

Cannabis-Related Episodic Memory Deficits and Hippocampal Morphological Differences in Healthy Individuals and Schizophrenia Subjects

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ABSTRACT: Cannabis use has been associated with episodic memory (EM) impairments and abnormal hippocampus morphology among both healthy individuals and schizophrenia subjects. Considering the hippocampus' role in EM, research is needed to evaluate the relationship between cannabis-related hippocampal morphology and EM among healthy and clinical groups. We examined differences in hippocampus morphology between control and schizophrenia subjects with and without a past (not current) cannabis use disorder (CUD). Subjects group-matched on demographics included 44 healthy controls (CON), 10 subjects with a CUD history (CON-CUD), 28 schizophrenia subjects with no history of substance use disorders (SCZ), and 15 schizophrenia subjects with a CUD history (SCZ-CUD). Large-deformation, high-dimensional brain mapping with MRI produced surface-based representations of the hippocampus that were compared across all four groups and correlated with EM and CUD history. Surface maps of the hippocampus were generated to visualize morphological differences. CON-CUD and SCZ-CUD were characterized by distinct cannabis-related hippocampal shape differences and parametric deficits in EM performance. Shape differences observed in CON-CUD were associated with poorer EM performance, while shape differences observed in SCZ-CUD were associated with a longer duration of CUD and shorter duration of CUD remission. A past history of CUD may be associated with notable differences in hippocampal morphology and EM impairments among adults with and without schizophrenia. Although the results may be compatible with a causal hypothesis, we must consider that the observed cannabis-related shape differences in the hippocampus could also be explained as biomarkers of a neurobiological susceptibility to poor memory or the effects of cannabis. © 2015 Wiley Periodicals, Inc.

KEY WORDS: hippocampus; Marijuana; neuroimaging; morphology; shape analysis

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INTRODUCTION

Over the past decade, policy makers have redefined state laws surrounding cannabis use in the United States, including the decriminalization or legalization of cannabis possession for medical and recreational purposes. In 2010, the National Survey on Drug Use and Health (SAMHSA, 2011) identified cannabis as the most commonly used illicit drug in the United States and recent policy changes regarding cannabis in Colorado resulted in an increased prevalence of cannabis abuse and a decrease in perceived risk of cannabis use among adolescents (Schuermeyer et al., 2014). Based on recent evidence that cannabis use beginning in adolescence has been linked to cognitive deficits (Meier et al., 2012), it is important to evaluate the relationship between cannabis use and the morphology of brain structures underlying specific cognitive functions.

Cannabis use and the acute administration of delta-9-tetrahydrocannabinol (Δ_9 -THC) (a CB1 receptor agonist and main psychoactive compound in cannabis) have been associated with impairments in episodic memory (EM) (see Ranganathan and D'Souza, 2006; Crane et al., 2013) for review), the type of memory associated with autobiographical events (Stark, 2007). Limbic structures, in particular the hippocampus, play an integral role in memory formation and are characterized by a high density of cannabinoid type 1 (CB1) receptors (Svizenska et al., 2008). Cannabis use disrupts memory by overactivating CB1 receptor expression in the hippocampus which inhibits glutamateric and GABAergic neurotransmission and suppresses LTP and LTD (Navakkode and Korte, 2014).

Recent evidence suggests that heavy cannabis users had altered hippocampal morphology (Medina et al., 2014; Yucel et al., 2008; Ashtari et al., 2011; Solowij et al., 2013) that was related to cannabis use history (e.g., age of onset, duration of use). Specifically, reduced hippocampal volume and shape differences were correlated with recent and overall duration of cannabis use (Ashtari et al., 2011; Solowij et al., 2013). However, these recent findings differ from older studies looking at hippocampal volume

differences between users and nonusers (Block et al., 2000; Tziolos, 2005). Moreover, the relationship between cannabis-related hippocampal morphology and cognition remains unclear. Accordingly, we sought to evaluate whether cannabis-related alterations in hippocampal morphology were associated with impaired EM performance.

Schizophrenia is frequently characterized by EM impairments (Leavitt and Goldberg, 2009) as well as anatomical abnormalities in the hippocampus (Schobel et al., 2009; Heckers and Konradi, 2010). Individuals with schizophrenia also demonstrate exacerbated EM impairments related to the acute administration of THC (Henquet et al., 2006); however, the literature on long-term cannabis use and cognition in schizophrenia is less clear (Yucel et al., 2012). Prior research found that cannabis-related differences in hippocampal morphology among individuals with schizophrenia were associated with the pattern of cannabis use (Solowij et al., 2013). However, the association between these differences and EM performance has not been explicitly examined in this clinical population. Further study of individuals with schizophrenia provides an ideal opportunity to examine the relationship among cannabis, hippocampal morphology, and EM in a clinical population.

This study used structural imaging methods in order to determine whether a past CUD was associated with volumetric or shape differences in the hippocampus, and whether such differences were associated with EM deficits. Based on prior work (Smith et al., 2014), we studied the hippocampus in two ways. We evaluated hippocampal morphology and EM performance in (i) controls and a matched group with a prior history of a cannabis use disorder (CUD) and (ii) in schizophrenia subjects with known EM deficits and a subset of this group with CUD. This approach allows a 2 x 2 assessment of combined cannabis and illness-associated EM deficits, as well as whether common cannabis-related associations exist among the control and clinical groups through testing of the following hypotheses: (1) healthy subjects with past CUDs (i.e., history of cannabis abuse or dependence, but not during the past 6 months) (CON-CUD) would demonstrate morphological differences in the hippocampus compared with healthy controls (i.e., subjects with no history of any substance use disorder) (CON); (2) schizophrenia subjects with a past CUD and no history of other substance use disorders (SCZ-CUD) would be characterized by (a) hippocampal 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) would be characterized by hippocampal differences that are consistent with prior studies; (4) CON-CUD and SCZ-CUD would have poorer EM performance than CON and SCZ, respectively; and (5) morphological differences characterizing the CUD groups would correlate with poorer EM performance, a greater duration of CUD abuse and shorter duration of CUD abstinence.

MATERIALS AND METHODS

Participants

Subjects included 44 CON, 10 CON-CUD, 28 SCZ, and 15 SCZ-CUD subjects group-matched on age, gender, handedness (Oldfield, 1971), and parental socioeconomic status (Hollingshead, 1975) who underwent neuroimaging and cognitive testing as part of their participation in a large cross-sectional neurobiological study of schizophrenia. These subjects are a subset of individuals from a prior study that provides in depth details on their characteristics and patterns of substance use (Smith et al., 2014). One CON subject from the prior sample had a poor quality scan of the hippocampus and was replaced by a subject selected from a large pool of available healthy controls with matched gender and handedness in order to achieve the same statistical power as the prior study (Karnik-Henry et al., 2012).

Subjects were recruited from the community by advertising in local psychiatric clinics and surrounding neighborhoods. The institutional review board 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

Clinical interviews using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID; First et al., 2002) obtained the psychiatric and substance use history of study subjects. The combination of SCID findings, a psychiatric evaluation, family report, and current medical records determined the diagnosis of schizophrenia, major depressive disorder, or an anxiety disorder (i.e., generalized anxiety disorder, social anxiety disorder, or panic disorder) and provided information regarding the duration of illness and lifetime history of abuse or dependence for cannabis, alcohol, cocaine, opioids, hallucinogens, stimulants, and sedatives. Subjects classified as having a “past substance use disorder” met SCID criteria for abuse or dependence greater than 6 months before enrolling in the study. SCID data also provided frequency of marijuana use (daily or weekly), age of CUD onset, duration of CUD, and duration of CUD abstinence.

Self-reported treatment with typical and atypical antipsychotic medications were computed into chlorpromazine dose-years using a standard method (Andreasen et al., 2010), while nicotine use (past year) was estimated using a semistructured interview detailed here (Smith et al., 2008). Psychopathology was assessed using global ratings from the Scale of the Assessment of Positive Symptoms (Andreasen, 1983b) and the Scale of the Assessment of Negative Symptoms (Andreasen, 1983a).

Cognitive Measures

The Vocabulary subtest from the Wechsler Adult Intelligence Scale, Third Edition (Wechsler, 1997) was used as a measure

of verbal intellect and as an estimate of premorbid functioning (Schoenberg et al., 2003). Memory performance in all subjects was evaluated using standard neuropsychological paradigms that measure the encoding and retrieval components of EM. As part of a larger neuropsychological battery, the Logical Memory II subtest from the Wechsler Memory Scale-Third Edition (Wechsler, 1997) was used to assess delayed recall of organized verbal information. Five subjects did not complete the Logical Memory II subtest (1 CON-CUD, 2 SCZ, and 2 SCZ-CUD). A group-level mean imputation replaced the missing data (Enders, 2010).

Imaging Acquisition

Magnetic resonance (MR) scans were collected with a standard head coil on a 1.5-Tesla Siemens VISION (Erlangen, Germany) scanner using a Fast Low-Angle Shot sequence (3D FLASH: TR = 20 msec, TE = 5.4 msec, flip angle = 30°, 180 slices, matrix = 256 × 256, voxel resolution = 1 mm³ isotropic; Venkatesan and Haacke, 1997). To control for total brain volume, we calculated an atlas scaling factor (ASF) for each individual. (Buckner et al., 2004). The ASF 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 to atlas space.

Surface Mapping

Hippocampal surfaces were derived through application of Large-Deformation High-Dimensional Brain Mapping (Csernansky et al., 2004). This is an atlas-based transformation technique where a previously generated template image 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, hippocampal surfaces with corresponding vertices were generated for all subjects by applying the transformations to a previously tessellated template surface (Csernansky et al., 2004). Hippocampal volume was derived from the space enclosed within the surface.

To assess shape, hippocampal surfaces from subjects' native space were first rigidly aligned into a previously established template space (Csernansky et al., 2004), and a population average was generated. A principal components (PCs) analysis was then performed on the aligned left and right surfaces. The PCs represented variations in the shape of the left and right surfaces. The first 10 PCs accounted for more than 80% of the total shape variance and were used in subsequent statistical analyses.

To visualize between-group shape differences, we calculated a T score at each surface vertex between the group of interest and a reference group and then color-coded the T scores on the average surface of the reference group.

Data Analysis

We conducted repeated measures analysis of variance models (RM-ANOVA) with hemisphere as a within-group effect and group membership as a between-subject factor to assess group,

group-by-hemisphere, group-by-PC, and group-by-PC-by-hemisphere effects in hippocampal shape across all four groups. Based on these five tests, we used a corrected threshold of $P \leq 0.01$ (0.05/5) for the RM-ANOVA assessing shape. Then we conducted between-group RM-ANOVAs as post hoc tests for (1) CON-CUD vs. CON, (2) SCZ vs. CON, (3) CON-CUD vs. SCZ, and (4) SCZ-CUD vs. SCZ. Nicotine use and the ASF (i.e., total brain volume) were examined as covariates. Dose years of second generation antipsychotic treatment were also examined as covariates given prior research suggesting that antipsychotic treatment is associated with changes in gray matter volume (Vita et al., 2012; Fusar-Poli et al., 2013; Lesh et al., 2015).

We also compared total hippocampal volume between group pairings using RM-ANOVA with group and hemisphere as fixed effects. Based on these two tests, we used a corrected threshold of $P \leq 0.025$ ($\leq 0.05/2$) for the RM-ANOVA assessing volume. We examined demographic, clinical, and EM variables across all subjects with ANOVAs to determine the significance of between-group differences. We reference the shape and volumetric differences observed in CON-CUD compared to CON and in SCZ-CUD compared to SCZ as "cannabis-related."

Between-group differences on clinical, EM, and morphology measures were evaluated using ANOVA and characterized using P-values and Cohen's effect sizes (*d*). Based on our directional hypotheses supported by prior work (Smith et al., 2014), we computed one-tailed Pearson correlation coefficients between hippocampal shape and volume and EM performance, symptoms, and the CUD history variables (i.e., age of onset, duration of CUD, duration of remission from CUD). To correlate shape differences with EM and cannabis use history, a maximum likelihood estimate of the linear predictor (i.e., xBeta) for each subject was generated from a logistic regression procedure. The xBeta was based on the 10 PCs per hemisphere representing overall shape, and was used to examine the relation between shape and EM and shape and CUD history. Verbal intelligence (IQ) was used as a covariate as groups differed on this measure.

RESULTS

Participant Characteristics

The ANOVAs revealed that groups did not differ with respect to age, gender, handedness, and parental socioeconomic status, while SCZ and SCZ-CUD did not differ with respect to a lifetime co-morbid diagnosis of major depressive disorder or an anxiety disorder ($P \geq 0.10$; Table 1). Nicotine use and verbal IQ differed across all groups ($F_{3,93} = 3.7$, $P \leq 0.05$ and $F_{3,93} = 8.8$, $P \leq 0.001$, respectively). Nicotine and verbal IQ were included as covariates in the shape and correlation analyses so the results can be interpreted above and beyond the potential effects of nicotine and a global measure of intelligence (Brody et al., 2004; Schumann et al., 2007; Jubelt et al., 2008),

TABLE 1.

Background Characteristics of Study Sample

	CON (n = 44)	CON-CUD (n = 10)	SCZ (n = 28)	SCZ-CUD (n = 15)
Demographic				
Age, mean (SD), y	25.0 (6.7)	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)
SES, mean (SD)	3.0 (0.9)	2.7 (0.9)	3.4 (1.1)	3.3 (1.1)
Cigarettes smoked, mean (SD; past year) ^a	983.6 (2185.7)	1799.9 (2007.7)	3100.6 (4329.8)	3617.8 (3105.7)
Verbal IQ Z score ^b	0.0 (1.0)	–0.26 (0.32)	–0.84 (0.90)	–1.18 (0.88)
Substance use disorders^c				
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%)
CUD				
% Met criteria for DSM-IV dependence	–	6 (60.0%)	–	10 (66.7%)
Frequency of use (% daily use) ^d	–	8 (80.0%)	–	14 (92.3%)
Age of onset of CUD, mean (SD), y	–	16.7 (2.5)	–	17.2 (1.8)
Duration of CUD, mean (SD), y	–	2.9 (3.1)	–	2.4 (2.0)
Duration since CUD abstinence, mean (SD), y ^e	–	2.2 (1.2)	–	2.6 (2.0)
Clinical characteristics				
Lifetime history of major depressive disorder ^f	–	–	3 (11.1%)	3 (20.0%)
Lifetime history of anxiety disorder ^f	–	–	2 (7.4%)	2 (13.3%)
Dose-years first-generation antipsychotic treatment	–	–	1.2 (3.3)	1.2 (2.3)
Dose-years second-generation antipsychotic treatment	–	–	2.0 (2.8)	3.6 (3.9)

Note: An earlier version of this table was published by Smith et al., 2014 in Schizophrenia Bulletin.

Abbreviations: CON: control subjects with no history of substance use disorders; CON-CUD: control subjects with a history of cannabis use disorder; SCZ: schizophrenia subjects with no history of substance use disorders; SCZ-CUD: schizophrenia subjects with a history of cannabis use disorder

^a $P < 0.01$.

^bAll groups Z scored using the group mean of CON, outlier excluded: 1 CON-CUD (3 SD above mean).

^c1 CON-CUD abused alcohol, cocaine, and hallucinogens; 1 CON-CUD abused cocaine and hallucinogens; and 1 CON-CUD subject abused all substances.

^d2 SCZ-CUD missing data on frequency of use but met criteria for dependence.

^eOutliers excluded: 1 CON-CUD, subject 12 years since disorder; 2 SCZ-CUDs: 20 and 32 years since disorder.

^fData on comorbid major depressive disorder or anxiety were not available for $n = 1$ SCZ.

As reported in Smith et al., 2014, the two CUD groups did not differ with respect to duration of CUD ($M = 2.6$ years, $SD = 2.5$) and duration since cannabis abstinence ($M = 2.4$ years, $SD = 1.7$). Sixty percent or greater of all subjects with a former CUD diagnosis met criteria for dependence, while eighty percent (or greater) of these same subjects reported daily cannabis use. The typical and atypical antipsychotic medication dose-years did not differ between the two SCZ groups ($F_{1,41} = 0.3$, $P \geq 0.10$, and $F_{1,41} = 2.6$, $P \geq 0.10$, respectively).

Hippocampus Shape

RM-ANOVA across all groups revealed a main effect for group ($F_{3,90} = 4.2$, $P \leq 0.01$), a group-by-PC interaction ($F_{9,84} = 2.6$, $P \leq 0.01$), and a PC-by-total brain volume interac-

tion ($F_{9,82} = 6.5$, $P \leq 0.001$), all meeting the correction for multiple comparisons. Trend-level effects were observed for hemisphere ($F_{1,90} = 3.0$, $P = 0.09$) and the group-by-hemisphere interaction ($F_{3,90} = 2.4$, $P = 0.07$).

Posthoc differences between CON-CUD and CON revealed a main effect for group ($F_{1,49} = 7.4$, $P = 0.011$), but the group-by-PC interactions were nonsignificant (both $P > 0.10$). Figure 1A visualizes the shape differences between-groups. The flame scale reflects T -values with cooler colors ($T < 0$) indicating inward shape differences and warmer colors ($T > 0$) reflecting outward shape differences. CON-CUD were characterized by inward differences in the anterior hippocampus as well as the mediodorsal and medioventral regions of the hippocampus and outward differences in the dorsolateral and anterioventral regions of the hippocampus. The global cannabis-related shape

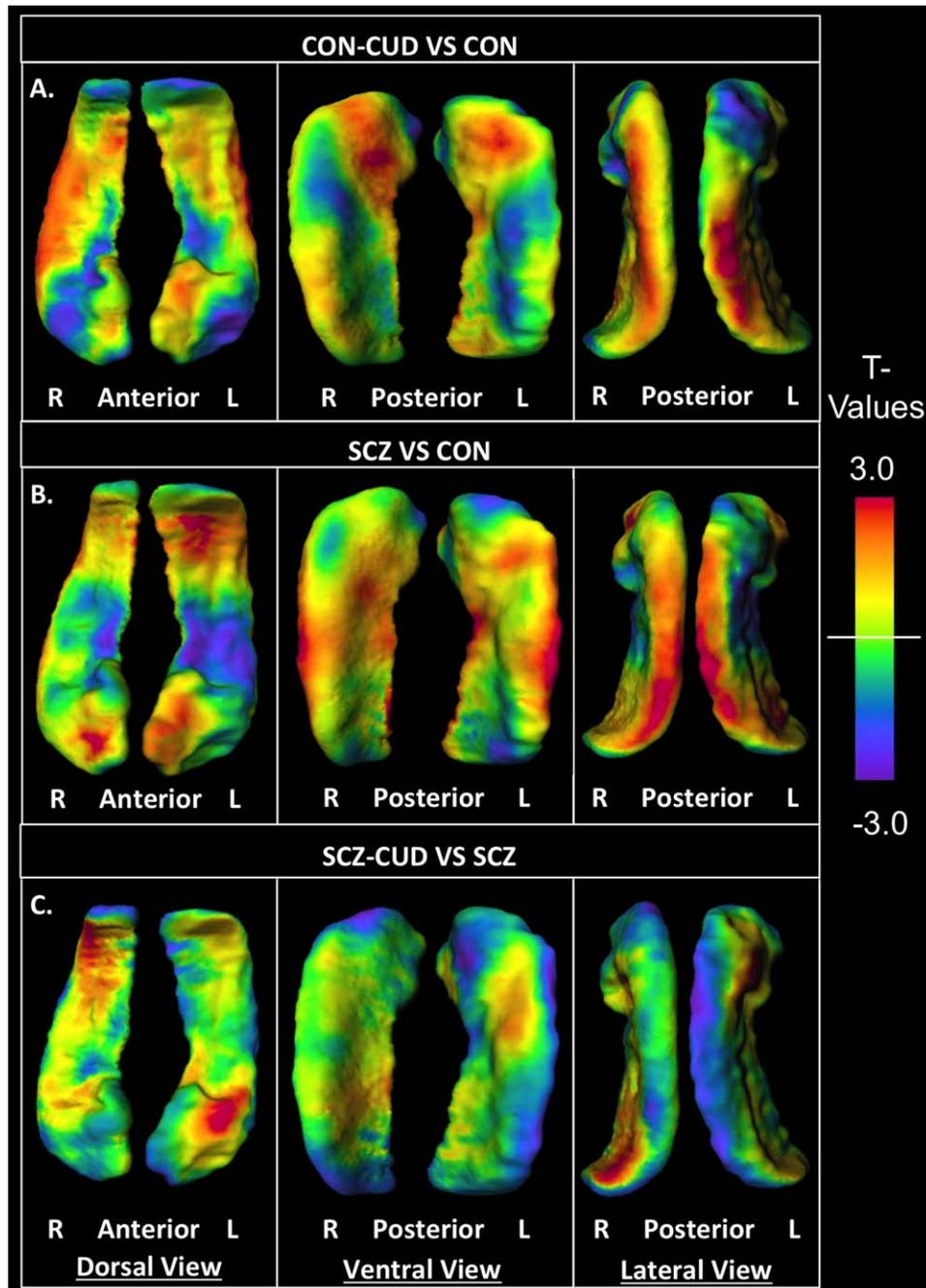


FIGURE 1. Hippocampal Surface Shape. Row A: cannabis-related shape in control subjects; Row B: schizophrenia-related shape; Row C: cannabis-related shape in schizophrenia subjects. T-values with cooler colors ($t < 0$) indicate inward shape differences and warmer colors ($t > 0$) indicate outward shape differences. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

difference was characterized by a large effect (Cohen's $d = 1.34$).

The posthoc differences between SCZ and CON revealed a main effect for group ($F_{1,67} = 5.5$, $P = 0.02$) and a group-by-PC interaction ($F_{9,59} = 2.2$, $P = 0.03$). SCZ were characterized by inward differences in the mediodorsal region of

the hippocampus as well as the anterior and posterior regions of the ventral hippocampus with outward differences observed in the dorsolateral and dorsal anterior regions of the hippocampus (Fig. 1B). The global schizophrenia-related shape difference was characterized by a large effect (Cohen's $d = 0.95$).

TABLE 2.

Estimated Mean (SD) of Hippocampal Volume (mm^3)

	Hemi	CON		CON-CUD		Cohen's d Effect Size	SCZ		SCZ-CUD		Cohen's d Effect Size
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Hippocampus	Left	2292	303	2353	305	0.17	2399	300	2212	303	-0.62
	Right	2702	378	2860	381	0.40	2855	417	2727	421	-0.31

The posthoc comparison of SCZ-CUD and SCZ revealed that the main effect for group and the group-by-PC interaction were nonsignificant ($P > 0.10$). The primary analysis observed a trend-level group-by-hemisphere interaction. As a secondary evaluation, we observed a significant group-by-hemisphere interaction ($F_{1,37} = 5.6$, $P = 0.02$). Based on this group-by-hemisphere interaction, SCZ-CUD were characterized by inward differences in the anterior, posterior, and lateral regions of the hippocampus that were most prominent in the left hemisphere (Fig. 1C). The global cannabis-related shape difference was characterized by a large effect (Cohen's $d = 0.90$).

The posthoc comparison of SCZ and CON-CUD did not reveal a main effect for group or group-by-PC interactions ($P > 0.10$).

The covariates for the above reported shape analyses included total brain volume, total cigarettes in the past year, and verbal IQ. Across all four groups, the RM-ANOVA revealed significant hemisphere-by-nicotine use and PC-by-total brain volume interactions (both $P < 0.05$). The RM-ANOVAs evaluating the post-hoc CON and CON-CUD, SCZ and CON, SCZ and CON-CUD, and SCZ-CUD and SCZ comparisons all revealed significant PC-by-total brain volume interactions (all $P < 0.05$). The SCZ and CON comparison revealed a significant verbal IQ-by-PC interaction ($P < 0.05$). The SCZ-CUD and SCZ comparison revealed a significant (atypical antipsychotic) dose-year-by-PC interaction ($P < 0.05$). All other covariate effects were nonsignificant.

Hippocampal Volume

RM-ANOVAs to determine between-group differences in hippocampal volume revealed a Right>Left asymmetry for each between-group comparison (all $P < 0.001$). The main effects of group and the group-by-hemisphere interaction were not significant for any comparison ($P > 0.10$; Table 2). Although the group-by-hemisphere interaction was nonsignificant ($P = 0.12$), percent differences in volume (and effect sizes) are reported to generate hypotheses for future research. The hippocampal volume was greater in CON-CUD compared with CON in the right (percent difference: +5.68%, $d = 0.42$), but not the left (percent difference: +2.62%, $d = 0.20$) hemisphere. Although the main effect of group was nonsignificant ($P = 0.16$), the hippocampal volume was lower in SCZ-CUD compared with SCZ in the left (percent differ-

ence: -8.11%, $d = -0.62$), but not the right (percent difference: -4.58%, $d = -0.31$) hemisphere. Nicotine use and dose-years of atypical antipsychotic medication use were not significant covariates (both $P > 0.10$).

Between-Group Differences on EM Performance and Symptoms

EM performance significantly differed across all four groups ($F_{3,93} = 28.94$, $P < 0.001$), while covarying for verbal IQ ($F_{1,92} = 22.55$, $P < 0.001$). CON-CUD scored lower than CON ($P = 0.046$, $d = -0.70$), while SCZ-CUD scored lower than SCZ at the trend level ($P = 0.071$, $d = -0.53$). SCZ scored lower than CON-CUD ($P < 0.01$, $d = -1.01$; Fig. 2; Table 3). Nicotine use and dose-years of atypical antipsychotic medication use (SCZ only) were not significant covariates (both $P > 0.10$) and were removed from the EM analyses.

SCZ-CUD scored significantly higher on avolition than SCZ ($F_{2,40} = 6.53$, $P = 0.02$), which was characterized by a large effect size ($d = 0.83$) after covarying for dose-years of atypical antipsychotic treatment. The remaining symptom ratings did not differ between groups (all $P > 0.10$; Table 3).

Correlations between Hippocampal Shape and EM, Symptoms, and CUD History

Among CON-CUD and CON, a more "cannabis-like" shape in the left hemisphere was correlated with poorer EM ($r = -0.25$, $P = 0.04$). Among CON-CUD, a longer duration of cannabis abuse was correlated with "cannabis-like" shape in the right hemisphere at moderate magnitudes ($r = -0.42$ to -0.48), but the results did not attain statistical significance (all $P > 0.10$). No other pairwise correlations among CUD history, EM, and hippocampal shape were significant (all $P > 0.10$). Among SCZ-CUD, we observed that greater duration of CUD was associated with a more "cannabis-like" shape in the right hemisphere ($r = 0.50$, $P = 0.04$), and a greater duration of abstinence from CUD was associated with a less "cannabis-like" shape in the left hemisphere ($r = -0.57$, $P = 0.03$). Remaining pairwise correlations among CUD history, EM, symptoms, and hippocampal shape were nonsignificant (all $P > 0.10$). Among SCZ and CON, we observed that a more "schizophrenia-like" shape in the left hemisphere was associated with poorer EM

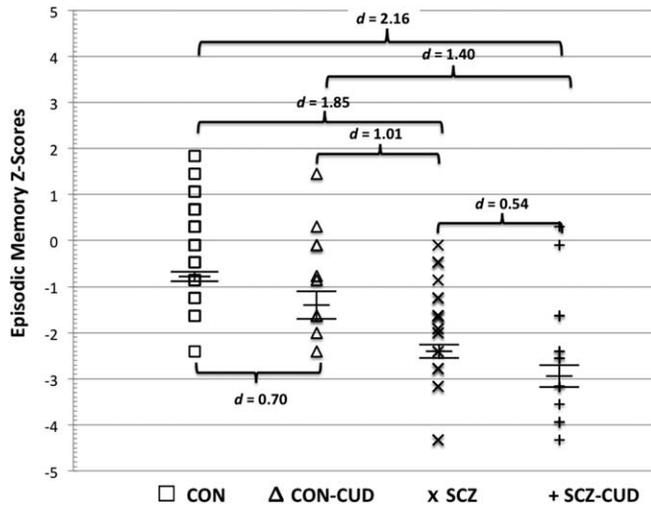


FIGURE 2. Between-group differences in EM (with standard error bars).

($r = -0.35, P = 0.003$), while we did not observe a significant correlation between hippocampal shape and avolition within SCZ ($P > 0.10$).

DISCUSSION

This study examined whether a prior history of CUD was associated with differences in hippocampal morphology and EM performance in otherwise healthy individuals and individu-

als with schizophrenia. The results suggest that the hippocampus in (1) CON-CUD subjects was characterized by both inward and outward surface shape differences compared to CON; (2) SCZ-CUD subjects was characterized by inward surface shape differences that were consistent with SCZ as well as distinct from both CON-CUD and SCZ. However, we did not find differences in SCZ-CUD that were observed among CON-CUD; and (3) SCZ subjects were characterized by surface shape differences that were partially consistent with prior studies. We also observed that CON-CUD and SCZ-CUD subjects demonstrated parametric deficits in EM performance compared to CON and SCZ, respectively. Moreover, “cannabis-like” hippocampal shape was correlated with poorer EM performance among CON and CON-CUD, but not among SCZ and SCZ-CUD. Lastly, a longer duration of CUD abuse and a shorter duration of CUD abstinence were correlated with more “cannabis-like” surface shape in schizophrenia subjects.

A past CUD diagnosis among controls was associated with both inward and outward shape differences. The observed inward shape differences are localized to regions where schizophrenia subjects are typically characterized by inward shape differences that may represent localized volume loss (Csernansky et al., 2002; Mamah et al., 2010; Johnson et al., 2013). This view is consistent with the current data indicating hippocampal shape did not differ between the CON-CUD and SCZ groups. The inward shape differences observed in this sample are also consistent with the results of a prior study suggesting that cannabis use is related to deflation of the hippocampal surface (Solowij et al., 2013). Other research suggests that hippocampal volume among heavy cannabis using adolescents was

TABLE 3.

Mean (SD) Between-Group Differences for EM and Symptoms

	CON (n = 44)	CON-CUD (n = 10)	SCZ (n = 28)	SCZ-CUD (n = 15)	Effect Size
EM	0.00 (1.00)	-0.77 (1.19)	-1.91 (1.06)	-2.55 (1.34)	– ^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. An earlier version of this table was published by Smith et al., 2014 in Schizophrenia Bulletin.

Abbreviations are explained in the first footnote to Table 1.

Note: n = 1 CON-CUD, n = 2 SCZ, and n = 2 SCZ-CUD did not have EM data.

^aCON > CON-CUD ($P = 0.046, d = -0.70$), SCZ ($P < 0.001, d = -1.85$), and SCZ-CUD ($P < 0.001, d = -2.16$), CON-CUD > SCZ ($P = 0.006, d = -1.01$), CON-CUD > SCZ-CUD ($P < 0.001, d = 1.40$), and SCZ-CUD < SCZ ($P = 0.071, d = -0.53$).

^bSCZ-CUD and SCZ did not differ ($P > 0.10$).

^cSCZ-CUD > SCZ ($P < 0.05$).

reduced compared to nonusers (Ashtari et al., 2011), however, results in this study regarding volume were inconclusive. A number of variables may explain the divergence between the observed shape and volume, such as the quantity, frequency or duration that cannabis was used, duration of abstinence, and the age of CUD onset.

A past CUD diagnosis among schizophrenia subjects was associated with inward shape differences in the left hippocampus that may reflect localized volume loss. This interpretation is consistent with the moderately sized volume difference in the left hemisphere observed between schizophrenia subjects with and without a prior CUD. These observations could potentially reflect cannabis neurotoxicity within the hippocampus that has been suggested via meta-analysis (Rocchetti et al., 2013) and is consistent with prior research on cannabis-related hippocampal morphology in schizophrenia (Solowij et al., 2013). Based on the global shape difference effect size, CON-CUD and SCZ-CUD appear to have a similar degree of sensitivity to the effects of cannabis. However, the visual maps suggest that the global shape difference is qualitatively different between CON-CUD and SCZ-CUD. Also, we found an interaction between treatment with antipsychotic medications and hippocampal shape (but not volume), which is partially consistent with prior research (Fusar-Poli et al., 2013; Lesh et al., 2015; Vita et al., 2012). Perhaps greater statistical power is needed to observe a relationship between antipsychotic medication treatment and volume.

We observed a general finding that all groups were characterized by Right > Left hippocampal volume, which is a trend typically found in the healthy human brain (Pedraza et al., 2004; Woolard and Heckers, 2012), but also exaggerated in schizophrenia subjects (Breier et al., 1992; Wang et al., 2001). Asymmetric shape findings were noted in SCZ-CUD where shape differences were more prominent in the left rather than right hemisphere. It appears a history of CUD may exaggerate the selective left hemisphere disruption caused by schizophrenia.

The observed hippocampal shape characterizing the SCZ group in this study was consistent with some (Johnson et al., 2013; Mamah et al., 2012; Qiu et al., 2013), but not all prior research (Csernansky et al., 2002; Mamah et al., 2010; Johnson et al., 2013). Noted differences may be reflective of prior studies evaluating schizophrenia subjects (and controls) with and without a past history of a substance use disorder as individual cohorts. In addition, the observed patterns of morphology were characterized using cross-sectional data, and as such, could reflect neurobiological susceptibilities to cannabis abuse. Thus, longitudinal research is needed to determine the direction of these relationships.

The lower EM observed in both CUD groups was consistent with known effects of acute and chronic cannabis use [see (Ranganathan and D'Souza, 2006; Crane et al., 2013) for review]. We observed that a more "cannabis-like" shape was related to poorer EM for CON-CUD. This may implicate that the near-daily use of cannabis during adolescence potentially interfered with synaptic pruning of the hippocampus during

neuromaturation (Lisdahl et al., 2013; CON-CUD in our study started cannabis at an average age of 16.7 years and 80% were daily users). In turn, the potential morphometric difference may have contributed to poorer EM that persisted even after two years of abstinence. Alternatively, shape differences may represent a vulnerability biomarker of poor memory given the cross-sectional nature of the data.

Among SCZ-CUD, we observed that a longer duration of CUD abuse and a shorter duration of abstinence were both associated with a more "cannabis-like" hippocampal shape, while we did not observe any relationships between hippocampal morphology and CUD history among CON-CUD. Low statistical power could explain the lack of significance that we observed in the moderately sized correlations between CUD history and shape among CON-CUD. An alternative explanation is that the observed morphological differences may represent neurobiological vulnerabilities to the effects of cannabis that predated cannabis use and could explain the non-significant relationships.

There are several limitations to this study. Primarily, there is an inability to infer a causal relationship between past history of cannabis use and chronically impaired EM or differences in hippocampal morphology given the cross-sectional nature of the data. Furthermore, a larger sample may provide additional statistical power necessary to determine whether the moderately-sized correlations were significant. We did not collect quantitative or biological markers of cannabis use, which could support an assessment of dose-response effects on both the hippocampus and EM, and there was no collection of treatment data other than antipsychotic medication. Along these lines, the CUD history data was collected during self-reported clinical interviews and is susceptible to the known limitations of self-report. Lastly, three CON-CUD subjects had lifetime histories of abuse of alcohol and/or other illicit substances. The analytic findings remained after excluding these subjects, thus they were included to optimize statistical power. Future research might consider longitudinal evaluations of whether cannabis-related hippocampal differences abate after a period of abstinence.

To conclude, the results suggest that a past CUD during adolescence may be associated with differences in hippocampal morphology and EM impairments in young adulthood even after a prolonged period of abstinence. Although the results may be compatible with a causal hypothesis, the cross-sectional nature of the study does not support testing causal relationships. Hence, the observed morphological differences could also be explained as biomarkers of a neurobiological vulnerability to poor memory or the effects of cannabis. Overall, there is still much to learn about the potential long-term implications of cannabis on cognition even after a period of abstinence.

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