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Journal

Journal of Studies on Alcohol and Drugs, 75(5)

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Publication Date

2014-09-01

DOI

10.15288/jsad.2014.75.729

Peer reviewed

Cortical Thickness and Neurocognition in Adolescent Marijuana and Alcohol Users Following 28 Days of Monitored Abstinence

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ABSTRACT. Objective: Adolescent marijuana use continues to increase in prevalence as harm perception declines. Better understanding of marijuana's impact on neurodevelopment is crucial. This prospective study aimed to investigate cortical thickness and neurocognitive performance before and after 28 days of monitored abstinence in adolescent marijuana and alcohol users. **Method:** Subjects ($N = 54$; >70% male) were adolescent marijuana users (ages 15–18 years) with regular alcohol use (MJ + ALC; $n = 24$) and non-using controls (CON; $n = 30$) who were compared before and after 4 weeks of sequential urine toxicology to confirm abstinence. Participants underwent magnetic resonance imaging, neuropsychological assessment, and substance use assessment at both time points. Repeated-measures analysis of covariance was used to look at the main effects of group, time, and Group \times Time interactions on cortical thickness and neurocognitive functioning. Bivariate correlations estimated associations between cortical thickness, substance use severity, and cognitive performance. **Results:** Marijuana users

showed thicker cortices than controls in the left entorhinal cortex ($ps < .03$) before and after monitored abstinence, after adjusting for lifetime alcohol use. More lifetime marijuana use was linked to thinner cortices in temporal and frontal regions, whereas more lifetime alcohol use and heavy episodic drinking episodes was linked to thicker cortices in all four lobes ($ps < .05$). Age of onset of regular marijuana use was positively related to cortical thickness ($ps < .03$). **Conclusions:** Adolescent alcohol and marijuana use may be linked to altered longer-term neurodevelopmental trajectories and compromised neural health. Cortical thickness alterations and dose-dependent associations with thickness estimates were observed both before and after monitored abstinence and suggest neural differences continue to persist 28 days after cessation of marijuana use. Neural recovery may be identified with longer follow-up periods; however, observed changes related to use severity could have implications for future psychosocial outcomes. (*J. Stud. Alcohol Drugs*, 75, 729–743, 2014)

ADOLESCENCE IS AN IMPORTANT developmental period associated with significant increases in alcohol and marijuana use (Brown et al., 2008). Sixty-eight percent of American 12th graders endorse lifetime alcohol use, with more than 20% reporting recent heavy episodic drinking (i.e., ≥ 5 drinks on one occasion) (Johnston et al., 2014). Marijuana is commonly used in conjunction with alcohol (Terry-McElrath et al., 2013), as 45% endorse lifetime use of marijuana by 12th grade (Johnston et al., 2014).

High rates of adolescent alcohol and marijuana use are concerning, given the significant neurodevelopment in gray and white matter during this period. Gray matter, consisting of neurons and glial cells, increases in volume during childhood and decreases during early adolescence. Gray matter reduction (including extensive cortical thinning) may repre-

sent the pruning of excess synapses, white matter encroachment, and/or changes in the extracellular matrix (Blakemore, 2012; Paus, 2005; Stiles and Jernigan, 2010). White matter continues to increase linearly throughout adolescence, likely driven by progressive axonal myelination (Gerber et al., 2009; Giedd, 2004; Gogtay et al., 2004; Simmonds et al., 2014). Both processes are associated with more efficient cognitive development, and any neurotoxic insults during these crucial processes could have long-lasting implications for cognitive development (Jacobus and Tapert, 2013, 2014).

Cross-sectional neuropsychological findings show that heavy marijuana and alcohol users perform worse on tests of psychomotor speed, complex attention, story memory, and planning and sequencing abilities, even after a month of abstinence (Medina et al., 2007), and show deficits on tests of verbal and visual memory (Solowij et al., 2011; Thoma et al., 2011). Longitudinal examinations have found that subtle deficits in cognitive functioning may remit with abstinence to some degree; however, this may not be the case for all aspects of cognitive functioning (Hanson et al., 2010). Early initiation of marijuana use in particular may have long-lasting consequences (Meier et al., 2012) in sustained attention, executive functioning (Fontes et al., 2011), impulse control

Received: October 21, 2013. Revision: March 25, 2014.

This study was supported by National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism Grants P20 DA024194, R01 DA021182, F32 DA032188, R01 AA013419, T32 AA013525, and U01 AA021692.

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(Gonzalez et al., 2012; Gruber et al., 2011, 2012a, 2012b), and verbal memory (Dougherty et al., 2013; Solowij et al., 2011).

Underlying brain structural changes, particularly cortical thinning, may help explain the cognitive abnormalities found in alcohol- and marijuana-using teens. Cross-sectional structural magnetic resonance imaging (MRI) studies have found thinner cortices in prefrontal and insular regions and thicker cortices in posterior regions in marijuana-using adolescents when compared to controls (Lopez-Larson et al., 2011). It remains unclear if structural differences exist before marijuana use. Although structural neuroimaging studies show marijuana-related effects on tissue (Jacobus et al., 2013b), smaller orbitofrontal volumes at age 12 predict marijuana initiation by age 16, suggesting cross-sectional findings may be partially attributable to premorbid structural brain differences (Cheetham et al., 2012). Perhaps an interaction of vulnerability and exposure leads to continued use and poorer neural and cognitive outcomes. Several functional neuroimaging studies have shown aberrations in brain response patterns and cerebral blood flow in marijuana- and alcohol-using adolescents, which may partially be explained by aberrant cortical thinning (Jacobus et al., 2012; Jager et al., 2010; Lopez-Larson et al., 2012; Schweinsburg et al., 2005, 2008, 2010; Tapert et al., 2007). Abstinence may aid in tissue recovery to some extent and diminish the observed marijuana-related differences in neural functioning (Jacobus et al., 2012). However, studies suggest deficits persist even after a month (Padula et al., 2007; Tapert et al., 2007).

The aims of this study were to examine the impact of heavy marijuana and alcohol use on cortical thickness in adolescents before and after 28 days of monitored abstinence. We hypothesized that heavy marijuana and alcohol users, compared to controls, would demonstrate thicker cortices across independent standardized neuroanatomical cortical regions (Desikan et al., 2006) at both baseline (pre-abstinence) and follow-up (post-abstinence) because of altered neurodevelopmental trajectories (e.g., interference with regressive events such as cortical thinning). We did not expect considerable within-group brain change in cortical thickness after 4 weeks of monitored abstinence in either group. Nevertheless, this has not been previously explored in the literature to our knowledge, and we predicted that, along with a between-group effect, substance users might demonstrate greater improvement in cortical thickness (subtle thinning), along with neurocognitive performance, during 1 month of abstinence from marijuana use.

Method

Participants

Adolescents ($N = 54$) were recruited from local San Diego schools and included 24 heavy marijuana users who

regularly used alcohol (MJ + ALC; lifetime marijuana episodes > 200) and 30 control teens (CON) with minimal substance use histories (lifetime marijuana episodes < 7) (Table 1). Teens were recruited for marijuana use; however, the majority of users also reported heavy lifetime alcohol use (Jacobus et al., 2012). Comprehensive screening interviews were administered to adolescents and parents/guardians; adolescents provided assent for their own participation, and guardians were required to provide consent in accordance with the University of California, San Diego Human Research Protections Program. Exclusionary criteria were history of a *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association, 2000), Axis I disorder other than alcohol or cannabis use disorder; psychoactive medications; learning disability or mental retardation; neurological condition (e.g., migraine) or traumatic brain injury with loss of consciousness greater than 2 minutes; prenatal alcohol or other drug exposure; premature birth; left handedness; and nonfluency in English.

Participants received neuroimaging and neuropsychological, substance use, and mental health assessment at baseline and follow-up (see Jacobus et al., 2012, for procedure timeline). Participants were asked to refrain from using all intoxicants for 28 days and underwent biweekly urine toxicology screening (nine total) to examine 11-nor-9-carboxy-tetrahydrocannabinol (THCCOOH)/creatinine excretion ratios for confirmation of completing the marijuana abstinence protocol (Smith et al., 2009). New cannabis use was determined by dividing each THCCOOH normalized to creatinine concentration collected by the previously collected specimen (urine 2 / urine 1) and factoring in time intervals between collections, per Huestis and Cone recommendations for determining new cannabis use as a function of time (Huestis and Cone, 1998; Smith et al., 2009). A change in metabolite/creatinine ratios greater than 1.5 is considered new use. Eight of our 24 users reported ≤ 4 days of light use within the first week of the abstinence period; however, we included them as abstinent given their decreasing THCCOOH/creatinine ratios (see Table 1 for values). Breath alcohol analysis was given at each in-person appointment (nine times over 28 days) to help affirm abstinence from alcohol; we did not have any positive breath-alcohol-analysis tests. For those individuals successfully completing the protocol and demonstrating decreasing THCCOOH ratios, self-reported alcohol use over the 28 days was ≤ 5 .

Measures

Neuropsychological battery. A comprehensive battery was administered at both baseline and follow-up covering the well-established domains of complex attention, processing speed, learning and memory, spatial processing, and executive functioning (Lezak et al., 2004). Twenty-five variables

TABLE 1. Participant characteristics at baseline, unless otherwise noted

Variable	CON (<i>n</i> = 30) <i>M</i> (<i>SD</i>) or %	MJ + ALC (<i>n</i> = 24) <i>M</i> (<i>SD</i>) or %
Age, in years	17.4 (0.8)	17.7 (0.7)
% Male	73%	71%
% White	73%	79%
Grade point average*	3.7 (0.6)	3.3 (0.8)
Annual household income	\$155K (79)	\$202K (196)
WASI Vocabulary <i>T</i> score*	58.2 (7.7)	53.6 (8.1)
% Family history negative for substance use disorder	47%	34%
Spielberger State Anxiety <i>T</i> score at baseline	36.0 (5.1)	38.0 (6.1)
Spielberger State Anxiety <i>T</i> score at follow-up	35.7 (6.3)	36.9 (7.6)
Beck Depression Inventory total at baseline*	1.9 (2.6)	5.3 (5.9)
Beck Depression Inventory total at follow-up	1.5 (2.3)	2.1 (2.6)
Lifetime marijuana use days*	0.9 (1.9)	408.8 (193.1)
Past-month marijuana use days at baseline*	0.1 (0.2)	17.3 (9.6)
Past-month marijuana use days at follow-up*	0.0 (0.0)	0.8 (1.2)
THCCOOH/creatinine at baseline (<i>SD</i> ; range)* ^a	0.0 (0.0)	1.2 (2.1; 0.0–10.0)
THCCOOH/creatinine at follow-up (<i>SD</i> ; range) ^a	0.0 (0.0)	0.3 (0.8; 0.0–3.8)
Lifetime alcohol use days*	6.1 (14.5)	102.8 (69.5)
Past-month alcohol use days at baseline*	0.2 (0.7)	3.1 (2.5)
Past-month alcohol use days at follow-up*	0.1 (0.6)	0.8 (1.5)
Lifetime heavy episodic drinking episodes* ^b	2.2 (8.2)	35.3 (42.00)
Past-month cigarettes smoked at baseline*	0.0 (0.0)	4.3 (8.6)
Past-month cigarettes smoked at follow-up*	0.0 (0.0)	5.0 (9.5)
Lifetime other drug use episodes*	0.0 (0.0)	6.5 (8.6)
Past-month other drug use days at baseline*	0.0 (0.0)	0.6 (0.9)
Past-month other drug use days at follow-up	0.0 (0.0)	0.2 (0.6)
Days since marijuana use baseline	328.2 (390.0)	5.7 (4.5)
Days since marijuana use at follow-up*	354.3 (392.0)	29.8 (8.2)
Days since alcohol use baseline	193.2 (209.3)	43.2 (103.0)
Days since alcohol use at follow-up	204.0 (287.6)	48.5 (77.4)
Age of onset, regular marijuana use ^c	–	15.4 (0.9)
Age of onset, regular alcohol use ^c	–	15.8 (0.9)

Notes: CON = control teens; MJ + ALC = heavy marijuana adolescent users with regular alcohol use; WASI = Wechsler Abbreviated Scale of Intelligence; THCCOOH = 11-nor-9-carboxy-tetrahydrocannabinol. ^aTHCCOOH/creatinine ratios in ng/mg; ^b≥4 drinks on one occasion for females and ≥5 drinks for males; ^c> 1 time/week for 52 weeks. **p* < .05.

were examined from 10 tests: (a) complex attention: California Verbal Learning Test-II Trial 1 and Trial 1–5 Total Recall (CVLT-II; Delis et al., 2001); Wechsler Adult Intelligence Scale–Third Edition (WAIS-III; Wechsler, 1997b) Arithmetic, and Digit Span Total, Forward and Backward subtests; (b) processing speed: WAIS-III Digit Symbol; Delis–Kaplan Executive Function System (D-KEFS) Trail Making Test, Visual Scanning, Number Sequencing, Letter Sequencing, and Motor Speed subtests (Delis and Kaplan, 2000); (c) verbal memory: Wechsler Memory Scale–Third Edition (WMS-III; Wechsler, 1997a) Logical Memory I, II, and Recognition; CVLT-II Short and Long Delay Free and Cued Recall, CVLT-II Recognition (Delis et al., 2001); (d) visuospatial functioning: Rey–Osterrieth Complex Figure (Rey-O, baseline) and Taylor Complex Figure (Taylor, follow-up) Copy and Delay Accuracy (Corwin and Bylsma, 1993; Hubley and Tremblay, 2002); Wechsler Abbreviated Scale of Intelligence (WASI) Block Design subtest (Wechsler, 1999); and (e) executive functioning: D-KEFS Trail Making Test Number-Letter Switching, Verbal Letter Fluency, and Color-Word Interference subtests (Inhibition and Inhibition-Switching;

Delis and Kaplan, 2000). Scaled scores corrected for age were used for all tests, excluding the Rey-O and Taylor Complex Figures, Logical Memory Recognition subtest, and the Digit Span Forward and Backward subtests.

Composite categories were developed for each of the five domains to reduce the number of dependent variables for correlations with cortical thickness. Individual *z* scores were created for each subject, neuropsychological variable, and time point based on the whole sample of adolescents and corresponding standard deviations (*N* = 54). Next, *z* scores within each domain were averaged to create the final composite *z* score for each of the five domains at each time point (Jacobus et al., 2013a; Medina et al., 2007). A global composite score was created for baseline and follow-up by averaging all five composite domains. Cronbach’s α coefficients were used to assess internal consistency ($\alpha > .50$).

Substance use and mental health assessment. The Customary Drinking and Drug Use Record was used to assess quantity and frequency of lifetime alcohol, marijuana, cigarette, and other drug use (Brown et al., 1998). The Timeline Followback was used to assess self-reported substance use

(e.g., alcohol, marijuana) in the 28 days before each scan session (Sobell and Sobell, 1992).

Emotional functioning and demographics. The Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al., 2001; Shaffer et al., 1996) was administered to youth and parents at the screening interview to identify and exclude those individuals with Axis I disorders other than alcohol or cannabis use disorder. The Beck Depression Inventory (Beck, 1978) and Spielberger State Trait Anxiety Inventory (Spielberger et al., 1970) assessed depression and state anxiety. The Family History Assessment Module (Rice et al., 1995) assessed family history of psychiatric and substance use disorders. Parental income and grade point average were collected during a clinical interview before the baseline imaging session. The WASI Vocabulary subtest was included as an estimate of premorbid intellectual functioning (Wechsler, 1999).

Procedures

Cortical thickness acquisition and processing. All scans were acquired on a 3.0 Tesla CXK4 short bore Excite-2 magnetic resonance system (General Electric, Milwaukee, WI) with an eight-channel phase array head coil at the University of California San Diego Center for Functional MRI. Subjects were asked to remain awake and still in the scanner while a high-resolution T1-weighted anatomical spoiled gradient recall scan was acquired (echo time / repetition time = minimum full; field of view = 24 cm; resolution = 1 mm³, 170 continuous slices).

The neuroimaging software FreeSurfer, which is well documented and freely available (Version 5.1, surfer.nmr.mgh.harvard.edu), was used for cortical surface reconstruction and thickness estimates (Dale et al., 1999; Fischl et al., 1999). The initial cross-sectional processing involves motion correction and averaging of T1 weighted images, removal of nonbrain tissue and transformation to standardized space, segmentation of subcortical white and deep gray matter structures, intensity normalization, and tessellation of the gray/white matter boundary. Local MRI intensity gradients then guide a surface deformation algorithm to place smooth borders where the greatest shift in intensity defines transition to other tissue classes (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999, 2004); this procedure allows for quantification of submillimeter group differences (Fischl and Dale, 2000).

Cortical thickness was calculated as the closest distance from the gray/white matter boundary to the gray matter/cerebral spinal fluid boundary at each vertex on the cortical surface (Fischl and Dale, 2000). Validity of the cortical thickness measurement procedures has been verified using manual measurements and histological analysis (Kuperberg et al., 2003; Rosas et al., 2002; Salat et al., 2004). Test-retest reliability across scanners and field strengths has been

shown using these standardized procedures (Han et al., 2006; Reuter et al., 2012).

Following cross-sectional processing of all time points, data were next fed through the longitudinal processing stream in FreeSurfer (Reuter et al., 2012). This approach extracts reliable volume and thickness estimates by creating an unbiased within-subject template space and image from the two cross-sectionally processed time points (baseline and follow-up) using a consistent robust inverse registration method (Reuter et al., 2010). Processing steps such as Talairach transforms, atlas registration, and spherical surface maps and parcellations are initialized with common information from the within-subject template, increasing reliability and statistical power (Reuter et al., 2012).

One rater (JJ), blind to participant characteristics, followed the reconstruction and longitudinal edit procedures to identify and correct any errors made during the cortical reconstruction process. This involved verification of the automated skull stripping and a coronal plane slice-by-slice inspection of the gray/white and gray/cerebral spinal fluid surfaces. Modifications to the surfaces were made as necessary to correct for tissue misclassifications (e.g., residual dura matter classified as cortex). No editing was necessary following the longitudinal processing, although all longitudinal runs were checked for quality.

Following inspection, an automated parcellation procedure divided each hemisphere into 34 independent cortical regions based on gyral and sulcal features (Desikan et al., 2006; Fischl et al., 2004). Cortical thickness estimates averaged over each parcellation region were extracted for statistical analyses in SPSS.

Data analysis

Demographic comparisons. Analysis of variance (ANOVA) and chi-square tests were run between groups to evaluate differences on demographic variables and to identify appropriate covariates for subsequent analysis.

Cortical thickness measurement. Repeated-measures analysis of covariance (ANCOVA) examined main effects of time, group, and Group \times Time interactions on cortical thickness values for 34 independent standard neuroanatomical cortical regions (Desikan et al., 2006) in each hemisphere. Intracranial volume was included as a covariate. Marijuana and alcohol are commonly used concomitantly (Johnston et al., 2014; Midanik et al., 2007; Substance Abuse and Mental Health Services Administration, 2013; Terry-McElrath et al., 2013). In fact, more than 80% of marijuana users in our studies report regular alcohol use. Given the literature on the deleterious effects of alcohol on neurodevelopment (Jacobus and Tapert, 2013) and between group differences known to exist in this sample, lifetime alcohol use was specified a priori and statistically adjusted for in follow-up post hoc ANCOVAs examining group differences at each time point for

TABLE 2. Dose-dependent associations with cortical thickness in the user group ($n = 24$)

Cortical region	Brodman area	Time point	Pearson's r	p
Correlations with lifetime marijuana use				
Left transverse temporal	41	Baseline	-.43	.03
Left paracentral	4; 3, 1, 2	Baseline	-.43	.03
Right transverse temporal	41	Baseline	-.43	.03
Right paracentral	4; 3, 1, 2	Baseline	-.54	<.01*
Left transverse temporal	41	Follow-up	-.44	.03
Right transverse temporal	41	Follow-up	-.45	.02
Correlations with lifetime alcohol use				
Left paracentral	4; 3, 1, 2	Baseline	.44	.03
Left postcentral	3, 1, 2	Baseline	.40	.04
Left temporal pole	38	Baseline	.40	.04
Right cuneus	17	Baseline	.55	<.01*
Right precuneus	7	Baseline	.43	.03
Left paracentral	4; 3, 1, 2	Follow-up	.54	<.01*
Left postcentral	3, 1, 2	Follow-up	.47	.01
Left precentral	4	Follow-up	.41	.04
Left supramarginal	40	Follow-up	.45	.02
Right cuneus	17	Follow-up	.56	<.01*
Right inferior temporal	20	Follow-up	.50	.01
Right middle temporal	21	Follow-up	.51	.01
Right paracentral	4; 3, 1, 2	Follow-up	.51	.01
Right precuneus	7	Follow-up	.40	.04

* $ps < .01$, relationships depicted in Figure 2 scatter plots.

regions in which a main effect of group or interaction was identified. Secondary analyses further evaluating the impact of substance use on cortical thickness included exploratory bivariate correlations between substance use variables (i.e., lifetime marijuana use, lifetime alcohol use, heavy episodic drinking episodes [≥ 4 drinks on one occasion for females and ≥ 5 drinks for males], and age of initiation) and cortical thickness estimates at each time point in the user group ($n = 24$).

Neuropsychological performance. Repeated-measures ANCOVA was used to evaluate neurocognitive performance over time with alcohol as a covariate for each neurocognitive subtest. Bivariate correlations between neurocognitive performance (global domain scores to reduce the number of correlations) and cortical thickness estimates were explored; if significant associations were identified, relationships between cortical thickness in that region and individual domain scores were examined within each group to identify correlates driving the relationship. Associations between age of onset of alcohol and marijuana use and neuropsychological outcome data (global domain scores) were also explored in the user group.

Results

Groups did not statistically differ on any demographic characteristics with the exception of grade point average and WASI Vocabulary T score ($ps < .05$), despite both groups falling within the average range. MJ + ALC reported slightly more depression-type symptoms compared to controls at baseline; however, neither group fell within the clinically significant

range, and this difference was not found at follow-up. Groups differed on lifetime marijuana, alcohol, and lifetime other drug use episodes, as anticipated ($ps < .05$, see Table 1).

Main effect of group on cortical thickness measurement

A main effect of group status on cortical thickness estimates was found in four regions (controlling for intracranial volume) in which MJ + ALC demonstrated significantly thicker cortices compared to controls: (a) left caudal anterior cingulate cortex, $F(1, 51) = 9.6$, $p < .01$; (b) left entorhinal cortex, $F(1, 51) = 8.3$, $p < .01$; (c) left lingual gyrus, $F(1, 51) = 4.4$, $p = .04$; and (d) left pericalcarine cortex, $F(1, 51) = 4.1$, $p = .04$. In no region did controls demonstrate thicker cortices than MJ + ALC.

Post hoc analyses revealed group differences at both baseline and follow-up (MJ + ALC with thicker cortices) in the left entorhinal cortex persisted after both lifetime alcohol use in addition to intracranial volume were controlled for ($ps \leq .03$). Between-group differences did not persist in the left caudal anterior cingulate, left lingual gyrus, or left pericalcarine cortex after covarying for alcohol use ($ps > .05$). Lifetime alcohol use was not significant in the post hoc models ($ps > .10$).

In substance users ($n = 24$), negative correlations were found between lifetime marijuana use and cortical thickness in the left and right transverse temporal cortex at both baseline and follow-up, and the left and right paracentral lobule at baseline ($ps < .05$); decreased cortical thickness estimates were associated with more reported lifetime marijuana use (Table 2, Figures 1 and 2). Relationships did not change

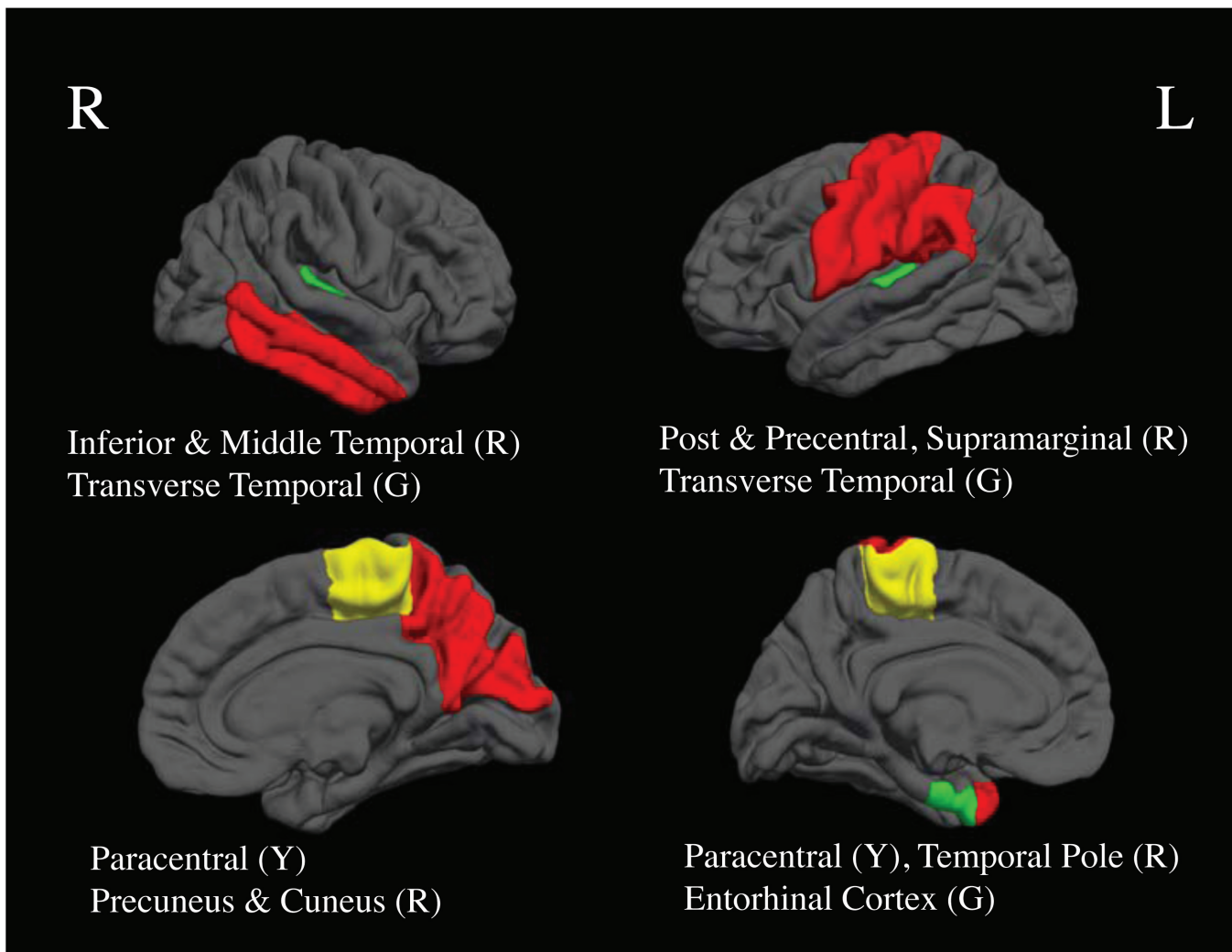


FIGURE 1. Cortical regions representing between-group (entorhinal cortex) and dose-dependent bivariate associations with marijuana (green; G), dose-dependent bivariate associations with alcohol (red; R), and dose-dependent bivariate associations with both substances (yellow; Y), at baseline and follow-up, $ps < .05$

holding lifetime alcohol use constant ($rs > -.40$, $ps < .05$). We found that age of onset of regular marijuana use was positively related to cortical thickness, in that initiation of regular use at a younger age was linked to thinner cortices at follow-up in the left inferior temporal gyrus ($r = .43$, $p = .03$), left middle temporal gyrus ($r = .53$, $p < .01$), left pars orbitalis ($r = .45$, $p = .02$), right lateral orbital frontal cortex ($r = .48$, $p = .01$), right pars triangularis ($r = .54$, $p = .02$), and right rostral anterior cingulate cortex ($r = .42$, $p = .03$) (Figure 3).

Interestingly, several positive correlations were found for users ($n = 24$) between lifetime alcohol use and cortical thickness at baseline and follow-up in areas including the left paracentral, postcentral, precentral, and supramarginal cortices; the left temporal pole; the right cuneus and precuneus; and the right inferior temporal gyrus ($ps < .05$; see Table

2, Figures 1 and 2). Increased cortical thickness estimates were associated with more reported lifetime alcohol use. Relationships did not change holding marijuana use constant ($rs > .41$, $ps < .05$). In the areas in which we saw positive correlations with lifetime alcohol use (Table 2), positive relationships with number of heavy drinking episodes, defined as ≥ 4 drinks on one occasion for females and ≥ 5 drinks for males, was observed in the left paracentral ($r = .54$, $p < .01$; $r = .61$, $p < .01$), right cuneus ($r = .57$, $p < .01$, $r = .63$, $p < .01$), and right precuneus ($r = .45$, $p = .03$, $r = .52$, $p = .01$) cortex at baseline and follow-up, and the left postcentral ($r = .54$, $p < .01$) and right inferior temporal ($r = .42$, $p = .02$) cortex at follow-up. Relationships did not change holding marijuana use constant ($rs > .43$, $ps < .05$). We did not see associations with cortical thickness and age of initiation of regular alcohol use.

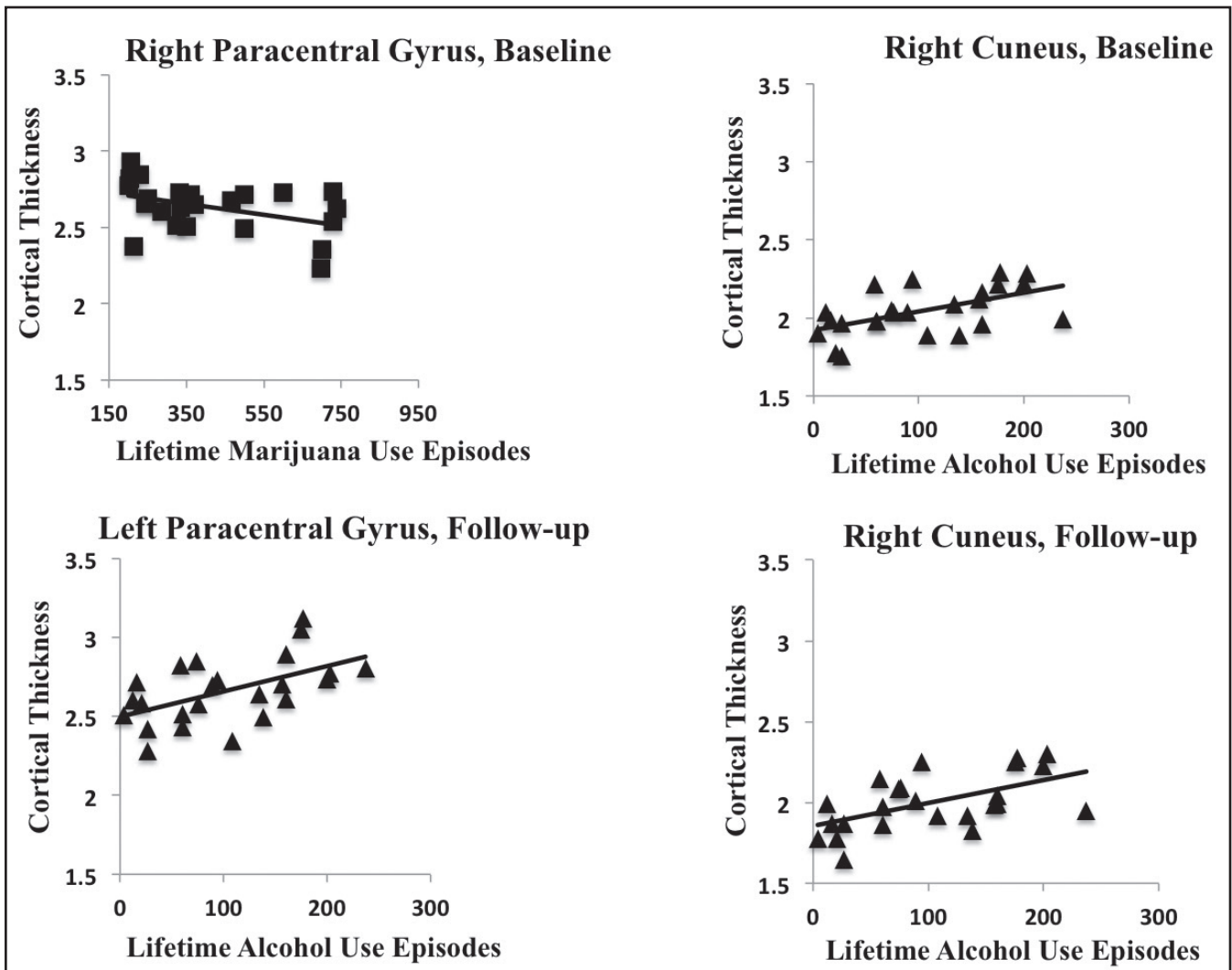


FIGURE 2. Scatter plots depicting dose-dependent relationships with lifetime marijuana (negative) and alcohol (positive) and cortical thickness in the user group only ($n = 24$, $ps < .01$)

Main effect of time on cortical thickness measurement

A main effect of time (i.e., decreasing cortical thickness for both ALC + MJ and CON) was found in seven regions, including the left and right fusiform gyrus, left postcentral gyrus, left and right temporal pole, right entorhinal cortex, and right superior parietal cortex, $F(1, 52) = 4.6-8.4$, $ps \leq .03$. We did not see any significant Group \times Time interactions ($ps > .10$).

Neuropsychological performance

When lifetime alcohol use was controlled for, repeated-measures ANCOVA found a main effect of time (increasing performance from baseline to follow-up) for the vast majority of neurocognitive measures (15 of 25 neurocognitive

tests) as expected, including the Complex Figure Delay, Logical Memory I, II, and Recognition, Color-Word Inhibition and Switching subtests, Trail Making Test Visual Scanning, Number Sequencing, Letter Sequencing, and Switching subtests, Block Design, Digit-Symbol Coding, Arithmetic, and Digit Span Backward and Total subtests, $F(1, 52) = 5.2-103.4$, $ps < .03$ (Table 3). A Group \times Time interaction was found for Complex Figure Copy condition $F(1, 52) = 4.8$, $p = .03$ (Table 3, Figure 4), as improved performance was seen for controls but not for MJ + ALC. No group effects were observed with or without controlling for alcohol ($ps > .20$).

To better understand if cortical thickness is associated with cognitive functioning in this sample, and to limit the number of comparisons, we examined associations between cortical thickness estimates and global neurocognitive

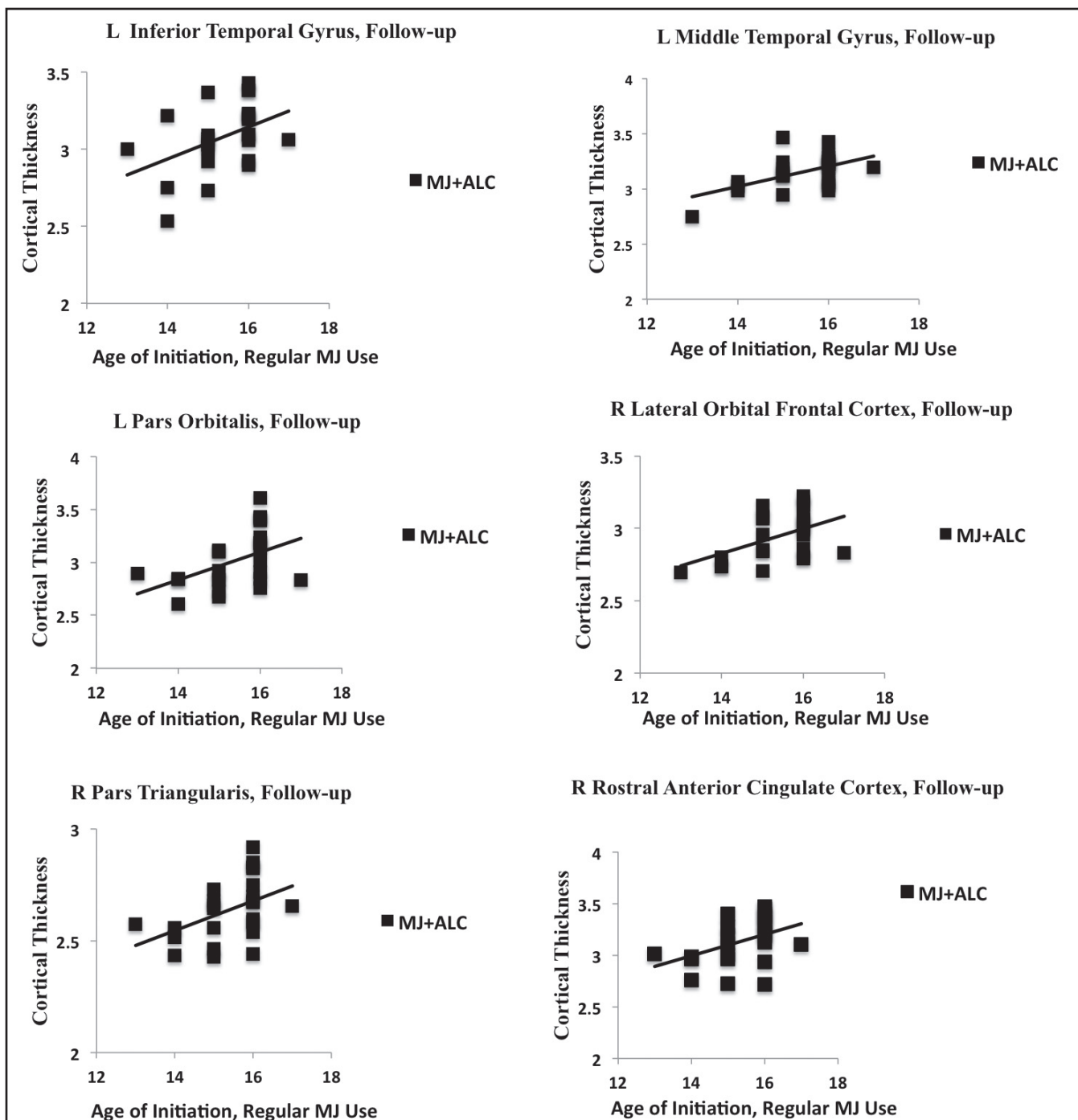


FIGURE 3. Scatter plots depicting associations between age of initiation of regular marijuana use and cortical thickness in the user group at follow-up ($n = 24$)

functioning at corresponding time points across the whole sample. We found negative associations between cortical thickness in the left frontal pole and global cognitive performance at baseline ($r = -.28, p = .04$) and follow-up ($r = -.31, p = .02$) such that increased cortical thickness was associated with poorer global cognitive performance in the larger sample (Figure 5). Likewise, we observed a negative

relationship between the right banks of the superior temporal sulcus and global functioning at follow-up ($r = -.28, p = .03$). These negative associations did not appear to be driven by group or a particular domain ($ps > .05$).

We observed a positive relationship between cortical thickness and global cognitive functioning at baseline ($r = .38, p < .01$) in only the right entorhinal cortex. These find-

TABLE 3. Descriptive statistics of neuropsychological composite variables by group

Variable	CON (n = 30)		MJ + ALC (n = 24)	
	M (SD)		M (SD)	
	Baseline	Follow-up	Baseline	Follow-up
Complex Attention, Composite Z score ^a	0.05 (0.78)	0.06 (0.64)	-0.06 (0.75)	-0.07 (0.67)
CVLT-II Trial 1 Z score	-0.05 (1.21)	-0.42 (0.73)	-0.58 (0.84)	-0.58 (0.89)
CVLT-II Trials 1-5 Total Recall T score	53.13 (8.99)	50.17 (10.72)	49.10 (10.45)	50.38 (10.72)
WAIS-III Arithmetic scaled score*	11.37 (3.08)	12.7 (2.85)	11.50 (2.65)	12.01 (2.60)
WAIS-III Digit Span Total scaled score*	10.77 (3.16)	11.77 (2.71)	10.92 (3.00)	11.41 (2.92)
WAIS-III Digit Span Forward, raw total score	11.33 (2.26)	11.40 (1.94)	11.33 (2.06)	11.63 (2.00)
WAIS-III Digit Span Backward, raw total score*	7.00 (2.45)	8.33 (2.23)	7.33 (2.75)	7.75 (2.44)
Processing Speed, Composite Z score ^a	0.06 (0.63)	0.12 (0.70)	-0.07 (0.60)	-0.15 (0.71)
WAIS-III Digit Symbol Scaled Score*	10.17 (2.36)	11.77 (2.71)	10.00 (2.34)	11.42 (2.92)
D-KEFS Trail Making Test Visual Scanning*	11.60 (2.13)	12.37 (1.56)	11.46 (1.56)	12.04 (1.52)
D-KEFS Trail Making Test Number Sequencing scaled score*	11.70 (1.86)	13.00 (1.31)	11.17 (1.95)	12.42 (1.91)
D-KEFS Trail Making Test Letter Sequencing scaled score*	11.40 (2.39)	12.93 (1.68)	10.71 (3.48)	12.25 (2.89)
D-KEFS Trail Making Test Motor Speed scaled score	11.93 (1.43)	12.43 (1.61)	11.92 (1.14)	12.13 (1.26)
Verbal Memory, Composite Z score ^a	0.06 (0.70)	0.01 (0.71)	-0.07 (0.82)	-0.01 (0.88)
WMS-III Logical Memory I scaled score*	8.87 (2.75)	11.77 (2.99)	7.75 (3.08)	10.96 (3.72)
WMS-III Logical Memory II scaled score*	9.23 (3.11)	12.97 (3.01)	8.33 (3.36)	11.63 (3.84)
WMS-III Recognition total raw score*	25.80 (2.30)	27.40 (1.85)	25.50 (3.00)	27.38 (2.12)
CVLT-II Short Delay Free Recall Z score	0.03 (0.87)	-0.23 (1.26)	0.10 (0.93)	-0.04 (1.35)
CVLT-II Short Delay Cued Recall Z score	-0.05 (0.70)	-0.10 (1.17)	-0.31 (1.2)	-0.02 (1.22)
CVLT-II Long Delay Free Recall Z score	-0.28 (0.82)	-0.47 (1.25)	-0.13 (1.05)	-0.44(1.44)
CVLT-II Recognition Discriminability Z score	-0.12 (1.19)	-0.45 (1.30)	-0.40 (1.15)	-0.04 (1.06)
Visuospatial Functioning, Composite Z score ^a	0.30 (0.73)	0.13 (0.64)	-0.03 (0.73)	-0.17 (0.80)
Rey-O/Taylor Complex Figure Copy Accuracy raw score**	27.6 (3.79)	29.62 (2.66)	28.71 (2.99)	28.75 (2.71)
Rey-O/Taylor Complex Figure Delay Accuracy raw score*	17.10 (4.98)	21.37 (4.33)	16.00 (5.09)	20.31 (5.22)
WASI Block Design T Score*	53.70 (6.13)	58.50 (5.44)	51.33 (9.40)	56.08 (7.70)
Executive Functioning, Composite Z score ^a	-0.07 (0.84)	0.05 (0.79)	0.09 (0.69)	-0.06 (0.72)
D-KEFS Trail Making Test Number-Letter Switching scaled score*	10.33 (1.71)	11.70 (1.34)	9.21 (2.72)	11.04 (1.60)
D-KEFS Verbal Letter Fluency scaled score	11.07 (2.98)	12.20 (3.40)	12.13 (2.51)	12.38 (3.36)
D-KEFS Color-Word Interference Inhibition scaled score*	10.77 (2.45)	11.93 (1.80)	10.79 (2.48)	11.67 (1.89)
D-KEFS Color-Word Interference Inhibition-Switching scaled score*	10.80 (2.73)	12.70 (2.12)	11.00 (2.19)	12.29 (2.24)

Notes: CVLT-II = California Verbal Learning Test-II; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WASI = Wechsler Abbreviated Scale of Intelligence; Rey-O = Rey-Osterrieth Complex Figure; D-KEFS = Delis-Kaplan Executive Function System Trail Making Test; WMS-III = Wechsler Memory Scale-Third Edition. ^aComposite variables presented above are corrected for age (excluding Rey-O, Taylor, Logical Memory Recognition, and Digit Span Forward/Backward) and were converted to Z scores for each test based on N = 54 participants.

*p < .05, main effect of time; **p < .05, Group × Time interaction.

ings appear to be driven by associations between cortical thickness and global functioning in the user group ($r = .57, p < .01$; Figure 5). Specifically, increased cortical thickness in the right entorhinal cortex was related to better performance in the domain of attention ($r = .65, p < .01$) in the user group only (Figure 5).

We did not identify any associations between age of onset of regular marijuana or alcohol use and global cognitive functioning in the user group ($ps > 10$).

Discussion

We prospectively examined cortical thickness estimates and neurocognition in a sample of adolescent heavy marijuana and alcohol users and matched controls before and after 28 days of monitored abstinence. Few group differences in cortical thickness were observed; the majority of areas (e.g., frontal and occipital cortices) were no longer significant after controlling for lifetime alcohol use. Thicker medial temporal lobe estimates (i.e., entorhinal cortex) were found in the user group at baseline and follow-up when ICV and

lifetime alcohol use were controlled for. We observed subtle decreasing thickness estimates from baseline to follow-up in seven regions, but no interactions were identified. We found quite divergent relationships between cumulative lifetime alcohol and marijuana use and cortical thickness in the user group. More reported marijuana use (and initiation of regular use at an earlier age) was related to thinner cortices in temporal and frontal regions, and more lifetime alcohol use was related to thicker cortices in all four lobes of the cortex bilaterally.

Improvement in cognitive functioning over time in both the users and controls was observed, given the short retest interval and anticipated gains in performance. We did not see greater improvement in cognition in the user group following abstinence or, surprisingly, consistent group differences in cognition across the five domains as suggested in the literature and previous studies in our laboratory (Hanson et al., 2011; Medina et al., 2007; Meier et al., 2012; Solowij et al., 2011; Tait et al., 2011). MJ + ALC did not improve in their performance on the Complex Figure Copy subtest; however, this pattern of performance was not found across the other

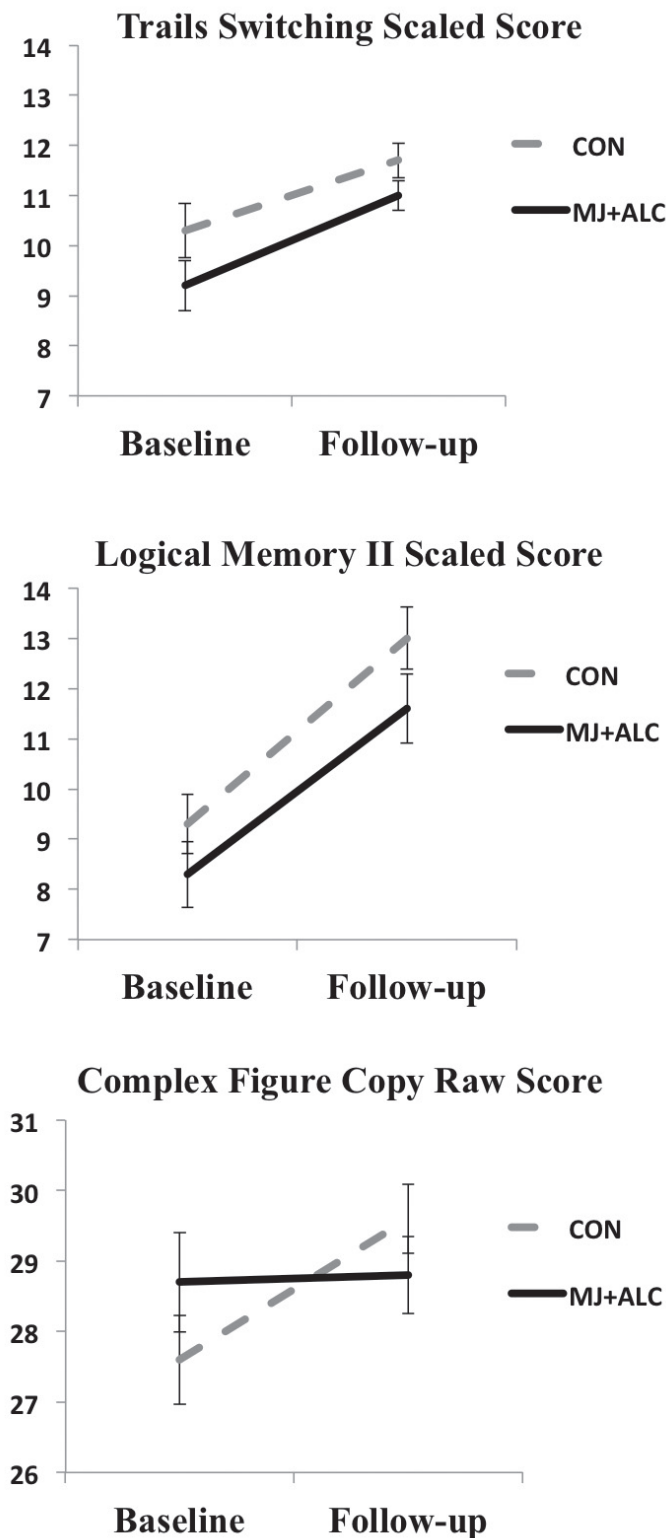


FIGURE 4. Neuropsychological performance ($N = 54$), showing a main effect of time (Trails, Logical Memory) and Group \times Time interaction (Complex Figure), $ps \leq .03$

tests. In general, thinner cortices were related to better global cognitive performance in the larger sample with the exception of the right entorhinal cortex and cognitive functioning in the user group at baseline, in which thicker cortices were associated with better attentional processing.

Lopez-Larson and colleagues (2011) cross-sectionally examined cortical thickness in teens, ages 16–19 years, with heavy marijuana use histories. They found decreased thickness in frontal regions and the insula, along with increased thickness in lingual, temporal, and parietal regions (Lopez-Larson et al., 2011). Our findings are similar given that we found increased thickness in temporal and posterior regions, such as the entorhinal (temporal) cortex (and lingual and pericalcarine cortex before controlling for alcohol), and relationships showing thinner cortices associated with increased severity of use (younger age of initiation and increased quantity) in frontal regions. The authors discuss multiple pathways for tissue disruption, including altered neurodevelopmental trajectories (interference with synaptic refinement) and/or tissue loss or remodeling. Similarly, Mata and colleagues (2010) found flattening and thinning of the sulci in frontal regions in adolescent marijuana users, suggesting chronic cannabinoid exposure may link to atypical trajectories of the gyral folding process.

The mechanism by which marijuana may alter brain tissue (and cortical thickness) during development remains unclear. Marijuana may interfere with the cannabinoid system by altering patterning, plasticity, and connectivity during neurodevelopment, and trigger neurochemical and protein activity in response to neural injury (Iversen, 2003; Rubino and Parolaro, 2008; Stella, 2013). Macrostructural findings typically focus on structures with a high density of cannabinoid type 1 (CB1) receptors (e.g., hippocampus, neocortex), and findings show larger structural volume in areas such as the anterior cerebellum and amygdala (Cousijn et al., 2012; McQueeney et al., 2011; Medina et al., 2010), whereas others show decreased gray matter volume and density (Ashtari et al., 2011; Demirakca et al., 2011; Matochik et al., 2005; Yücel et al., 2008). Cousijn and colleagues (2012) found that amygdala and hippocampal volume negatively correlated with weekly cannabis use, as more use was related to smaller limbic structures. In our study, cortical thickness differences persisted after controlling for alcohol in the entorhinal cortex. Given the high concentration of CB1 receptors in temporal lobe structures (i.e., hippocampus), marijuana use may be particularly influencing developmental events in this anatomical region.

Positive associations between thickness in the entorhinal cortex and cognitive functioning (i.e., thinner cortices related to poorer cognitive functioning for our marijuana users) is in contrast to the finding that thinner cortices are related to better global cognitive performance in the larger sample. However, greater reported marijuana use (at baseline and follow-up) and earlier age of initiation (at follow-up) were

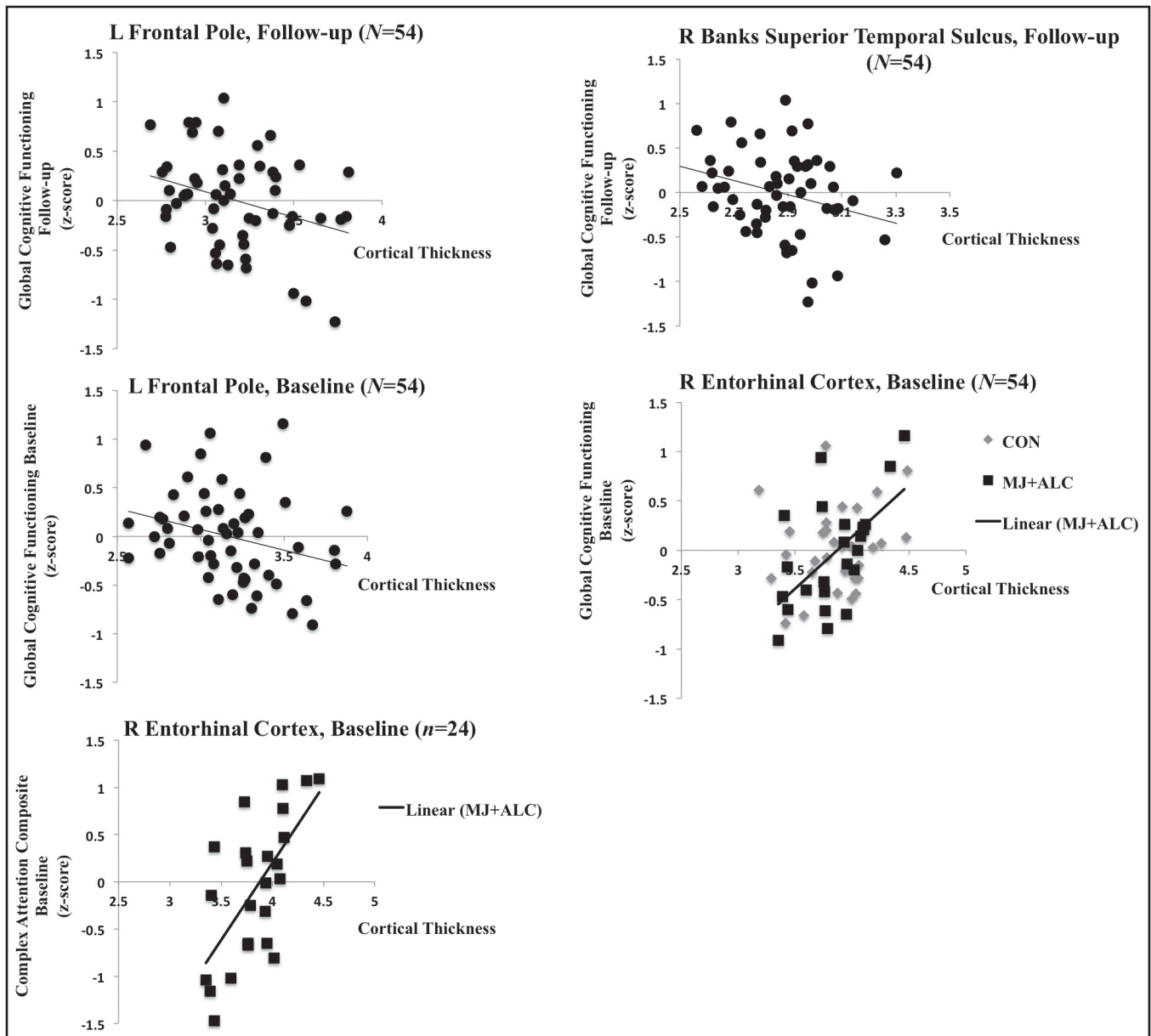


FIGURE 5. Scatter plots depicting associations between global cognitive functioning and cortical thickness

also associated with thinner cortices in frontal and temporal brain regions. We suggest that endocannabinoid system alterations or marijuana-related toxicity may trigger developmental consequences such as premature cortical thinning and subsequent declines in cognitive functioning. It is unclear why associations between age of initiation and thickness estimates were observed at follow-up only. Subtle neural architectural changes may be occurring over the abstinence period, and the acute impact on neural development may not be fully captured at baseline for this predictor. Neural recovery is likely to extend past 28 days and well into the year following cessation of use, as residual effects of marijuana use

have been reported in cognitive and neuroimaging markers from days to months following cessation of use (Ashtari et al., 2011; Bava et al., 2009; Matochik et al., 2005; Medina et al., 2007; Meier et al., 2012; Pope et al., 2001; Schweinsburg et al., 2008; Tapert et al., 2007). Pre-existing structural differences are also likely to contribute, as smaller orbitofrontal cortex volume predicted initiation of cannabis use by age 16 (Cheetham et al., 2012).

The positive dose-dependent relationships with lifetime alcohol use are particularly notable given the subclinical heavy episodic drinking patterns reported by the sample. Thickness estimates in these regions were related to number

of heavy drinking episodes reported, which is particularly concerning given the consistently high rates of heavy episodic drinking reported by adolescents in the United States (Johnston et al., 2014). The cerebral cortex is highly vulnerable to the effects of alcohol (Jacobus and Tapert, 2013). Squeglia and colleagues (2012) found that female heavy episodic drinkers had thicker cortices in frontal brain regions compared to female controls, and thicker cortices were associated with worse cognitive functioning for both males and females. However, thinner cortices were identified for male heavy episodic drinkers compared to controls (Squeglia et al., 2012), similar to recent prospective findings showing decreased thickness estimates in adolescents who transitioned into subclinical heavy episodic drinking (Luciana et al., 2013). Our findings suggest widespread (frontal, parietal, temporal, and occipital) increases in cortical thickness with increased lifetime alcohol use and heaving drinking episodes. The present study, combined with Squeglia et al. (2012), suggests that more often thicker cortices are associated with worse neurobehavioral performance. Despite the quantity of reported alcohol use in our users being more modest compared to that of treatment seeking individuals, differences in these studies of adolescents reporting similar alcohol use patterns may be attributed to methodological design (e.g., cross sectional, pre/post initiation, pre/post abstinence) or an interaction between co-occurring alcohol and marijuana use.

Neuroprotective properties of marijuana may modulate neurotransmission and mitigate ethanol-induced neural injury; however, marijuana may trigger neurotoxic chemical cascades leading to changes in endocannabinoid signaling, altered developmental trajectories, increased alcohol administration, and worse psychosocial outcomes in the developing brain (Ceccarini et al., 2013; Hamelink et al., 2005; Hansen et al., 2008; Pope et al., 2010; Rezaoyof et al., 2012; Swartzwelder et al., 2012). Although initial cross-sectional studies in our laboratory suggested evidence for white matter neuroprotection in those using marijuana and alcohol (Jacobus et al., 2009), poorer outcomes for co-occurring use from adolescence to young adulthood were found after a 3-year follow-up (Jacobus et al., 2013a). The mechanism of alcohol-related toxicity on the cerebral cortex remains unclear. Alcohol may interfere with temporal sequences of neurodevelopment (e.g., thinning), myelination, and/or generation and survival of cortical cells (Crews and Nixon, 2009); overall, the unanticipated associations with alcohol found in this study underscore the deleterious impact adolescent alcohol use likely has on neurodevelopment when used independently or concomitantly with marijuana.

Our sample was predominantly male (>70%). Therefore, it is unlikely that excluding our female participants would have changed the observed relationships. However, gender may moderate these findings (Bramen et al., 2012; Crane et al., 2013; Squeglia et al., 2012). Studies have found gender

to play a significant role in gray and white matter neural architecture and neurocognition in both healthy adolescents/young adults and those engaging in substance use (Lisdahl and Price, 2012; Medina et al., 2009; Simmonds et al., 2014; Squeglia et al., 2012). We suspect that findings represent a “longer-term” impact of marijuana and alcohol use, given the monitored abstinence period. The majority of findings present at baseline were present at follow-up, but this was not the case for all regions (e.g., left paracentral cortex and lifetime marijuana use). The prospect of neural recovery after cessation of use is understudied in the adolescent literature, although there is some suggestion that brain structural changes can occur within the initial 24 months of abstinence from alcohol in an adult sample of former heavy alcohol users reporting 1 month to 26 years of abstinence (Fortier et al., 2011). Our preliminary findings need to be replicated and expanded upon. Longer follow-up periods are necessary to understand changes in marijuana use trajectories over time and differences in residual versus acute effects. Given the preliminary and exploratory nature of this work, large number of analyses conducted, and modest effect sizes, replication of findings is crucial.

Subtle alterations in neurodevelopmental trajectories may have long-term consequences for cognition and daily functioning. To identify how alcohol and marijuana use leads to brain changes, disentangling pre-existing, substance-related, and acute versus residual effects is important. The present findings raise concern for adolescent alcohol and marijuana users and provide more evidence for a longer-term effect on neural tissue development. Our future work will integrate longer follow-up periods with pre- and post-initiation data to understand how such commonly used substances affect the developing brain.

Acknowledgments

The authors extend appreciation to Anthony Scarlett, Diane Goldenberg, and Rachel Thayer for their assistance with data collection and to participating families and schools.

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