses due to the between-group differences and its potentially confounding effects on neuromorphology.[52]

Subcortical Surface Shape Analyses

Striatum. RM-MANOVA across all groups revealed a significant group-by-eigenvector interaction ($F_{9,85} = 2.5$, $P ≤ .05$). Post hoc comparisons found significant group-by-eigenvector interactions between CON-CUD

Table 1. Demographic, Clinical, and Pharmacological Characteristics of Study Sample

	CON-Clean ($n = 44$)	CON-CUD ($n = 10$)	SCZ-Clean ($n = 28$)	SCZ-CUD ($n = 15$)
Age, mean (SD), y	24.5 (5.5)	25.2 (10.6)	27.3 (7.6)	25.3 (8.8)
Duration of illness, mean (SD), y	—	—	7.0 (7.3)	5.4 (8.1)
Gender, no. (% male)	22 (50.0)	5 (50.0)	17 (60.7)	10 (66.7)
Handedness, mean (SD)	0.8 (0.3)	0.7 (0.2)	0.6 (0.5)	0.8 (0.2)
Parental SES, mean (SD)	3.0 (0.9)	2.7 (0.9)	3.4 (1.1)	3.3 (1.1)
Cigarettes smoked, mean (SD) (over past year)**	983.6 (2185.7)	1799.9 (2007.7)	2843.4 (4291.0)	3611.1 (3102.4)
Substance use disorders[a]				
Cannabis, no. (%)	0 (0.0)	10 (100)	0 (0.0)	15 (100)
Cocaine, no. (%)	0 (0.0)	3 (30.0)	0 (0.0)	0 (0.0)
Hallucinogen, no. (%)	0 (0.0)	3 (30.0)	0 (0.0)	0 (0.0)
Alcohol, no. (%)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)
Stimulants, no. (%)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Opioids, no. (%)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Sedatives, no. (%)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Cannabis use disorder				
Age of onset[b]	—	16.7 (2.5)	—	17.2 (1.8)
% met criteria for DSM-IV dependence	—	60.0	—	66.7
Frequency of use (% daily use)[c]	—	80.0	—	92.3
Duration of CUD, mean (SD), y	—	2.9 (3.1)	—	2.4 (2.0)
Duration since CUD remission, mean (SD), y[d]	—	2.2 (1.2)	—	2.6 (2.0)
Antipsychotic medication				
First generation (dose-years)	—	—	1.2 (3.3)	1.2 (2.3)
Second generation (dose-years)	—	—	2.0 (2.8)	3.6 (3.9)

Note: CON-Clean, control subjects with no history of substance use disorders; CON-CUD, control subjects with a history of cannabis use disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SCZ-Clean, schizophrenia subjects with no history of substance use disorders; SCZ-CUD, schizophrenia subjects with a history of cannabis use disorder; SES, socioeconomic status.
[a]CON-CUD abused alcohol, cocaine, and hallucinogens ($n = 1$); CON-CUD abused cocaine and hallucinogens ($n = 1$); and CON-CUD subject abused all substances ($n = 1$).
[b]Outlier excluded: CON-CUD subject 39 years old at age of CUD onset ($n = 1$).
[c]SCZ-CUD missing data on frequency of use but met criteria for dependence ($n = 2$).
[d]Outliers excluded: CON-CUD, subject 12 years since disorder ($n = 1$); SCZ-CUDs: 20 and 32 years since disorder ($n = 2$).
**$P < .01$.

and CON-Clean ($F_{9,42} = 2.2$, $P \leq .05$) and between SCZ-CUD and SCZ-Clean ($F_{9,30} = 2.2$, $P \leq .05$), but not between SCZ-Clean and CON-Clean ($F_{9,60} = 1.2$, $P \geq .10$) and between CON-CUD and SCZ-CUD ($F_{9,13} = 1.7$, $P \geq .10$). CON-CUD were characterized by inward differences in the dorsal regions of the striatum and outward differences in the nucleus accumbens. SCZ-CUD were characterized by inward differences of the anterior striatum that extended dorsally to the tail and by inward differences in the nucleus accumbens (figure 1).

Globus Pallidus. RM-MANOVA across all groups revealed a significant group-by-eigenvector interaction ($F_{9,85} = 3.2$, $P \leq .01$). Post hoc comparisons found significant group-by-eigenvector interactions between CON-CUD and CON-Clean ($F_{9,42} = 3.2$, $P \leq .01$) and between SCZ-CUD and SCZ-Clean ($F_{9,30} = 2.4$, $P \leq .05$), but not between SCZ-Clean and CON-Clean ($F_{9,60} = 0.8$, $P \geq .10$) or between CON-CUD and SCZ-CUD ($F_{9,13} = 0.9$, $P \geq .10$). Both CON-CUD and SCZ-CUD were characterized by inward shape differences in the anteriodorsal and ventral regions compared with their respective comparison groups (figure 2).

Thalamus. RM-MANOVA across all groups revealed a significant group-by-eigenvector interaction ($F_{9,85} = 3.5$, $P \leq .001$). Post hoc comparisons found significant group-by-eigenvector interactions between CON-CUD and CON-Clean ($F_{9,42} = 3.1$, $P \leq .01$) and between SCZ-CUD and SCZ-Clean ($F_{9,30} = 2.9$, $P \leq .05$), but not between SCZ-Clean and CON-Clean ($F_{9,60} = 1.6$, $P \geq .10$) and between CON-CUD and SCZ-CUD ($F_{9,13} = 1.2$, $P \geq .10$). Both CON-CUD and SCZ-CUD were characterized by inward differences in the anterior, mediodorsal,
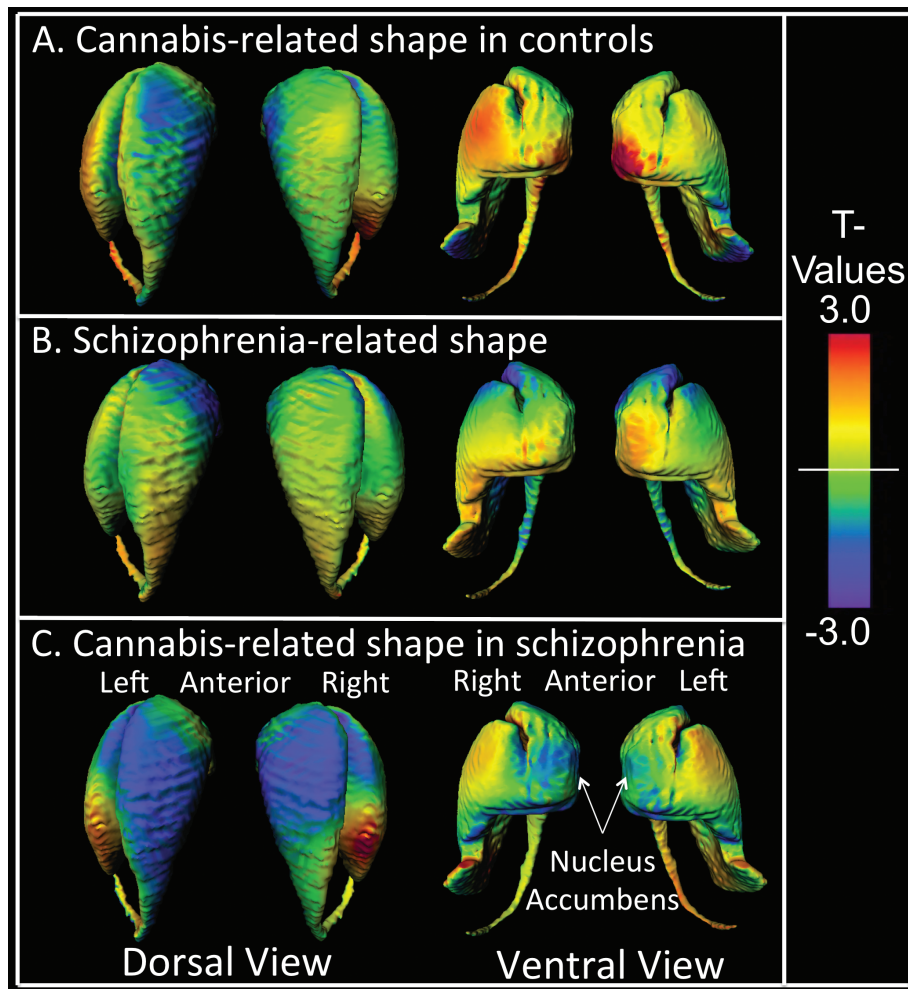
Fig. 1. Striatal surface shape differences. (A) Control subjects with a history of cannabis use disorder (CON-CUD) contrasted with control subjects with no history of substance use disorders (CON-Clean), (B) schizophrenia subjects with no history of substance use disorders (SCZ-Clean) contrasted with CON-Clean, (C) schizophrenia subjects with a history of cannabis use disorder (SCZ-CUD) contrasted with SCZ-Clean. *T*-values with cooler colors (*T* < 0) indicate inward shape differences and warmer colors (*T* > 0) indicate outward shape differences.

ventrolateral, pulvinar, and lateral geniculate regions of the thalamus (figure 3).

Shape Asymmetry and Covariates

We found significant hemisphere-by-group-by-eigenvector interactions across groups for the thalamus ($F_{9,85}$ = 4.3, $P ≤ .001$). Post hoc comparisons found thalamic shape deformations were greater for the left hemisphere for CON-CUD compared with CON-Clean ($F_{9,42}$ = 3.3, $P ≤ .01$), greater for the right hemisphere for SCZ-CUD compared with SCZ-Clean ($F_{9,30}$ = 2.6, $P ≤ .05$), and SCZ-CUD had greater shape deformation in the left hemisphere compared with CON-CUD ($F_{9,13}$ = 5.4, $P ≤ .01$). No other between-group hemisphere-by-group-by-eigenvector interactions were significant (all $P ≥ .10$).

Total brain volume was a significant covariate in each comparison (all $P ≤ .05$). Duration of illness was a significant

covariate when comparing the 2 SCZ groups on the globus pallidus ($F_{9,30}$ = 2.4, $P ≤ .05$) and thalamus ($F_{9,30}$ = 2.7, $P ≤ .05$), and a trend-level covariate for the striatum ($F_{9,30}$ = 1.9, $P = .09$). The nicotine-by-eigenvector-by-hemisphere interaction was significant for the globus pallidus ($F_{9,85}$ = 2.1, $P ≤ .05$) and at the trend level for the striatum ($F_{9,85}$ = 1.8, $P = .07$), but nonsignificant for the thalamus ($F_{9,85}$ = 1.2, $P ≥ .10$). No other effects of nicotine were significant (all $P ≥ .10$).

Subcortical Volume Analyses

There was a trend-level effect of group on thalamic volume ($F_{3,92}$ = 2.5, $P = .06$). CON-CUD had significantly reduced thalamic volume compared with CON-Clean in the right hemisphere (percent difference: −6.0%, $P ≤ .05$, $d = 0.58$), but not the left hemisphere (percent difference: −3.2%, $P ≥ .10$, $d = 0.35$). SCZ-CUD had significantly reduced thalamic volume compared with SCZ-Clean in
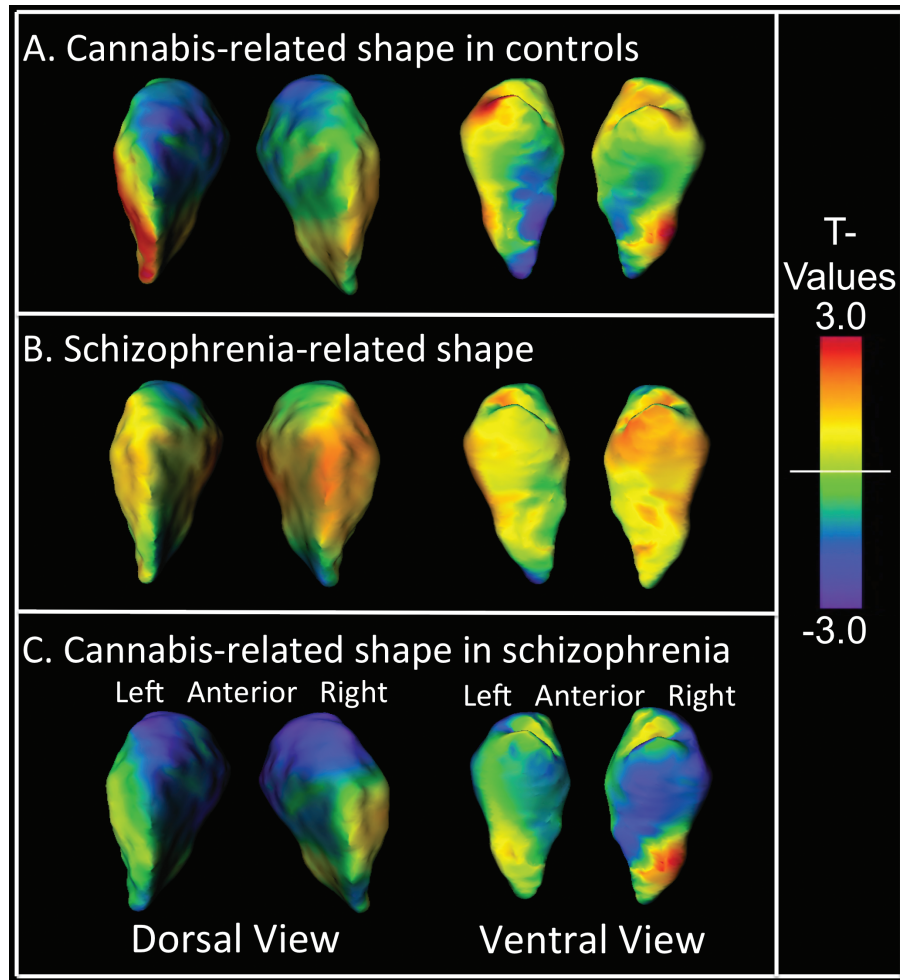
Fig. 2. Globus pallidal surface shape differences. (A) Control subjects with a history of cannabis use disorder (CON-CUD) contrasted with control subjects with no history of substance use disorders (CON-Clean), (B) schizophrenia subjects with no history of substance use disorders (SCZ-Clean) contrasted with CON-Clean, (C) schizophrenia subjects with a history of cannabis use disorder (SCZ-CUD) contrasted with SCZ-Clean. *T*-values with cooler colors (*T* < 0) indicate inward shape differences and warmer colors (*T* > 0) indicate outward shape differences.

the left hemisphere (percent difference: -7.7%, $P \leq .05$, $d = 0.73$), but not the right hemisphere, which was characterized by a medium effect size (percent difference: -6.2%, $P \geq .10$, $d = 0.50$). There were no group effects on striatal or globus pallidal volume (both $P \geq .10$).

Volume Asymmetry and Covariates

We found a significant effect of hemisphere on the striatum ($F_{1,92} = 13.4$, $P \leq .001$) suggesting a left > right asymmetry ($9312\,mm^3$ vs $9097\,mm^3$). There was no effect of hemisphere on the globus pallidus or thalamus (both $P \geq .10$) (table 2). Nicotine and duration of illness did not explain significant variation in volume for any structure (all $P \geq .10$).

Between-Group Differences on WM and Psychopathology

There was a significant effect of group for WM while covarying for nicotine ($F_{4,87} = 8.9$, $P \leq .001$) and SGA treatment (SCZ groups only) ($F_{3,35} = 4.5$, $P \leq .05$). CON-Clean

scored higher than CON-CUD ($d = 0.53$) but did not attain significance ($P = .14$). SCZ-Clean scored significantly higher than SCZ-CUD ($P \leq .05$, $d = 0.73$). WM did not differ between CON-CUD and SCZ-Clean ($P \geq .10$, $d = 0.28$), while CON-CUD had higher WM than SCZ-CUD ($P \leq .05$, $d = 1.04$) (table 3 and figure 4). SCZ-CUD had significantly greater avolition than SCZ-Clean ($F_{2,40} = 6.5$, $P \leq .05$; $d = 0.83$) after covarying for SGA treatment, while SCZ-CUD did not differ from SCZ-Clean on remaining symptoms (all $P \geq .10$, $d < .40$) (table 3).

Shape-Difference Correlations with WM

xBetas were generated for each thalamic hemisphere due to the hemisphere-by-group-by-eigenvector interaction, while single xBetas were generated for the striatum and globus pallidus. Cannabis-related shape differences in the striatum ($r = -.33$, $P \leq .05$) and right thalamus ($r = -.31$, $P \leq .05$) across controls (ie, xBeta for CON-CUD vs CON-Clean) were inversely correlated with WM (figure 4), while cannabis-related shape differences in the
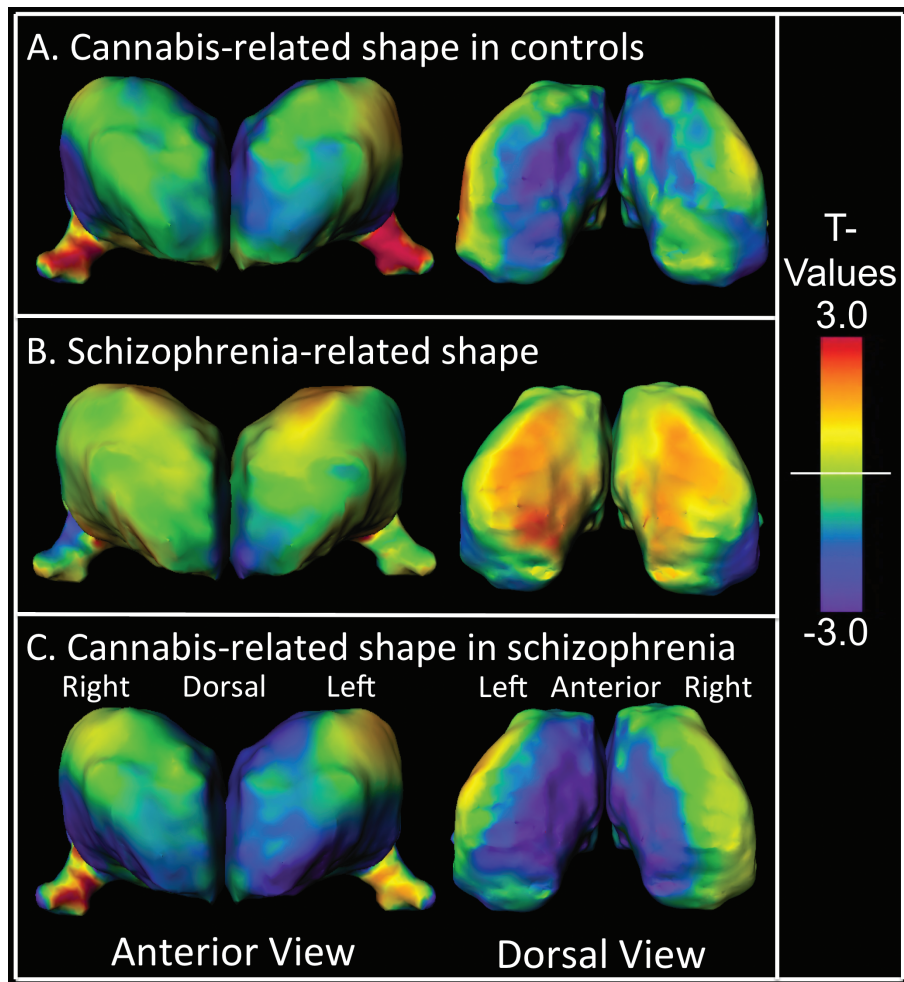
Fig. 3. Thalamic surface shape differences. (A) Control subjects with a history of cannabis use disorder (CON-CUD) contrasted with control subjects with no history of substance use disorders (CON-Clean), (B) schizophrenia subjects with no history of substance use disorders (SCZ-Clean) contrasted with CON-Clean, (C) schizophrenia subjects with a history of cannabis use disorder (SCZ-CUD) contrasted with SCZ-Clean. *T*-values with cooler colors (*T* < 0) indicate inward shape differences and warmer colors (*T* > 0) indicate outward shape differences.

left thalamus and globus pallidus were not (*P* > .80). Cannabis-related shape in the left thalamus of CON-CUD trended toward an inverse correlation with age at CUD onset (*r* = −.58, *P* = .08), while the right hemisphere had a similar magnitude correlation that did not attain significance (*r* = −.51, *P* = .13). Cannabis-related striatal and globus pallidal shape did not correlate with age of CUD onset (all *P* ≥ .10).

Cannabis-related shape differences in the right thalamus (*r* = −.39, *P* ≤ .05), left thalamus (*r* = −.30, *P* = .069; trend level), and striatum (*r* = −.32, *P* = .058: prior to covarying for nicotine, *r* = −.33, *P* ≤ .05), across schizophrenia subjects (ie, xBeta for SCZ-CUD vs SCZ-Clean), were inversely correlated with WM (figure 4), but not for the globus pallidus (*r* = −.26, *P* = .12). Cannabis-related shape differences in the striatum (*r* = −.59, *P* ≤ .05), left thalamus (*r* = −.60, *P* ≤ .05), and globus pallidus (*r* = −.49, *P* = .09; trend level) of SCZ-CUD were inversely correlated with age at CUD onset. Years of

CUD duration and years since CUD remission were not correlated with shape measures for SCZ-CUD or CON-CUD (all *P* ≥ .10).

Discussion

We examined the relationship of a remote CUD with WM and morphology of basalganglio-thalamic regions that support WM. Our results suggest that (1) CON-CUD were characterized by subcortical shape that differed from CON-Clean; (2) SCZ-CUD were characterized by subcortical shape that differed from SCZ-Clean and were consistent with the subcortical shape observed in CON-CUD and schizophrenia; (3) SCZ-Clean shape findings contrasted prior studies; (4) cannabis-related shape asymmetries were observed in the thalamus; (5) CON-CUD and SCZ-CUD demonstrated parametric deficits in WM performance compared with CON-Clean and SCZ-Clean, respectively; and (6) cannabis-related shape differences

Table 2. Mean (SD) Volumes of Subcortical Structures Supporting Working Memory (mm^3)

	Hemi	CON-Clean	CON-CUD	SCZ-Clean	SCZ-CUD
Striatum	Left	9260 (931)	9543 (932)	9278 (1007)	9159 (1011)
	Right	9013 (939)	9287 (915)	9060 (952)	8969 (955)
Globus pallidus	Left	1708 (197)	1706 (192)	1760 (230)	1642 (230)
	Right	1682 (196)	1700 (192)	1757 (199)	1660 (200)
Thalamus	Left	7617 (702)	7372 (685)	7653 (813)	7061 (816)
	Right	7734 (806)	7271 (786)	7719 (948)	7242 (952)

Abbreviations are explained in the first footnote to table 1.

Table 3. Mean Between-Group Differences for Working Memory and Clinical Symptoms (SD)

	CON-Clean ($n = 44$)	CON-CUD ($n = 10$)	SCZ-Clean ($n = 28$)	SCZ-CUD ($n = 15$)	Effect Size
Working memory	0.37 (0.69)	0.01 (0.68)	−0.19 (0.73)	−0.73 (0.74)	—[a]
Positive symptoms					
Hallucinations	—	—	1.01 (1.47)	0.82 (1.49)	−0.13[b]
Delusions	—	—	1.67 (1.45)	1.88 (1.46)	0.14[b]
Negative symptoms					
Flat affect	—	—	1.89 (1.33)	2.15 (1.34)	0.20[b]
Alogia	—	—	1.29 (1.32)	1.79 (1.31)	0.38[b]
Avolition	—	—	1.50 (1.24)	2.54 (1.26)	0.83[c]
Anhedonia	—	—	1.75 (1.40)	2.00 (1.42)	0.18[b]
Disorganized symptoms					
Attention	—	—	1.71 (1.30)	2.14 (1.31)	0.33[b]
Bizarre behavior	—	—	0.34 (0.68)	0.51 (0.69)	0.25[b]
Thought disorder	—	—	0.79 (1.17)	0.93 (1.18)	0.12[b]

Note: WM data were not analyzed for CON-CUD ($n = 1$), SCZ-Clean ($n = 2$), and SCZ-CUD ($n = 2$). Abbreviations are explained in the first footnote to table 1.
[a]CON-Clean > CON-CUD ($P = .14$, $d = 0.53$), SCZ-Clean ($P < .001$, $d = 0.79$), and SCZ-CUD ($P < .001$, $d = 1.52$); CON-CUD > SCZ-CUD ($P < .05$, $d = 1.04$) and SCZ-Clean ($P > .10$, $d = 0.28$); SCZ-Clean > SCZ-CUD ($P < .05$, $d = 0.73$).
[b]SCZ-CUD and SCZ-Clean did not differ ($P > .10$).
[c]SCZ-CUD > SCZ-Clean ($P < .05$).

were correlated with more severe WM performance deficits and age of CUD onset in CON-CUD and SCZ-CUD.

A remote CUD diagnosis in controls was associated with inward shape differences in the dorsal striatum, anteriodorsal and ventral globus pallidus, and anterior and mediodorsal thalamus. These findings were consistent with prior work suggesting that chronic cannabis use was associated with hippocampal shape difference in controls and exacerbated schizophrenia-related hippocampal shape.[31] The subcortical regions in the present study are typically characterized by high-to-moderate CB1 receptor expression.[13] Thus, CB1 receptor activation by Δ_9-THC affects GABAergic and glutamatergic neurotransmission (eg, Tebano et al[10]), and alterations in these neurotransmissions could potentially disrupt synaptic synchrony[8] within the cortico-basalganglio-thalamic circuit subserving WM.[11] This hypothesized mechanism appears consistent with the known influence of Gamma Amino Butyric Acid (GABA) and glutamate on WM,[53,54] and as such, could be an important direction for future research.

We hypothesized that SCZ-CUD would be characterized by an exaggeration of cannabis-related shape differences in CB1-rich regions, because of changes in WM and the neural circuits supporting WM that are inherent to schizophrenia. This hypothesis was supported by inward shape differences in the dorsal striatum, anterior thalamus, and anteriodorsal and ventral globus pallidus observed in SCZ-CUD and that overlapped with the shape differences found in CON-CUD. SCZ-CUD was also characterized by exaggerated inward shape differences in the mediodorsal thalamus and dorsal striatum that appeared more marked than the observed shape characterizing SCZ-Clean (both structures) and CON-CUD (left thalamus). These results suggest that a remote CUD may have parallel effects in CON-CUD and SCZ-CUD in the striatum and globus pallidus and that a comorbid CUD could augment the underlying disease process associated with schizophrenia in the mediodorsal thalamus. Due to the cross-sectional nature of our study, the observed shape differences characterizing the CUD groups could predate the onset of cannabis use and
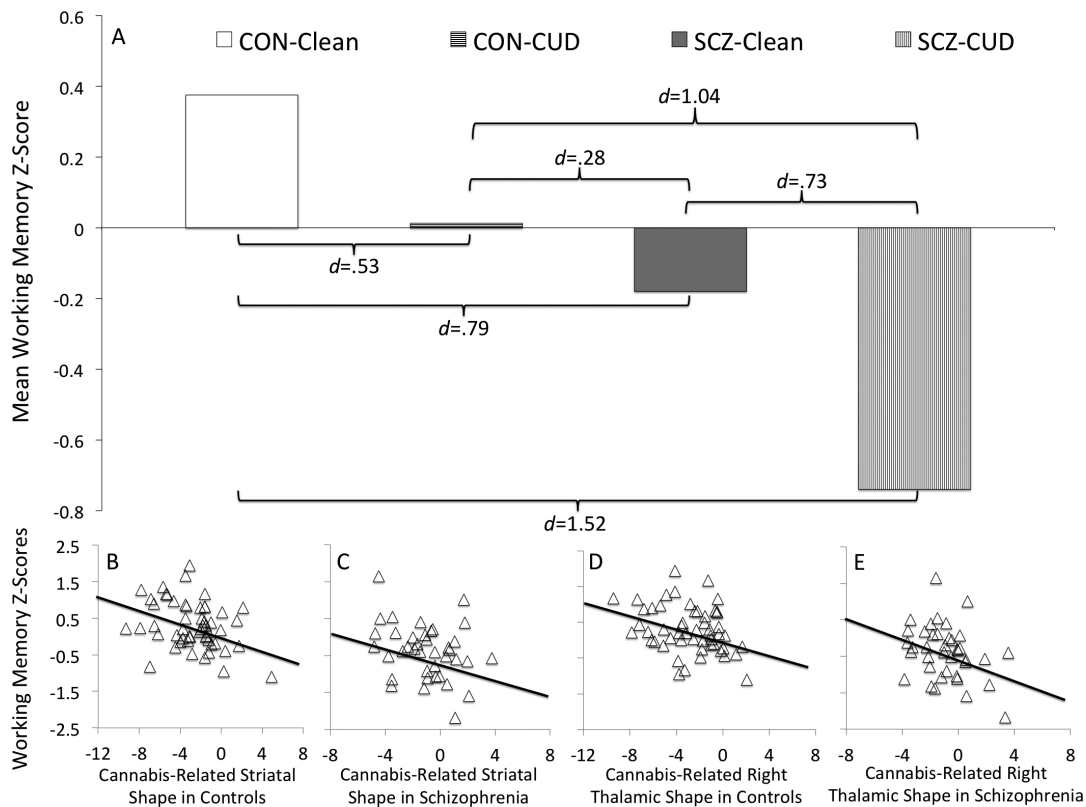
Fig. 4. Between-group differences in working memory (WM) and scatterplots of cannabis-related shape correlations. (A) Control subjects with a history of cannabis use disorder (CON-CUD) had lower WM than control subjects with no history of substance use disorders (CON-Clean) characterized by a medium effect size, and schizophrenia subjects with a history of cannabis use disorder (SCZ-CUD) had lower WM than schizophrenia subjects with no history of substance use disorders (SCZ-Clean) characterized by a medium effect size. Striatal shape variations progressing from CON-Clean to CON-CUD (B) and from SCZ-Clean to SCZ-CUD (trend) (C) were correlated with poorer WM ($r = -.33$, $P = .016$ and $r = -.31$, $P = .058$, respectively). Right thalamic shape variation progressing from CON-Clean to CON-CUD (D) and from SCZ-Clean to SCZ-CUD (E) were correlated with poorer WM ($r = -.31$, $P = .022$ and $r = -.39$, $P = .016$, respectively).

reflect neurobiological susceptibilities to cannabis misuse. Longitudinal studies could be conducted to confirm these relationships.

We observed a disruption of brain laterality and while cortical asymmetries in healthy individuals are well defined,[55] subcortical asymmetry receives much less attention. We found thalamic asymmetries in shape, but not volume, suggesting that both CUD groups were asymmetric compared with non-CUD groups. The thalamus is a symmetric structure, with subtle asymmetries related to individual nuclei.[56,57] Our methods may reflect these minor fluctuations along the surface, thus characterizing asymmetries not broadly appreciated by global volumes among the subgroups. Schizophrenia is known to perturb cortical development and the "typical" pattern of anatomical asymmetry.[58] Less is known about the effects of cannabis on brain symmetry, although 1 study noted disruption in the hippocampus.[59] One could hypothesize the observed asymmetry represents the effects of cannabis, which induces a loss of normal variation in subcortical nuclei. However, the observed asymmetry could also represent a neurobiological vulnerability that predisposes

individuals to substance abuse, which has been suggested in studies of cocaine addiction.[33] Ultimately, such shifts in anatomical variation signal the complex interplay between development and disease, which impacts our understanding of their etiology.

SCZ-Clean demonstrated shape differences in the striatum and thalamus that were visually consistent with prior studies but did not attain statistical significance. These findings contrast prior studies of subcortical shape in schizophrenia that did not covary for nicotine.[19,60–63] We found that SCZ-Clean demonstrated significant thalamic shape difference from CON-Clean prior to covarying for nicotine use ($P \leq .05$ to $P = .13$). Thus, the addition of nicotine as a covariate may have limited the available explanatory power.

Inward shape differences in the absence of corresponding outward shape differences in neighboring brain regions can be interpreted as localized volume loss. This interpretation is partially supported by our observation of a trend-level difference in thalamic volume, which was characterized by medium-to-large effect sizes in both CUD groups. These findings are consistent with prior research reporting lower cannabis-related thalamic

volumes in individuals at familial high risk for schizophrenia.[64] However, we did not find evidence of lower striatal and globus pallidal volume in schizophrenia, as previously described (eg, Ballmaier et al[19]).

Consistent with prior studies of both transient (eg, Bossong et al[5]) and chronic (eg, Meier et al[3]) cannabis use in healthy subjects, we found WM impairments in both CUD groups. In the context of schizophrenia, these findings contradict the results of a recent meta-analysis where cannabis-using schizophrenia subjects had similar or better WM compared with nonusing schizophrenia subjects.[23] Recent evidence suggests that the relative absence of WM deficits in comorbid schizophrenia subjects is associated with better premorbid cognitive functioning in this group than noncomorbid subjects.[65] Alternatively, our subjects demonstrated cannabis abuse by age 17, which may have increased the risk for their subsequent WM impairment[3,4] and development of schizophrenia.[66] Also, we found elevated avolition in SCZ-CUD, which is consistent with prior reports that cannabis use alone can "produce" negative symptoms.[67]

We found that more severe "cannabis-related" striatal and thalamic shape differences were associated with more marked deficits in WM in both control and schizophrenia subjects. The dorsal striatum and the mediodorsal thalamus are critically involved in a dorsolateral prefrontal circuit that mediates WM as well as other executive functions.[11] Our results suggest that a CUD history could be associated with alterations in these regions to an extent that WM functioning is disrupted and support the theory that activation of CB1 receptors may impair WM possibly due to their role in the cortico-basalganglio-thalamic circuit subserving this cognitive function.

Our data also suggest that an earlier age of CUD onset was associated with greater "cannabis-related" shape differences in both CUD groups. These findings suggest that subcortical regions subserving WM may be more susceptible to the effects of cannabis if abuse starts at an earlier age. However, we did not observe significant relationships between "cannabis-related" shape differences and either the years of CUD duration or years since CUD remission. Although low statistical power could explain these negative findings, the lack of correlations between the observed shape differences in the CUD groups and the measures of CUD duration or remission since prior CUD diagnosis could support the interpretation that these shape differences reflect a neurobiological marker for susceptibility that predates cannabis misuse.

Although not hypothesized, we found CON-CUD were characterized by outward shape differences in the nucleus accumbens, while SCZ-CUD were characterized by inward shape differences in this region. The former observation is consistent with animal models demonstrating cannabis-related increases in dendritic length in this region,[68] while the latter observation is consistent with prior human studies demonstrating lower "cannabis-related" gray matter volume.[69] Although group-specific shape differences in the nucleus accumbens were difficult to explain, this region consists of medium spiny neurons that produce GABA,[70] and alterations in GABAeric processes associated with cannabis use (eg, Tebano et al[10]) could produce differences in shape possibly due to underlying disease-specific abnormalities in GABAergic function.[70] However, longitudinal data would be needed to confirm this potential explanation.

There were several limitations to the study. The data are cross-sectional and as such, we cannot infer causality. Subsequently, we attempted to interpret the findings with regard to the observed shape differences as possibly reflecting the effects of chronic cannabis abuse or reflecting a neurobiological susceptibility (ie, biomarker) that predated the onset of the CUD. Our sample was large enough to detect several significant shape differences; however, it appears less sufficient at detecting significant volume differences and correlations. Additionally, we did not assess quantitative measures of cannabis use, which would support the evaluation of dose-response effects on WM and subcortical shape. We did not collect pharmacologic treatment data other than antipsychotic medication, which may have impacted the findings. Lastly, 3 CON-CUD subjects had a lifetime history of other substance use disorders that may have influenced the results; however, the robust findings were maintained after excluding these subjects from shape analyses. Thus, we retained the 3 subjects to optimize statistical power. Moreover, studies evaluating the dose-dependent effects of cannabis on WM neural circuitry and longitudinal research examining whether cannabis-related neuromorphological differences abate after abstinence could be key areas for future research.

In conclusion, our findings suggest that a remote CUD may be associated with differences in WM-related subcortical morphology in both control and schizophrenia subjects. Although our data may be compatible with a causal hypothesis, the cross-sectional data do not allow us to test causal relationships or reject alternative explanations. Thus, the shape differences could be explained as either due to the effects of chronic cannabis abuse or the presence of biomarkers that characterize a vulnerability to the effects of cannabis. The observed patterns of neuromorphological differences in subjects who used cannabis were also consistent with the known distribution of CB1 receptor expression across various subcortical regions. Longitudinal research should focus on the mechanistic basis of the interaction of cannabis- and disease-related effects on brain structure and function as well as evaluate the possibility that the observed morphological differences could be neurobiological markers of vulnerability to cannabis misuse. Moreover, these findings argue that efforts to legalize recreational and medicinal cannabis use should more carefully consider the potential impact of cannabis use on WM and the underlying structures that

support it in vulnerable populations. Of special concern is that cannabis use could begin long before an adolescent or young adult would know if they were in one of these vulnerable groups.

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