Marijuana use and major depressive disorder are additively associated with reduced verbal learning and altered cortical thickness

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Abstract

Marijuana (MJ) use and major depressive disorder (MDD) have both been associated with deficits in verbal learning and memory as well as structural brain abnormalities. It is not known if MJ use by those with MDD confers additional impairment. The goal of this study was to examine unique and combined effects of MDD and MJ use on verbal memory and brain structure. Young adults ($n=141$) aged 18–25 years with MJ use and no lifetime MDD (MJ, $n=46$), MDD and no MJ use (MDD, $n=23$), MJ use and lifetime MDD (MDD+MJ, $n=24$), and healthy controls without MDD or MJ use (CON, $n=48$) were enrolled. Participants completed the California Verbal Learning Test, Second Edition (CVLT-II), a measure of verbal learning and memory. A subsample of 82 participants also underwent a structural magnetic resonance imaging (MRI) scan. Group differences in CVLT-II performance, cortical thickness, and hippocampal volume were assessed. We found an additive effect of MDD and MJ on memory recall. Only MDD, but not MJ, was associated with poorer initial learning, fewer words recalled, more intrusion errors, and lower percent retention. There was also an additive effect of MDD and MJ use on reduced cortical thickness in the middle temporal gyrus. Findings indicate that MJ use and MDD have additive adverse associations with verbal recall and cortical thickness in the middle temporal gyrus, suggesting that MJ use among those with MDD may be contraindicated. Prospective studies are warranted to determine whether this association may be causal.

Keywords Major depressive disorder · MDD · Marijuana · Cannabis · Verbal memory · CVLT-II · MRI · Cortical thickness

Introduction

The prevalence of marijuana (MJ) use among individuals with major depressive disorder (MDD) is an increasing concern.

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National estimates suggest higher prevalence of MJ use among adolescents with past year MDD (24.3%) than those without past year MDD (10.1%) (SAMHSA, 2017). MDD is the third most common reason why individuals seek medical MJ, after pain and sleep disorders (Reinarman, Nunberg, Lanthier, & Heddleston, 2011). Increasing MJ availability and potency are likely to lead to increased MJ use among individuals with MDD, making it vitally important to understand any additive effects of MJ use and MDD on brain structure and function.

Memory deficits, particularly on verbal memory tasks, are evident in MJ-using adolescents and young adults (Schweinsburg et al., 2008; Hanson et al., 2010; Meier et al., 2012; Solowij et al., 2011). Compared to non-using controls, adolescent MJ users recall fewer words and demonstrate worse learning (Solowij et al., 2011), particularly in the encoding phase (Schuster, Hoepfner, Evins, & Gilman, 2016). The degree of impairment has been associated with duration, frequency, and amount of MJ use (Ashtari et al., 2011; Bolla et al., 2002; Solowij, 2002), as well as age of onset of MJ use (Becker, Collins, & Luciana, 2014; Gruber,

Dahlgren, Sagar, Gonenc, & Killgore, 2012; Schuster et al., 2016; Solowij et al., 2011). There is evidence to suggest that these memory impairments may be attributable to the effects of delta-9-tetrahydrocannabinol (THC), the principal psychoactive ingredient of MJ. THC acts in the brain through endogenous cannabinoid CB1 receptors densely located in the hippocampus, anterior cingulate and prefrontal cortices, entorhinal cortex, and temporal pole (Mackie, 2005; Piomelli, 2003), and in regions involved in manipulating and integrating information, such as the inferior temporal lobe and the orbitofrontal cortex (OFC) (Goldman-Rakic, 1987; Schoenbaum & Roesch, 2005). CB1 receptor activation in these brain regions, especially in the hippocampus, inhibits the release of amino acid and monoamine neurotransmitters causing changes in neuronal firing patterns (Ashton, 2018; Iversen, 2003). Disruption of hippocampal firing rhythms can prevent induction of long-term potentiation critical for learning and memory (Hampson & Deadwyler, 2000; Stella, Schweitzer, & Piomelli, 1997).

Mild to moderate verbal learning and memory deficits have also been reported in MDD (Otto, 1994; Roca et al., 2015). Compared to healthy controls, adults with MDD recall fewer words after a delay on verbal list-learning tasks and appear to utilize less efficient strategies to encode novel information, while memory retrieval and retention are unaffected, pointing to a primary impairment in encoding (Kizilbash, Vanderploeg, & Curtiss, 2002). Some studies suggest that these memory deficits are more pronounced in people with earlier-onset MDD (Bora, Harrison, Yucel, & Pantelis, 2013; Lee, Hermens, Porter, & Redoblado-Hodge, 2012) and recurrent MDD (Ahern & Semkovska, 2017; Galecki, Talarowska, Anderson, Berk, & Maes, 2015; Talarowska et al., 2015), and are likely to endure even after MDD remission (Conradi, Ormel, & de Jonge, 2011; Gorwood, Corruble, Falissard, & Goodwin, 2008; Yamamoto & Shimada, 2012). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has emerged as a plausible mechanism, whereby over-release of stress hormones (Burke, Davis, Otte, & Mohr, 2005) inhibits hippocampal neurogenesis, disrupting memory encoding (Bemelmans, Goekoop, & van Kempen, 1996; Dillon & Pizzagalli, 2018; Turner, Furey, Drevets, Zarate, & Nugent, 2012).

Structural abnormalities, particularly cortical thinning, in brain circuits underlying memory have also been reported in MJ users and in adults with MDD. In cross-sectional magnetic resonance imaging (MRI) studies, compared to non-users, MJ users had thinner caudal middle frontal, insular, superior frontal and entorhinal cortices (Gilman, Ulysse, Schoenfeld, & Evins, 2018; Levar, Francis, Smith, Ho, & Gilman, 2018; Lopez-Larson et al., 2011), and thicker lingual, inferior parietal, superior temporal, and paracentral regions (Jacobus et al., 2015; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014). While differences in brain structure among those who use MJ are still debated, a more consistent characterization of

cortical changes has been reported in individuals with MDD. In a recent study, compared to healthy controls, adults with MDD ($N=2,148$) had decreased cortical thickness in orbitofrontal, anterior and posterior cingulate cortices, and insular and temporal lobes (Schmaal et al., 2017). Cross-sectional studies have also shown that compared to healthy controls, those with MDD have thinner lateral and medial orbitofrontal, inferior and superior temporal, and superior frontal cortices (Won, Choi, Kang, Lee, & Ham, 2016; Zhao et al., 2017). It is not known whether these structural abnormalities underpin the cognitive abnormalities described above.

Co-morbid MJ use and MDD is increasingly common, with many using MJ in an attempt to ameliorate symptoms of MDD. However, the impact of MJ use in those with MDD on verbal memory or brain structure is largely unknown. Previous studies did not find performance differences between MJ users with and without co-occurring MDD (Roebke, Vadhan, Brooks, & Levin, 2014; Secora et al., 2010). However, these studies lacked optimal comparison groups (e.g., healthy controls), and neither collected neuroimaging measures. In the current study, we aimed to compare verbal memory performance in young adults with and without both MJ use and MDD using a 2 x 2 full factorial design. We hypothesized independent, putative effects of MJ use and MDD on CVLT-II performance, as well as a possible interaction. Our secondary and exploratory hypothesis was that similar additive and interactive effects of MJ use and MDD would be seen on measures of brain regions underlying memory.

Methods

One hundred and forty-one young adults (aged 18–25 years) were recruited from Greater Boston to participate in a larger neuroimaging study examining the effects of MJ use on brain structure and function. Prior to participation, participants reviewed the study protocol and signed a written informed consent form. Partners Health Subjects Committee Institutional Review Board approved the study procedures. Participants were compensated for their time in the form of a check upon completion of the study.

Participants

The study sample was comprised of 46 young adults with MJ use and no lifetime MDD (MJ), 23 with MDD and no MJ use (MDD), 24 with MJ use and lifetime MDD (MDD+MJ), and 48 healthy controls without MDD or MJ use (CON). Individuals enrolled in the MJ and MDD+MJ groups reported using MJ at least weekly, while non-MJ users (CON and MDD) had used MJ on fewer than five occasions in their lifetime and not in the past year. All participants were asked

to abstain from using any intoxicating substance on the day of the study. MDD participants (MDD and MDD+MJ) met lifetime criteria for unipolar MDD without psychotic features, as verified by the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002).

Participants were excluded if they met criteria for any Axis I disorder other than alcohol abuse or dependence in the full cohort, MJ abuse or dependence in the MJ-using groups, or MDD and anxiety disorders in the MDD groups. Also exclusionary were self-reports of daily nicotine use, a score over 16 on the Alcohol Use Disorder Identification Test (AUDIT; (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993)), current or past history of major medical illness (e.g., diabetes, cardiovascular disease, HIV, hepatitis C, traumatic brain injury), current suicidal ideation, claustrophobia or other contraindications to MRI, positive urine drug screen (except for THC for the MJ groups) or positive pregnancy test. Of the 141 participants included in the present study, only 82 participants completed an MRI scan; the remaining 59 individuals were enrolled prior to the addition of the scanning component to the study protocol.

Assessments

Past 90-day MJ and alcohol exposure were quantified using a timeline-follow-back (TLFB) calendar method (Sobell, Sobell, Klajner, Pavan, & Basian, 1986), during which participants indicated the number of days in the past 90 days that they used MJ, along with the quantity they used (in joint equivalents) on each occasion. Participants also indicated the number of standard drinks consumed daily in the past 90 days. The Wechsler Test of Adult Reading (WTAR; (Carter, 2001)) was used to estimate full-scale IQ, and all participants completed the Mood and Anxiety Symptom Questionnaire (MASQ; (Clark & Watson, 1991)) to assess past week depressive and anxious symptoms. The MASQ contains four sub-scales, measuring depressive symptoms, anxious symptoms, anhedonic depression, and anxious arousal.

Verbal memory was assessed using the California Verbal Learning Test, Second Edition (CVLT-II; (Delis et al., 1987)). This test involves verbal presentation of 16 words from four different semantic categories (e.g., vegetables, ways of traveling, animals, and furniture). The list was presented verbally five consecutive times, and after each presentation participants were asked to recall as many words as possible (Learning Trials 1–5). Finally, participants were asked to recall as many words as possible after a short (approximately 1 min) and long (approximately 20 min) delay, with and without provision of semantic cues (cued and free recall, respectively). Dependent variables included words recalled after Trial 1 (Trial 1 immediate recall, range: 0–16), total words recalled after Trials 1 through 5 (total learning; range 0–80), learning slope (i.e., words recalled in Trial 5 minus words recalled in Trial 1),

short-delay cued recall (SDCR; range: 0–16), short-delay free recall (SDFR; range: 0–16), long-delay cued recall (LDCR; range: 0–16), long-delay free recall (LDFR; range: 0–16), percent recall ([LDFR/Trial 5 free-recall score] x 100), total intrusions and repetitions, semantic clustering (i.e., number of times two adjacently recalled words were from the same semantic category), and serial clustering (i.e., number of times two adjacently recalled words were in the original presentation order).

Acquisition and analysis of structural neuroimaging data

The scanning cohort consisted of 20 MJ, 18 MDD, 21 MDD+MJ, and 23 CON. Participants were scanned using a 3 T Siemens (Erlangen, Germany) Skyra scanner with a 32-channel head coil at the Martinos Center for Biomedical Imaging. Whole-brain T1-weighted 1-mm isotropic structural scans were collected using a 3D multiecho MPRAGE sequence (176 sagittal slices, 256-mm FoV, TR 2,530 ms, TI 1,200 ms, 2x GRAPPA acceleration, TE 1.64/3.5/5.36/7.22 ms, BW 651 Hz/px, T_{acq} 6:03 min) (van der Kouwe, Benner, Salat, & Fischl, 2008). All acquisitions were automatically positioned using AutoAlign (van der Kouwe et al., 2005). T1-weighted images were analyzed using Freesurfer (Martinis Center for Biomedical Imaging, Massachusetts General Hospital, Boston; <http://surfer.nmr.mgh.harvard.edu>). Images were aligned and registered to the MNI152 2 mm³ standard space template (with 0.7-mm resolution) and corrected for spatial distortion and smoothed using a FWHM of 5 mm. Whole brain segmentation and cortical parcellation were applied to the corrected T1-weighted images (Desikan et al., 2006; Fischl et al., 2002). Cortical thickness data were extracted from the corrected images and examined in the following brain regions from both left and right hemispheres: lateral and medial orbitofrontal cortices, parahippocampal gyrus, middle temporal gyrus, entorhinal cortex, superior frontal gyrus, caudal middle frontal gyrus, and rostral middle frontal gyrus. We additionally extracted bilateral hippocampal volumes.

Statistical analysis

Group differences in continuous demographic variables, substance use variables, MASQ sub-scales scores, and CVLT-II outcomes were examined using two-way ANOVA models with MDD (No-MDD [$_{\text{CON}}$, MJ] vs. MDD [$_{\text{MDD}}$, MDD+MJ]) and MJ use (Non-users [$_{\text{CON}}$, MDD] vs. MJ users [$_{\text{MJ}}$, MDD+MJ]) as group factors and their interaction as independent variables. For gender, we used an analogous logistic regression model. To estimate effect sizes, we calculated Cohen's d (Cohen, 1988) for the main effect of MDD, the main effect of MJ use, and the interaction effects of MJ use within each MDD group for all continuous outcomes in Table 1. In follow-up models, we added alcohol use (number of drinks per week)

and FSIQ as covariates to all the CVLT-II outcome variables. To adjust for multiple comparisons, we used the false discovery rate adjustment by Benjamini and Hochberg (Benjamini & Hochberg, 1995).

For all cortical thickness variables and hippocampal volume, we conducted exploratory generalized linear mixed models (GLMMs), using MDD, MJ use, hemisphere, and their interactions as independent variables,

Table 1 Demographic, substance use, and clinical characteristics

Descriptive	CON		MJ		MDD		MDD+MJ		MDD effect		MJ effect		Interaction effect	
									(CON and MJ vs.		(CON and MDD vs.			
	(n=48)		(n=46)		(n=23)		(n=24)		MDD and MDD+MJ		MJ and MDD+MJ		MJ effect within MDD status	
									<i>p</i>	ES	<i>p</i>	ES	<i>p</i>	ES CON ES MDD
Demographics														
Male (% , n)	48	(23)	52	(24)	52	(12)	48	(11)		1.00		1.00	1.19	0.84
Age (years)	21.5	(2.0)	20.3	(2.1)	22.1	(2.5)	21.3	(2.4)	*	0.35	*	-0.48	-0.60	-0.32
Education completed (years)	15.1	(1.9)	13.8	(1.7)	15.7	(2.1)	14.6	(1.6)		0.32	***	-0.66	-0.72	-0.57
Predicted FSIQ (WTAR), M(SD)	113.9	(4.3)	114.1	(6.0)	110.0	(10.0)	109.6	(9.5)	**	-0.60		-0.01	0.04	-0.05
Current SCID diagnoses														
Alcohol abuse (% , n)	0	(0)	0	(0)	9	(2)	13	(3)	.	.	.	.	.	.
Alcohol dependence (% , n)	0	(0)	0	(0)	9	(2)	0	(0)	.	.	.	.	.	.
Marijuana abuse (% , n)	0	(0)	33	(15)	0	(0)	67	(16)	.	.	.	.	.	.
Marijuana dependence (% , n)	0	(0)	7	(3)	0	(0)	54	(13)	.	.	.	.	.	.
Major depressive disorder (% , n)	0	(0)	0	(0)	39	(9)	29	(7)	.	.	.	.	.	.
Any anxiety disorder (% , n)	0	(0)	0	(0)	48	(11)	54	(13)	.	.	.	.	.	.
Substance use														
Alcohol														
Drinks/week (TLFB)	2.3	(2.2)	3.2	(3.3)	2.1	(2.4)	4.8	(4.4)		0.24	**	0.50	0.34	0.76
AUDIT score	3.1	(2.1)	4.1	(2.0)	3.4	(3.8)	4.0	(2.5)		0.05		0.35	0.50	0.17
Marijuana use (TLFB)														
# MJ use days per week	..		3.0	(1.6)	..		4.8	(1.4)	***	1.24		n/a	n/a	n/a
# MJ joints per week	..		7.8	(8.4)	..		17.3	(20.0)	**	0.71		n/a	n/a	n/a
Age of onset (years)	..		16.2	(1.6)	..		16.4	(1.8)		0.09		n/a	n/a	n/a
Years of regular use, years	..		2.0	(1.4)	..		2.7	(2.6)		0.36		n/a	n/a	n/a
Recency of MJ use, days	..		2.0	(2.2)	..		1.1	(0.9)	*	-0.51		n/a	n/a	n/a
Depressive Symptoms														
MASQ¹														
Anxious Symptoms	15.9	(4.3)	19.8	(5.3)	23.4	(7.3)	24.2	(8.0)	***	0.98		0.42	0.82	0.10
Anxious Arousal	20.3	(2.9)	22.8	(5.9)	26.7	(7.4)	28.2	(10.1)	***	0.88		0.35	0.58	0.17
Depressive Symptoms	18.0	(6.0)	21.5	(6.7)	37.6	(11.1)	30.9	(10.1)	***	1.65		0.01	**	0.57 -0.63
Anhedonic Depression	56.4	(12.7)	52.5	(13.3)	75.5	(13.0)	65.6	(15.4)	***	1.12	*	-0.31	-0.31	-0.69

Note. All values are means and standard deviations unless otherwise noted. P-values are based on ANOVA main effects and interactions for continuous variables and on logistic regression main effects or interactions for categorical variables, where * < 0.05, ** < 0.01, *** < 0.001. As for the SCID diagnoses, significance and effect sizes could not be estimated due to most diagnoses being specific to only some of the groups (i.e., quasi-complete separation issues in logistic models). Effect sizes (ES) are Cohen's *d* for continuous variables and odds ratios for categorical variables

CON healthy controls, MJ marijuana users without lifetime MDD, MDD non-users with lifetime MDD, MDD+MJ MJ users with lifetime MDD, FSIQ(WTAR) full-scale IQ, as estimated by the Wechsler Test of Adult Reading, AUDIT Alcohol Use Disorder Identification Test, TLFB time-line follow-back, MASQ Mood and Anxiety Symptom Questionnaire

¹ MASQ was completed by 32 CON and 21 MJ because the questionnaire was introduced later in the study protocol

including gender, gender by hemisphere, and age as covariates. Hemispheres were modeled as repeated measures within person using an unstructured covariance matrix. We calculated effect sizes as described above for each brain region and hemisphere separately, using Cohen's *d*.

In *post hoc* analyses, within the MJ sample, we investigated whether MJ use severity was associated with CVLT-II performance, cortical thickness or hippocampal volume and, likewise, within the MDD sample whether mood symptom severity was associated with these outcomes. To do so, we conducted partial correlations (1) between MJ use patterns (MJ use days per week, joints per week, age of onset of use, years of regular use, and recency of use) and CVLT-II performance, cortical thickness, and hippocampal volume, controlling for MDD status, among the MJ participants, and (2) between mood severity (measured via the four subscales from the MASQ) and CVLT-II performance, cortical thickness, and hippocampal volume, controlling for MJ status, among the MDD participants. These analyses were conducted for outcome variables for which there were significant group differences in the primary analyses detailed above.

Differences were considered significant at a two-tailed $\alpha < .05$. All analyses were performed using SAS (Version 9.4 of the SAS System for Windows).

Results

Participant characteristics

Demographic, substance use, and mood characteristics are presented in Table 1. Gender distribution was comparable across the four groups. Participants with MDD [MDD, MDD+MJ] were older, had lower estimated full-scale IQs, and had more severe mood symptoms across all subscales on the MASQ than participants without MDD [CON, MJ] (Table 1; for full model parameters and *p*-values, see Supplemental Table 1). MJ users [MJ, MDD+MJ] completed fewer years of education, reported more alcoholic drinks per week, and had lower anhedonic depression scores than MJ non-users [CON, MDD]. MDD+MJ, compared to MJ, were heavier and more frequent MJ users, and used MJ more proximally to the study visit. MDD+MJ and MDD groups were comparable in the percentage of participants with current MDD and/or anxiety disorder, as well as lifetime alcohol abuse and dependence. There was a significant interactive effect of MDD and MJ use on general depressive symptoms from the MASQ, such that among those with MDD those who did not use MJ had more severe depressive symptoms compared to those who used MJ.

Memory

MDD and MJ use had additive – but not interactive – associations with multiple aspects of verbal learning and memory (Table 2 and Fig. 1; for full model parameters, see Supplemental Table 2). There were main effects of both MDD and MJ use on recall, with both groups recalling fewer words after short (free and cued) and long (free only) delays. There was a main effect of MDD, but not MJ use, on poorer initial learning during Trial 1, fewer words recalled across all learning trials, more intrusion errors, fewer words recalled with cues after a long delay, and lower percent retention. There was a trend-level main effect of MDD on semantic clustering; non-depressed individuals, particularly those who did not currently use MJ (CON), had greater semantic clustering during recall. There were no significant interactions between MDD and MJ use on any aspect of verbal learning and memory. Given the presence of significant main effects and non-significant interactions, the effects of MDD and MJ use are likely to be additive. That is, the combination of both MDD and MJ use is not notably larger or smaller than expected by summing the simple main effects. See Supplemental Table 2 for a comparison of raw and adjusted *p*-values. Using age-standardized scores instead of raw scores (correlation between all raw and standardized scores: $r > .94$) did not alter these findings aside from weakening the observed association between MDD and trial 1 learning slightly (though the association remained significant).

We also adjusted CVLT-II outcome models for FSIQ and alcohol use (TLFB drinks/week) to determine if these factors influenced findings. FSIQ was a significant predictor in eight out of the 12 CVLT-II models, while alcohol use was not a significant predictor in any of the models. After adjusting *p*-values from the covariate-adjusted models for multiple comparisons, several models became significant for MJ use, including lower total learning ($p=.04$), and lower long-delay cued recall ($p=.02$). The only model in which the addition of covariates rendered effects non-significant was the model of short-delay cued recall, where the MDD effect became non-significant ($p=.09$) but the MJ effect remained ($p < .01$). All other associations that were significant between MJ and MDD with CVLT-II outcomes in the unadjusted models remained significant after controlling for FSIQ and alcohol (*p*-values $< .05$).

Cortical thickness and hippocampal volume

Among the sub-sample of young adults who participated in structural brain scanning ($n = 82$), MJ use was associated with reduced cortical thickness in the medial orbitofrontal, middle temporal, and superior frontal brain regions, all with small to medium effect sizes. MDD was associated with reduced cortical thickness in the middle temporal gyrus. All other

Table 2 Memory performance as measured by the California Verbal Learning Test (Second Edition; CVLT-II)

CVLT-II outcomes	CON		MJ		MDD		MDD+MJ		MDD effect		MJ effect		Interaction effect	
									(CON and MJ vs.		(CON and MDD vs.			
	(n=48)		(n=46)		(n=23)		(n=24)		MDD and MDD+MJ)		MJ and MDD+MJ)		MJ effect within MDD status	
	<i>p</i>	ES	<i>p</i>	ES	<i>p</i>	ES CON	ES MDD							
Trial 1														
raw	9.6	(2.5)	8.6	(2.8)	7.7	(1.9)	8.0	(2.7)	*	-0.50		-0.23	-0.39	0.13
Z score	1.3	(1.4)	0.6	(1.5)	0.2	(1.1)	0.4	(1.5)						
Total Learning														
raw	66.0	(7.6)	61.9	(9.7)	60.3	(8.8)	57.5	(10.3)	**	-0.56		-0.41	-0.47	-0.30
T score	65.3	(10.7)	61.2	(11.7)	59.2	(10.8)	55.8	(11.4)						
Learning Slope														
raw	1.3	(0.6)	1.3	(0.6)	1.5	(0.5)	1.3	(0.5)		0.27		-0.04	0.08	-0.36
Z score	-0.3	(1.1)	-0.3	(1.1)	0.1	(0.9)	-0.3	(1.1)						
Total Intrusions														
raw	1.5	(2.5)	1.8	(3.0)	3.2	(3.9)	3.8	(5.0)	**	0.55		0.13	0.13	0.14
Total Repetitions														
raw	6.8	(9.1)	5.7	(3.4)	5.9	(4.1)	7.0	(7.2)		0.04		-0.05	-0.16	0.19
Z score	0.2	(1.5)	0.2	(0.8)	0.1	(0.9)	0.4	(1.5)						
Short-Delay Free Recall														
raw	14.6	(1.5)	13.3	(2.5)	13.3	(2.6)	11.8	(3.0)	**	-0.61	*	-0.57	-0.62	-0.53
Z score	1.2	(0.7)	0.7	(0.9)	0.7	(1.0)	0.2	(1.1)						
Short-Delay Cued Recall														
raw	14.6	(1.6)	13.6	(2.5)	13.7	(2.1)	12.2	(3.7)	*	-0.49	*	-0.48	-0.49	-0.48
Z score	0.8	(0.6)	0.5	(0.9)	0.5	(0.9)	-0.1	(1.5)						
Long-Delay Free Recall														
raw	14.6	(1.7)	13.7	(2.4)	13.5	(2.1)	12.0	(3.8)	**	-0.59	*	-0.44	-0.43	-0.48
Z score	0.9	(0.6)	0.6	(0.9)	0.6	(0.8)	0.0	(1.4)						
Long-Delay Cued Recall														
raw	14.9	(1.4)	13.9	(2.3)	13.6	(2.3)	12.9	(2.8)	**	-0.56		-0.43	-0.55	-0.27
Z score	0.8	(0.6)	0.4	(0.9)	0.3	(1.0)	0.0	(1.1)						
Percent recall, %														
raw	98.3	(10.4)	96.9	(11.3)	94.9	(11.3)	85.8	(22.3)	**	-0.54		-0.29	-0.13	-0.52
Semantic Clustering														
raw	3.3	(3.0)	2.0	(2.7)	1.8	(2.6)	1.9	(2.1)		-0.31		-0.29	-0.44	0.07
Z score	1.5	(1.9)	0.8	(1.7)	0.6	(1.8)	0.8	(1.4)						
Serial Clustering														
raw	0.7	(1.7)	1.2	(2.0)	1.0	(1.6)	0.6	(0.9)		-0.10		0.11	0.26	-0.29
Z score	0.0	(1.6)	0.4	(1.7)	0.2	(1.6)	-0.1	(0.9)						

Note. All values are means and standard deviations. *p*-values are based on 2-way ANOVAs (see Supplemental Table 2) and were adjusted for false discovery rate; * < 0.05, ** < 0.01, *** < 0.001. Effect sizes (ES) are Cohen's *d*. Only raw score outcomes were analyzed; means and standard deviations of standardized scores are only provided for clinical comparison purposes

CON healthy controls, MJ marijuana users without lifetime MDD, MDD non-users with lifetime MDD, MDD+MJ MJ users with lifetime MDD

interactions between MDD and MJ use on cortical thickness were not significant (Table 3, Supplemental Table 3). We note that an additive effect of MJ use and MDD is likely in the middle temporal gyrus, given the main effects of both MDD

and MJ use and a non-significant interaction. While we were not able to detect any significant associations between MDD or MJ use with hippocampal volume (both $p > .05$, Table 3), the large negative effect sizes of MJ use within the group of

Fig. 1 Differences in verbal learning across five learning trials (free recall) and during both short (approximately 1-min) and long (approximately 20-min) delay recall trials among young adults with a lifetime history of major depressive disorder (MDD) with or without concurrent marijuana (MJ) use. Young adults with MDD performed

more poorly at all recall trials than those without MDD, and young adult MJ users recalled fewer words at short- and long-delay free-recall trials than non-users. *CON* healthy controls, *MJ* MJ users without MDD, *MDD* non-users with MDD, *MDD+MJ* MJ-users with MDD, *SDFR* short-delay free recall, *LDFR* long-delay free recall

participants with MDD (left hippocampus: $d = -0.87$, right hippocampus: $d = -0.74$) suggest that this association may warrant further study in a larger sample.

Hemisphere-specific associations between MDD or MJ use and cortical thickness and hippocampal volume were largely absent, except for an interaction between MJ use with hemisphere in the entorhinal cortex, which indicated that the right-hemisphere thickness was less in MJ users compared to non-users.

Associations with symptom severity

Partial correlations among MJ users, controlling for the effect of MDD, showed that MJ age of onset was associated with CVLT-II long-delay cued recall ($r = .26$, $p = .03$), indicating that participants with a later age of onset of MJ recalled more words after a delay than those who started using MJ earlier in life. No other partial correlations between MJ use severity measures and either memory performance or cortical thickness/volume were significant (p -values $> .30$).

In MDD participants, after controlling for MJ use, there were no significant partial correlations between MASQ ratings with any of the CVLT-II outcomes examined (all p -values $> .20$). A higher level of anxious arousal on the MASQ was

associated with lower cortical thickness in the right middle temporal gyrus among MDD participants ($r = -0.33$, $p = 0.045$). No other partial correlations between MASQ subscales and cortical thickness/volume were significant (p -values $> .07$).

Discussion

Marijuana is the most commonly used illicit drug among individuals with MDD (SAMHSA, 2017). Given that MJ use and MDD have been independently associated with memory decrements and structural brain abnormalities, it is critical to examine whether MJ use is associated with worsening (or improvement) of these impairments in MDD patients. The current investigation, to our knowledge, marks the first study to examine the associations of MJ use with both verbal memory performance and cortical thickness in individuals with MDD.

As hypothesized, our results showed that MJ use and MDD were both independently associated with decrements on the CVLT-II: MDD participants had lower initial acquisition and total learning, lower short- and long-delay recall, lower percent retention, more intrusion errors, as well as a trend-level

Table 3 Cortical thickness and volumes in brain regions related to memory

Brain region	CON		MJ		MDD		MDD+MJ		MDD effect		MJ effect		Interaction effect	
									(CON and MJ vs.		(CON and MDD vs.			
	(n=23)		(n=20)		(n=18)		(n=21)		MDD and MDD+MJ)		MJ and MDD+MJ)		MJ effect within MDD status	
									p	ES	p	ES	p	ES
													CON	MDD
Lateral orbitofrontal cortex														
Left hemisphere	2.80	(0.15)	2.74	(0.11)	2.72	(0.14)	2.73	(0.12)	-0.36		-0.27		-0.50	0.04
Right hemisphere	2.65	(0.14)	2.58	(0.12)	2.59	(0.16)	2.55	(0.12)	-0.40		-0.45		-0.57	-0.29
Medial orbitofrontal cortex														
Left hemisphere	2.56	(0.15)	2.49	(0.10)	2.52	(0.15)	2.51	(0.12)	-0.10		-0.33		-0.61	-0.03
Right hemisphere	2.52	(0.17)	2.46	(0.17)	2.52	(0.15)	2.46	(0.15)	-0.05		-0.40		-0.40	-0.40
Middle temporal gyrus														
Left hemisphere	2.96	(0.14)	2.91	(0.10)	2.91	(0.12)	2.86	(0.08)	-0.44		-0.47		-0.40	-0.53
Right hemisphere	3.03	(0.12)	2.96	(0.09)	2.95	(0.13)	2.91	(0.10)	-0.62		-0.54		-0.61	-0.42
Parahippocampal gyrus														
Left hemisphere	2.92	(0.31)	2.88	(0.31)	2.92	(0.33)	2.78	(0.29)	-0.16		-0.30		-0.14	-0.45
Right hemisphere	2.90	(0.22)	2.86	(0.20)	2.90	(0.34)	2.78	(0.19)	-0.19		-0.32		-0.16	-0.43
Caudal middle frontal gyrus														
Left hemisphere	2.66	(0.14)	2.60	(0.13)	2.63	(0.11)	2.58	(0.12)	-0.24		-0.45		-0.44	-0.42
Right hemisphere	2.57	(0.13)	2.55	(0.11)	2.53	(0.13)	2.53	(0.13)	-0.27		-0.11		-0.18	0.00
Rostral middle frontal gyrus														
Left hemisphere	2.50	(0.15)	2.48	(0.12)	2.48	(0.13)	2.45	(0.10)	-0.19		-0.22		-0.16	-0.27
Right hemisphere	2.39	(0.13)	2.34	(0.12)	2.35	(0.10)	2.31	(0.09)	-0.36		-0.44		-0.46	-0.37
Superior frontal gyrus														
Left hemisphere	2.78	(0.12)	2.73	(0.09)	2.75	(0.13)	2.69	(0.10)	-0.30		-0.49		-0.41	-0.52
Right hemisphere	2.68	(0.13)	2.65	(0.10)	2.65	(0.09)	2.59	(0.10)	-0.43		-0.47		-0.32	-0.62
Entorhinal cortex														
Left hemisphere	3.45	(0.29)	3.46	(0.31)	3.37	(0.20)	3.36	(0.24)	-0.35		-0.03		0.01	-0.04
Right hemisphere	3.80	(0.20)	3.65	(0.31)	3.69	(0.24)	3.54	(0.36)	-0.40		-0.55		-0.60	-0.47
Hippocampus (volume)														
Left hemisphere	4367.96	(562.89)	4354.48	(357.29)	4474.40	(353.89)	4165.28	(358.99)	-0.12		-0.37		-0.03	-0.87
Right hemisphere	4587.78	(497.92)	4517.60	(366.98)	4605.88	(292.17)	4322.74	(446.98)	-0.24		-0.43		-0.16	-0.74

Note. All values are means and standard deviations. *p*-values are based on GLMM main effects or interactions, not hemisphere-specific effects, where * < 0.05, ** < 0.01, *** < 0.001. Effect sizes (ES) are Cohen's *d*. Means are not adjusted for gender or age effects, and hippocampus volume means are not adjusted for intracranial volumes

CON healthy controls, MJ marijuana users without lifetime MDD, MDD non-users with lifetime MDD, MDD+MJ MJ users with lifetime MDD

tendency to employ a less efficient memory strategy (i.e., serial clustering). MJ participants recalled fewer words after short and long delays. Findings replicate previous work showing mild to moderate verbal learning and memory decrements, including poorer immediate and delayed recall of verbal information in regular MJ users and in individuals with MDD (Schweinsburg et al., 2008; Hanson et al., 2010; Kizilbash et al., 2002; Otto, 1994; Solowij et al., 2011). The effects of

MJ use and MDD on memory performance were additive, but not interactive. This indicates that each condition was independently associated with worse memory performance, but the combination of both was not notably larger or smaller than expected by summing the simple main effects. Though we cannot determine whether MJ was exacerbating memory weaknesses in the MDD participants, or whether poor memory preceded MJ use, it is possible that memory weaknesses could improve if MDD patients

abstained from using MJ, as other studies in non-depressed samples show that MJ abstinence is associated with improved memory performance (Hanson et al., 2010; Medina et al., 2007; Schuster, Gilman, Schoenfeld, Evenden, Hareli, Ulysse, Nip, Hanly, Zhang, & Evins, 2018). Future studies should examine this effect in MDD patients with co-morbid MJ use.

Neuroimaging results of the present study indicated that MJ use and MDD were negatively correlated with cortical thickness. MJ use was associated with decreased cortical thickness in medial orbitofrontal cortex, middle temporal gyrus, and superior frontal gyrus, while MDD was associated with reduced cortical thickness in the middle temporal gyrus. None of these effects were interactive. Findings replicate previous work showing that heavy MJ use in adolescence is associated with decreased cortical thickness in the frontal cortices and the insula (Lopez-Larson et al., 2011). Other previous reports had also shown that heavy MJ use in adolescence is associated with reduced hippocampal volume (Demirakca et al., 2011; Schacht, Hutchison, & Filbey, 2012), but we were unable to detect this general association in our sample. However, the strong negative effect sizes of MJ use in the left- and right-hemisphere hippocampal volumes estimates among young adults with MDD we observed in our sample indicates that further investigation in larger samples is warranted to investigate whether MJ use and MDD may have an interactive association within this brain region.

Effects of MJ use and MDD on the middle temporal gyrus are likely to be additive. Studies of memory have shown that episodic memory involves both frontal and medial temporal regions, with the frontal cortex providing an input to medial temporal lobe structures during encoding (Buckner, 1999; Buckner, Kelley, & Petersen, 1999; Moscovitch, 1992). Though relatively few studies have examined structural correlates of memory, and no meta-analyses or systematic reviews have been conducted to date, a recent study reported that in healthy adults greater gray matter in medial orbitofrontal cortex, inferior frontal gyrus, and superior frontal gyrus were associated with better working memory performance (Nissim et al., 2016). The largest study to date on memory and cortical thickness ($N=1,064$) found correlations between working memory performance and cortical thickness in the lateral orbitofrontal cortex ($r=.12$, $p=.0001$), cuneus ($r=.12$, $p=.0001$), and middle temporal gyrus ($r=.11$, $p=.0002$) (Owens, Duda, Sweet, & MacKillop, 2018). While these effect sizes were small, and likely not detectable in the current study with the sample size of 82, it is notable that we observed a cortical thickness decrease in the middle temporal gyrus, supporting the hypothesis that this structural difference may be linked to weaknesses in memory.

MJ users with MDD in the current study had more problematic MJ use than MJ users without MDD. Those with MDD were more likely to have a diagnosis of MJ dependence (54% in the MDD+MJ group vs. 7% in the MJ group), MJ

abuse (67% in the MDD+MJ group vs. 33% in the MJ group), and alcohol abuse (13% in the MDD+MJ group vs. 0% in the MJ group). Furthermore, MDD+MJ participants self-reported heavier MJ use compared with MJ users without MDD (17.3 joints/week in the MDD+MJ group vs. 7.8 joints/week in the MJ group). These differences in the amount of MJ use by MDD status did not appear to be driving the additive effects of MJ and MDD on memory performance or cortical thickness/volume, as joints per week did not correlate with any outcome measure. The increased severity of MJ use in the MDD group replicates other studies that have reported that psychiatric illness is associated with a worse trajectory of MJ use (Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006; Lagerberg et al., 2011; Patton et al., 2002; van Laar, van Dorsselaer, Monshouwer, & de Graaf, 2007), though the direction of this association is unclear. The relationship between MJ use and psychiatric illness is likely bi-directional, as longitudinal studies have shown that those with more severe depressive symptoms have higher rates of subsequent MJ use (Hooshmand, Willoughby, & Good, 2012; Wittchen et al., 2007). It is also interesting to note that MDD and MDD+MJ groups were generally comparable on all MASQ indices except for anhedonic depression, where those with MDD who did not use MJ had higher scores compared to those who used MJ.

We acknowledge that the present study has limitations. First, the study sample was moderate in size, particularly the neuroimaging cohort, which may limit the generalizability of our results as well as the power to detect significant interactions. Second, because this study was cross-sectional, we cannot determine whether MJ use worsened verbal memory performance in the MJ-using groups, or whether memory decrements preceded MJ use. Future investigations of the MJ-MDD interaction in young adults should include longitudinal designs or incentivize abstinence to investigate change in memory performance (Schuster et al., 2018). Third, the confounding effects of heavier alcohol use (confounded with MJ use) and anxiety disorders (confounded with MDD) may limit our interpretation of results. Fourth, it is not known whether cortical differences observed in people with MJ use or MDD underlie the verbal memory deficits also associated with MJ use and with MDD. Larger and longitudinal studies are needed to clarify these relationships. Finally, our study sample included highly educated individuals, some of whom scored perfectly on the CVLT-II measures, thus ceiling effects may have affected our power to detect group differences. Relatedly, it is important to note that despite finding group differences on many measures of memory functioning, the functional significance of findings is unknown given that groups generally scored in the average range compared to normative samples.

In summary, our findings provide evidence of additive adverse effects of MDD and MJ use on learning and memory performance, with cortical thickness reductions in memory-

related brain regions predominantly in current MJ users. Findings from the current study suggest that the combined effect of MJ use and MDD may result in greater adverse effects on learning and memory, compared to MJ use or MDD alone. While further research is required to establish the clinical significance of these findings, MJ use among depressed patients may be contraindicated.

Authors' Contributions Conceived and designed the experiments: JMG, AEE. Performed the experiments: MR, JMG. Oversaw clinical aspects: AEE. Analyzed the data: SSH, JMG. Wrote the paper: MR, SSH, RMS, JMG, AEE. All authors have approved the final article.

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Compliance with ethical standards

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