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Adolescent Cortical Thickness Pre- and Post Marijuana and Alcohol Initiation

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Abstract

Cortical thickness abnormalities have been identified in youth using both alcohol and marijuana. However, limited studies have followed individuals pre- and post initiation of alcohol and marijuana use to help identify to what extent discrepancies in structural brain integrity are pre-existing or substance-related.

Adolescents ($N=69$) were followed from ages 13 (pre-initiation of substance use, baseline) to ages 19 (post-initiation, follow-up). Three subgroups were identified, participants that initiated alcohol use (ALC, $n=23$, >20 alcohol use episodes), those that initiated both alcohol and marijuana use (ALC+MJ, $n=23$, >50 marijuana use episodes) and individuals that did not initiate either substance regularly by follow-up (CON, $n=23$, <3 alcohol use episodes, no marijuana use episodes). All adolescents underwent neurocognitive testing, neuroimaging, and substance use and mental health interviews.

Significant group by time interactions and main effects on cortical thickness estimates were identified for 18 cortical regions spanning the left and right hemisphere ($p<.05$). The vast majority of findings suggest a more substantial decrease, or within-subjects effect, in cortical thickness by follow-up for individuals who have not initiated regular substance use or alcohol use only by age 19; modest between-group differences were identified at baseline in several cortical regions (ALC and CON $>$ ALC+MJ). Minimal neurocognitive differences were observed in this sample.

Findings suggest pre-existing neural differences prior to marijuana use may contribute to initiation of use and observed neural outcomes. Marijuana use may also interfere with thinning trajectories

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that contribute to morphological differences in young adulthood that are often observed in cross-sectional studies of heavy marijuana users.

Introduction

Marijuana use has doubled among US adults compared to previous decades (Hasin et al., 2015). Concurrent marijuana and alcohol use among adolescents and young adults is steadily on the rise. Lifetime alcohol use increases from 27% to 66% between 8th and 12th grade, with reports of 9% of 8th graders and 37% of 12th graders having used in the past 30 days (Johnston, O'Malley, Bachman, & Schulenberg, 2015). Marijuana remains the most commonly used illicit substance among adolescents with reports of increases from 16% to 44% between 8th and 12th grade. Seven percent of 8th graders and 21% of 12th graders report having used marijuana in the past 30 days (Johnston et al., 2015). With strong evidence of comorbid substance use during adolescence, it is important to examine how marijuana and alcohol use impacts the adolescent brain as it undergoes changes in cortical volume and refinements in cortical connections.

Cortical gray matter follows an inverted U-shaped developmental course, with cortical volume peaking around early adolescence (Giedd, 1999; Gogtay et al., 2004; Sowell et al., 2003). Cortical gray matter loss during late childhood and adolescence is likely related to refinement and pruning of neural synapses. Longitudinal studies of gray matter reduction during adolescence reveal declines in the medial parietal cortex, posterior temporal and middle frontal gyri, and the cerebellum (Giorgio et al., 2010). The mechanisms underlying the decline in cortical volume and thickness are suggested to involve pruning of the superfluous synaptic connections, reduction in the glial cells, and decrease in neuropil and intra-cortical myelination (Huttenlocher & Dabholkar, 1997; Paus, Keshavan, & Giedd, 2008; Tamnes et al., 2009). The adolescent brain undergoes dynamic neurodevelopment and likely more susceptible to neurotoxins that could potentially affect higher-order cognitive functions (Bava, Jacobus, Mahmood, Yang, & Tapert, 2010; Casey & Jones, 2010).

Cross-sectional studies using structural magnetic resonance imaging (MRI) report smaller hippocampal, prefrontal cortical, and cerebellar volumes in heavy-drinking teens compared to their non-drinking counterparts (Jacobus & Tapert, 2013). Squeglia and colleagues (2014) examined 40 healthy adolescents, ages 12 to 17; half ($n=20$) transitioned into heavy alcohol use over a 3-year period (Squeglia et al., 2014). At baseline, prior to initiating alcohol use, participants who later transitioned into heavy drinking showed smaller left cingulate, pars triangularis, and rostral anterior cingulate volume, and less right cerebellar white matter volumes, compared to continuous non-using teens. Over time, participants who initiated heavy drinking showed significantly greater volume reduction in the left ventral diencephalon, left inferior and middle temporal gyri, and left caudate and brain stem, compared to substance-naïve youth. Squeglia and colleagues (2015) also examined within subject changes over an 8-year period (Squeglia et al., 2015). Serial MRI sessions were conducted (upwards of 6 sessions per person) on 75 adolescents who transitioned into heavy use and 59 who remained light to non-drinkers. Those adolescents who transitioned into heavy drinking showed accelerated gray matter reduction in cortical lateral frontal and

temporal volumes. An accelerated reduction on cortical indices in heavy drinking suggests a potential neurotoxic effect that alcohol has on the developing brain.

Likewise, marijuana use during adolescence is associated with altered brain development. Cross-sectional structural MRI studies have found thinner cortices in prefrontal and insular regions and thicker cortices in posterior regions in marijuana-using adolescents when compared to non-users (Lopez-Larson et al., 2011; Mashhoon, Sava, Sneider, Nickerson, & Silveri, 2015). Utilizing a longitudinal approach, Epstein and colleagues (2015), examined adolescents with cannabis use disorder. Greater lifetime exposure to marijuana predicted greater cortical thickness in the left and right superior frontal gyri, left pars opercularis, right pars triangularis, right supramarginal, and left inferior parietal cortex after adjusting for baseline cortical thickness, suggesting that heavy marijuana use during adolescence alters the trajectory of cortical indices (Epstein & Kumra, 2015).

As previously mentioned, most adolescents who engage in marijuana use also consume high levels of alcohol simultaneously. Jacobus and colleagues (2014) examined marijuana users with simultaneous heavy alcohol use ($n = 34$) and non-using controls ($n = 30$) who completed 28 days of monitored abstinence (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014). When compared to controls, marijuana and alcohol using youths showed thicker cortices before and after monitored abstinence. More marijuana use was linked to thinner cortices in temporal and frontal regions; whereas, more alcohol use was linked to thicker cortices in all four lobes. Jacobus and colleagues (2015) also examined cortical thickness in heavy marijuana and concomitant alcohol users ($n = 30$) ages 16 to 22. When compared to their non-users counterparts ($n = 38$), marijuana and alcohol users showed thicker cortices in frontal and parietal lobes. More lifetime marijuana use was associated with increased thickness over the three-year follow-up (Jacobus, Squeglia, Meruelo, et al., 2015). Taken together, marijuana and alcohol use may be indicative of atypical cortical development, and therefore, it is important to examine how concurrent marijuana and alcohol use impacts cortical thickness development prior to and after the onset of substance use.

There have been no prospective studies that examined the impact of marijuana use on cortical thickness estimates pre- and post initiation of marijuana use. The aim of this prospective study was to identify differences in cortical thickness between adolescents that initiated alcohol use, compared to those that initiated both alcohol *and* marijuana use by age 19, approximately. Adolescents were initially assessed prior to initiation of substance use (age 13), and re-assessed ~ 6 years later. Participants were categorized as controls (did not initiate substance use), those initiating heavy alcohol use only, or those that initiated marijuana use *and* alcohol use. We hypothesized, based on previous investigations (Epstein & Kumra, 2015; Filbey, McQueeney, DeWitt, & Mishra, 2015; Jacobus, Squeglia, Meruelo, et al., 2015) that those individuals who initiated heavy marijuana and alcohol use during adolescence would show thicker cortices over time compared to our control teens by young adulthood in frontal and temporal brain regions, likely a result of interference with typical neuromaturational processes.

Methods

Participants

Adolescents ($N=69$) were recruited from local San Diego schools and followed for approximately 6-8 years, which included a baseline assessment (ages 12-14 at enrollment) and an in-person follow-up visit following initiation of alcohol and/or marijuana use for those identified as substance users (ages 18-21) (see Table 1). Participants underwent neuroimaging, neurocognitive, and substance use assessment at both time points. Inclusion in the present study required valid 3.0 Tesla neuroimaging data at both time points to avoid asymmetrical processing in the longitudinal cortical thickness processing approach. Individuals were stratified into groups based on their reported substance use, and cut-offs were determined *a priori*, as those in the ALC+MJ group were determined, at minimum, to have slightly more than monthly marijuana use at follow-up, and individuals in the substance initiations groups were subsequently matched on alcohol use. Notably, substance use reported was within 12-36 months prior to follow-up. Inclusion in the marijuana and alcohol initiation group (ALC+MJ) required >50 cumulative marijuana use episodes by follow-up (range 53-1720). Participants were demographically matched for inclusion in an alcohol initiation group (ALC), and non-using control group (CON) to help isolate the contribution of marijuana use on structural brain changes. Inclusion in the ALC group required <40 cumulative marijuana use episodes by follow-up (range 0-37), but similar lifetime alcohol use by follow-up, as both groups reported >20 cumulative alcohol use episodes by age 19 (see Table 1). Control participants reported <3 lifetime alcohol use episodes and no marijuana use episodes by follow-up. All participants underwent written informed consent (or assent if under age 18 and consent from their guardians) in accordance with the University of California, San Diego Human Research Protections Program

Exclusionary criteria at study entry included: history of a lifetime DSM-IV Axis I disorder (other than cannabis or alcohol abuse/dependence), history of learning disability; history of neurological disorder or traumatic brain injury with loss of consciousness >2 minutes; history of a serious physical health problem; complicated or premature birth including prenatal substance use; uncorrectable sensory impairments; left handedness; and use of psychoactive medications.

Measures

Substance Use and Mental Health Assessment—The Customary Drinking and Drug Use Record was used to assess lifetime alcohol, marijuana, cigarette, and other drug use (S. A. Brown et al., 1998), defined as cumulative use (e.g., alcohol, marijuana) episodes (i.e., number of days) reported at study entry (baseline) and follow-up. The Timeline Followback was used to assess self-reported substance use (e.g., alcohol, marijuana) in the 28 days prior to each scan session (Sobell & 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 parent 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

(BDI; Beck, 1978) and Spielberger State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 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 prior to the baseline imaging session. The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest was included as an estimate of premorbid intellectual functioning (D. Wechsler, 1999).

Neurocognitive Testing—A comprehensive neuropsychological battery was administered at baseline and follow up to assess cognitive functioning. At baseline, the assessment included (see Table 2): Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) Color-Word Interference and Trail Making Test (TMT) subtests; California Verbal Learning Test-Children's Version (CVLT-Children; Delis, Kramer, Kaplan, & Ober, 1994); Wechsler Abbreviated Scale of Intelligence (WASI; D. Wechsler, 1999) Block Design subtest; Wechsler Intelligence Scale for Children 3rd edition (WISC-III; D. Wechsler, 1991) Arithmetic, Coding, and Digit Span subtests; and the Complex Figure task (Loring & Meador, 2003; Rey, 1999). At follow up, participants age 18 years and older were administered the adult versions of the CVLT (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) and Wechsler Arithmetic, Digit Symbol and Digit Span subtests (WAIS-III; D. Wechsler, 1997).

Procedures

Cortical thickness acquisition and processing—All scans were acquired on the same 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 still in the scanner while a high-resolution T1-weighted anatomical spoiled gradient recall scan was acquired (Baseline: FOV 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, TE/TR=min full, flip angle 12°, 176 continuous slices; Follow-up: FOV 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, TE/TR=min full, flip angle 8°, 170 continuous slices).

Cortical thickness estimates were extracted using previously published methods by our laboratory (Jacobus et al., 2014). 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, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). The initial cross-sectional process involves motion correction and averaging of T1 weighted images, removal of non-brain tissue and transformation to standardized space, segmentation of subcortical white and deep grey matter structures, intensity normalization, and tessellation of the grey/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 & Dale, 2000; Fischl et al., 1999; Fischl et al., 2004); this procedure allows for quantification of submillimeter group differences (Fischl & Dale, 2000).

Cortical thickness was calculated as the closest distance from the grey/white matter boundary to the grey matter/cerebral spinal fluid boundary at each vertex on the cortical surface (Fischl & 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, Schmansky, Rosas, & Fischl, 2012).

Following cross-sectional processing of both time points, data was 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-ups) using a consistent robust inverse registration method (Reuter, Rosas, & Fischl, 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).

To identify errors made during cortical reconstruction processing, one rater (JJ), blind to participant characteristics, followed the reconstruction and longitudinal edit procedures to 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). All longitudinal runs were checked for quality, and no editing was necessary following the longitudinal processing.

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 and substance use variables and to identify appropriate covariates for subsequent analysis (see Table 1 and Figure 1 for substance use characteristics of this sample).

Cortical Thickness and Neurocognitive Measurement—Repeated measures analysis of covariance (ANCOVA) examined main effects of group, time, and Group by Time interactions on cortical thickness values for 34 independent standard neuroanatomical cortical regions (Desikan et al., 2006) in each hemisphere. Significant main effects and interaction effects were followed-up post-hoc to determine what time point or group was driving the statistically significant between-group or within-group differences ($\alpha=.05$). Intracranial volume (ICV) was included as a covariate. Similarly, a repeated measures analysis of variance examined the main effects of group, time, and Group by Time

interactions on neuropsychological performance for 23 tests completed at baseline and follow-up.

Secondary Correlational Analysis—Bivariate correlations exploring change in cortical thickness between baseline and follow-up and 1) cumulative substance use, 2) neuropsychological performance at follow-up, and 3) depression at follow-up were examined. Significant correlations were further examined by linear regression analyses predicting follow-up neuropsychological functioning (dependent variable) and change in cortical thickness (independent variable) controlling for baseline neuropsychological performance (independent variable) for the corresponding neuropsychological outcome variable in each group. This approach helped determine if change in cortical thickness over the follow-up interval predicted neuropsychological outcomes for these groups, controlling for their baseline performance.

Results

Demographics

No demographic differences were observed between groups (see Table 1), except for externalizing symptomology at baseline and follow-up, internalizing symptomology at follow-up, and depression symptomology at follow-up ($p < .05$). Groups differed on reported substance use as anticipated.

Cortical thickness measurement

Examination of 34 independent cortical regions in each hemisphere revealed significant Group by Time effects, largely consistent with a significant decrease in cortical thickness over time in the ALC group compared to the ALC+MJ group ($p < .05$). Findings within each lobe of the brain are presented below (see Figures 2-4). Intracranial volume (ICV) was identified *a priori* as a covariate.

Left frontal and parietal lobe cortical thickness—In the left hemisphere, the group by time interaction predicted cortical thickness in the left superior frontal gyrus $F(2,65)=4.1$, $p=.02$. While all groups demonstrated a significant decrease in cortical thickness over time ($p < .01$), follow-up analysis revealed group differences at baseline only (ALC > ALC+MJ, CON, $p < .02$) and no group differences at follow-up. The group by time interaction effect predicted cortical thickness in the left precentral gyrus, $F(2,65)=3.7$, $p=.03$. Follow-up analysis revealed between group differences at baseline only (ALC > ALC+MJ, $p=.03$) in addition to significant decreasing thickness estimates over time for all groups ($p < .01$).

The group by time interaction predicted cortical thickness in the left paracentral gyrus $F(2,65)=4.1$, $p=.02$; the within-subjects effect was significant for all groups ($p < .01$), however a more substantial decrease was observed over time for the ALC group and no between-group differences were observed. The group by time interaction effect predicted cortical thickness in the left superior parietal lobe, $F(2,65)=3.0$, $p=.04$ and the left supramarginal gyrus. $F(2,65)=3.8$, $p=.02$. Follow-up analysis revealed a significant decrease

in thickness over time for all groups ($p < .01$), and a between-group effect at baseline (ALC > ALC+MJ, $p < .05$), not present at follow-up ($p > .70$) (see Figure 2).

Left temporal and occipital lobe cortical thickness—The group by time interaction predicted thickness in the left lingual gyrus, $F(2,65)=4.1$, $p=.02$ and left pericalcarine gyrus, $F(2,65)=5.4$, $p<.01$, as groups demonstrated significant decreasing cortical thickness estimates, particularly ALC and CON groups ($p < .01$), but no between-group effects.

The main effect of group (trend) predicted thickness estimates in the left parahippocampal gyrus, $F(2,65)=6.57$, $p=.07$. Between group differences were found at both baseline ($p=.04$) and follow-up ($p=.01$) between ALC and ALC+MJ only (see Figure 3).

Right frontal, parietal, and insula cortical thickness—The group by time interaction predicted cortical thickness estimates in the right superior parietal cortex, $F(2,65) = 3.8$, $p=.02$ and the right frontal pole, $F(2,65)=4.0$, $p=.02$. In these regions, the within-group effect was significant for all groups ($p < .01$). While between-group effects were not significant ($p > .05$), the ALC and CON groups demonstrated thicker cortices at baseline and a greater decline in cortical thickness over time compared to ALC+MJ.

The group by time interaction predicted cortical thickness estimates in the right inferior parietal cortex, $F(2,65)=3.2$, $p=.04$; the right precentral gyrus, $F(2,65)=5.6$, $p<.01$; the right paracentral gyrus, $F(2,65)=4.0$, $p=.02$; the right rostral middle frontal gyrus, $F(2,65)=4.2$, $p=.01$; the right pars triangularis, $F(2,65)=3.9$, $p=.02$; the right superior frontal gyrus, $F(2,65)=2.3$, $p=.04$; and a trend in the right supramarginal gyrus $F(2,65)=2.8$, $p=.07$. In all regions the ALC group demonstrated thicker cortices at baseline compared to ALC+MJ ($p < .05$), however no significant between group differences were observed at follow-up. The CON group demonstrated thicker cortices in the right rostral middle frontal gyrus only compared to ALC+MJ ($p=.03$), and no significant differences were observed between ALC and CON groups in the right hemisphere. For all regions, (with the exception of the precentral gyrus), the within-group effect was significant for each group; ALC and CON groups tended to demonstrate a more substantial decrease in cortical thickness over time ($p < .01$).

The main effect of group predicted thickness estimates in the right insula, $F(2,65)=4.1$, $p=.02$, between group differences were identified at both baseline and follow-up (ALC > ALC+MJ, $p < .01$) (see Figure 4).

Given between group differences identified between lifetime other drug use episodes, findings were re-run with lifetime other drug use episodes as a covariate; however findings remain unchanged.

Neurocognitive Measurement

The main effect of group predicted performance on two tasks, WAIS-III Arithmetic Scaled Score, $F(2,65)=4.2$, $p=.01$ (CON, ALC > ALC+MJ, $p < .02$), and CVLT Trials 1-5 Total Score, $F(2,65) = 3.2$, $p=.04$ (CON > ALC+MJ, $p=.01$) (see Table 2)

Correlational Analyses

Substance use—Negative correlations were observed in the substance initiation group ($n=46$) between change in cortical thickness and cumulative marijuana use reported at follow-up. This includes left ($r=-.40$, $p=.01$) and right superior parietal cortex ($r=-.43$, $p<.01$), left lingual gyrus ($r=-.29$, $p=.04$), left pericalcarine cortex ($r=-.41$, $p<.01$), right precentral gyrus ($r=-.30$, $p=.04$), and right paracentral gyrus ($r=-.41$, $p<.01$). More substantial thinning was related to less reported marijuana use by follow-up. We did not observe dose-dependent correlations with alcohol use.

Neurocognition—Positive bivariate correlations ($N=69$) were observed between follow-up performance on the DKEFS TMT motor speed condition and change in thickness estimates in the left lingual gyrus ($r=.35$, $p<.01$) and left superior frontal gyurs ($r=.27$, $p=.02$); findings were determined to be driven by the ALC group (standardized $\beta=.57$, $p<.01$, $n=23$) for the lingual gyrus after controlling for baseline performance in each group. Findings were not driven by a particular group for the left superior frontal gyrus. A more substantial change in thickness (i.e., thinning) was associated with better performance at follow-up in both cortical regions.

The bivariate correlation ($N=69$) between follow-up performance on the DKEFS TMT visual scanning condition and thickness change in left ($r=.26$, $p=.02$) and right superior frontal gyrus ($r=.25$, $p=.04$) was significant, and remained significant after controlling for baseline performance ($ps<.03$). Findings were driven by performance in the ALC group (standardized $\beta=.44$, $p=.02$). Similarly, a positive relationship was observed between DKEFS TMT letter condition performance at follow-up and change in thickness estimates in the right pars triangularis ($r=.24$, $p=.04$), driven by the ALC+MJ group after controlling for baseline performance (standardized $\beta=.46$, $p=.02$, $n=23$). A larger degree of change in thickness (i.e., thinning) was associated with better performance at follow-up for both DKEFS tests.

Positive relationships were observed between follow-up performance on the DKEFS Color Word test naming and switching conditions and change in cortical thickness in the right supramarginal gyrus, right superior frontal gyrus, right frontal pole, and right precentral gyrus ($rs>.30$, $ps<.04$), however after controlling for baseline performance these relationships did not remain significant.

Follow-up performance on the WAIS-III Digit Span forward condition was positively associated with change in thickness in the right frontal pole ($r=.26$, $p=.03$) and remained significant after controlling for baseline performance, however this relationship was not found to be driven by a particular group. A positive correlation between WAIS-III arithmetic performance at follow-up and change in left hemisphere supramarginal gyrus thickness ($r=.25$, $p=.04$), did not remain significant after controlling for baseline performance.

Depression: We found negative correlations between change in cortical thickness and depression (BDI) scores at follow-up in the left superior parietal cortex ($r=-.25$, $p=.04$), left lingual gyrus ($r=-.26$, $p=.03$), left pericalcarine cortex ($r=-.29$, $p=.01$), and right superior parietal cortex ($r=-.33$, $p<.01$). Lower scores on the BDI at follow-up were associated with

more substantial thinning over time. We examined the correlations in each group to explore if the observed relationships were driven by one particular group. In the ALC+MJ group only, thickness changes in the right superior parietal cortex was negatively correlated with depression scores at follow-up ($r=-.49$, $p=.01$); no other correlations remained significant when explored at the group level only.

Discussion

This study looked at cortical thickness estimates pre-initiation (~ age 13) and post-initiation (~age 19) of alcohol and marijuana use in $N=69$ adolescents over six years of follow-up. The sample included individuals that initiated alcohol use only, alcohol *and* marijuana use, and minimal to no substance use by age 19. We found several group by time interaction effects that predicted cortical thickness in 18 widespread cortical regions, bilaterally. Specifically, in the left hemisphere, a more substantial decrease in cortical thickness was typically observed over time in the ALC and CON groups; the ALC group also demonstrated significantly thicker cortices at baseline in frontal and parietal areas most consistently, such as the left superior frontal gyrus, precentral gyrus, superior parietal lobe, and supramarginal gyrus. In the right hemisphere, a similar pattern emerged whereas the ALC and CON groups demonstrated a greater decline in cortical thickness from ages 13-19, and ALC demonstrated thicker cortices at baseline in frontal and parietal regions such as precentral gyrus, paracentral gyrus, rostral middle frontal gyrus, superior frontal gyrus, pars triangularis, and insula cortex compared to ALC+MJ.

It is important to put the current findings into the context of our previous work examining cortical thickness alterations in adolescent and young adult marijuana users. Jacobus and colleagues (2014) found, in a study of heavy marijuana users pre- and post 28 days of monitored abstinence, increased thickness estimates in the entorhinal cortex compared to matched controls (Jacobus et al., 2014). In a longer-term prospective study in our laboratory that examined the influence of marijuana use on cortical thickness trajectories over three years and three independent time points (~ages 18, 19, and 21 respectively), marijuana users showed thicker estimates in widespread brain regions by follow-up (~age 21); findings also suggested positive correlations between cortical thickness and lifetime marijuana use (Jacobus, Squeglia, Meruelo, et al., 2015), notably consistent with our present finding of less substantial thinning associated with more reported marijuana use. Earlier studies examined marijuana and alcohol user *after* initiation of heavy use, despite the longitudinal design. The present study expands on these previous investigations, and suggests that to some extent, pre-existing differences may contribute to neural outcomes in those individuals initiating both marijuana and alcohol use. Alcohol initiators appear to demonstrate thicker cortices prior to initiation, similar to controls, but also undergo a more substantial decrease in cortical thickness into young adulthood. Between-group differences are not widely evident at follow-up in this study, but perhaps thicker cortices would be observed in ALC+MJ with continued follow-up of these young adults, similar to previous work by our laboratory and others (Epstein & Kumra, 2015; Filbey et al., 2015; Jacobus, Squeglia, Meruelo, et al., 2015). For instance, it is reasonable to speculate, based on the observed trajectory of the groups, the marijuana initiators may demonstrate subtle yet thicker cortices by age 21

compared to controls and alcohol initiators, if use remains consistent and they stay within their substance use patterns.

Limited effects were observed for neurocognitive performance over time, with the exception of two between-group effects on measures of complex attention (i.e., CVLT Trials 1-5, WAIS-III Arithmetic). The CON and ALC group demonstrated better baseline and follow-up neurocognitive performance. A greater degree of change (i.e., thinning) in posterior and inferior frontal lobe cortical thickness estimates was associated with better neurocognitive performance on several tests in this sample.

Correlational findings between cortical thickness and neurocognitive functioning in the present investigation were modest, however studies do show that adolescent alcohol and marijuana users tend to have poorer neurocognitive outcomes by young adulthood (Jacobus, Squeglia, Infante, et al., 2015) that correlate with changes in structural tissue integrity (Jacobus, Squeglia, Bava, & Tapert, 2013; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013). Limited relationships found in correlational analyses between change in cortical thickness and neurocognitive functioning may have to do with neurodevelopmental temporal specificity patterns and/or curvilinear relationships (Ducharme et al., 2016); there are also inconsistencies in the literature as to the age range of peak cortical thickness and neurodevelopmental estimation trajectories (Ducharme et al., 2016). For example, anterior and higher-order association regions may peak in thickness estimates later and therefore the degree of change may not be fully captured in this study, or these particular cortical areas are not adequately represented by a linear thinning trajectory (e.g., quadratic). Nevertheless, the majority of the cortical mantle is thought to be best represented by a linear decline that peaks around ages 5-8 years old or later (Brown & Jernigan, 2012; Ducharme et al., 2016; Giedd, 1999).

The present study found that more substantial cortical thinning was linked to less self-reported depression, consistent with existing studies of young adults with depression. Alterations in cortical thickness may modulate emotion processing circuits (Fonseka et al., 2016, Reynolds 2014). Medina and colleagues (2007) found that white matter abnormalities predicted fewer depression symptoms in marijuana users. Suboptimal alterations in neural health due to alcohol and marijuana use during adolescence, whether gray or white matter tissue, may increase vulnerability to mental health distress and co-occurring substance use disorders in adulthood.

Few studies have looked at pre-existing differences among adolescent marijuana and alcohol users in cortical thickness, or structural brain integrity in general (Jacobus, Squeglia, Infante, et al., 2013). Cheetham et al, found that smaller orbitofrontal cortex volume pre-initiation of use (age 12) was associated with progression into marijuana use by age 16 (Cheetham et al., 2012). Squeglia and colleagues (2015) found accelerated declining brain volume trajectories in individuals age 12-24 who transitioned into heavy drinking (Squeglia et al., 2015). The present findings also share similarities with cross-sectional structural imaging work conducted outside of our laboratory that has focused on gray matter tissue integrity in adolescent and young adult alcohol and marijuana users. Lopez-Larson and colleagues (2011) found decreased thickness in frontal regions and the insula, along with increased

thickness in lingual, temporal, and parietal regions in marijuana-using adolescents (ages 16-19) in a cross-sectional investigation (Lopez-Larson et al., 2011). More recently Filbey and colleagues found that more years of marijuana use and marijuana consumption was associated with thicker cortices in regular marijuana users ages 21-50 (Filbey et al., 2015). Epstein and Kumra (2015) report increased thickness estimates in marijuana users ages 10-23 with more lifetime reported marijuana use, and suggest that marijuana use may attenuate age-related cortical thinning. The study measured cortical thickness in heavy marijuana users compared to controls at baseline (after initiation) and at 18-month follow-up, and cortical thickness trajectories mirror the present findings in many brain regions. The authors suggest that synapses may be preserved that would typically be eliminated as part of refinement, and align with attenuation of cortical thinning in the presence of cannabis exposure (Epstein & Kumra, 2015).

The present study, taken together with findings from other laboratories, suggests that pre-existing differences may play a role in initiation, continuation of substance use, and neural health outcomes, as evidenced by baseline differences observed in our study; however marijuana-related interference with neurodevelopmental processes is likely a contributor to the unique neurodevelopmental trajectories observed in this study that often influence dynamic neurocognitive and mental health outcomes such as depression (Epstein & Kumra, 2015). Findings suggest a pre-existing vulnerability, coupled with exogenous factors such as marijuana use, may suboptimally impact cortical refinement and thus efficient cognitive processing and psychopathology.

We have observed similar findings in investigations of white matter integrity in adolescent marijuana users (Jacobus, Squeglia, Infante, et al., 2013). There are several neural mechanisms that may contribute to marijuana- and alcohol-related alterations in cortical thickness as well as pre-existing differences, including variability in neural size, cell density, and neurovasculature. Notably, studies have suggested an increased peak cortical thickness and more dramatic rate of change in cortical thickness in children and adolescents with more superior intellectual functioning (Shaw et al., 2006).

Strengths of this study include the prospective design and assessment of pre-existing differences over a six-year follow-up interval. However, there are limitations that need to be addressed. The sample size is small and multiple comparison corrections were not stringent, therefore replication is important given the large number of analyses conducted and modest effect sizes. Future work will focus on controlling for varying degrees of substance use consumption within each episode, as the quantity of alcohol and/or marijuana consumed per episode could differentially alter neurocognitive performance and cortical thickness trajectories in young adults. Similarly, sex differences may contribute to discrepant neural trajectories and should be the focus of future prospective studies with larger sample sizes.

Better understanding of how alcohol and marijuana use impact neural outcomes in the context of pre-existing differences will help us better understand addictions science, as well as develop better tailored interventions for problematic substance use. Longitudinal studies should continue to follow existing cohorts beyond early adulthood to understand the neural progression and neurocognitive and mental health correlates.

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Highlights

- Pre-existing neural differences prior to marijuana use may contribute to initiation of use and observed neural outcomes
- Combined alcohol and marijuana use may also interfere with cortical thinning trajectories that contribute to morphological differences in young adulthood
- Altered cortical thinning trajectories in young adult marijuana users may be linked to poorer neurocognition and increased risk for depression .

Figure 1.
Substance use characteristics of sample (N=69)

Figure 2.

Left hemisphere frontal and parietal lobe cortical thickness estimates measured in millimeters and controlling for ICV ($N=69$). * $p<.05$ (ALC>ALC+MJ); ** $p<.05$, ALC>CON, ALC+MJ ‡ $p<.05$, (baseline>follow-up CON, ALC, ALC+MJ)

Figure 3. Left hemisphere temporal and occipital lobe cortical thickness estimates measured in millimeters and controlling for ICV ($N=69$). * $p<.05$ (ALC+MJ>ALC, baseline & follow-up); ‡ $p<.05$, (baseline>follow-up for CON, ALC, ALC+MJ)

Figure 4. Right hemisphere frontal lobe, parietal lobe, and insula cortical thickness estimates measures in millimeters and controlling for ICV (N=69). * $p < .05$ (ALC > ALC+MJ, baseline); ‡ $p < .05$, (baseline > follow-up CON, ALC, ALC+MJ); ‡‡ $p < .05$, (baseline > follow-up ALC and CON only)

Participant characteristics.

Table 1

	Controls (CON) <i>n</i> = 23, Mean (SD)	Alcohol initiators (ALC) <i>n</i> = 23, Mean (SD)	Marijuana initiators (ALC+MJ) <i>n</i> = 23, Mean (SD)
Age (SD; range), baseline *	13.4 (0.6; 12.3-14.5)	13.8 (0.6; 12.3-14.9)	13.9 (0.6; 12.8-14.9)
Age (SD; range), follow-up *	18.7 (0.9; 17.3-21.3)	19.2 (0.8; 18.1-20.8)	19.5 (0.9; 18.1-21.2)
% Caucasian	82%	87%	70%
% Male	56.5%	56.5%	56.5%
Grade point average, follow-up	3.5 (0.5)	3.6 (0.5)	3.4 (0.7)
Household income, follow-up	161.2K (101.4)	151.8K (60.1)	193.2K (128.0)
Maternal education (years)	16.2 (2.6)	16.4 (1.7)	16.0 (1.8)
Family history of alcohol use disorder density (range 0-2)	0.01 (0.1)	0.1 (0.2)	0.2 (0.3)
Family history of drug use disorder density (range 0-2)	0.05 (0.1)	0.04 (0.1)	0.04 (0.2)
% with Alcohol Use Disorder, follow-up	0%	0%	4.3%
Age of initiation, alcohol use *	-	16.1 (1.3)	15.1 (1.1)
Age of initiation, marijuana use	-	16.6 (1.7)	15.7 (1.7)
% with Cannabis Use Disorder, follow-up	0%	0%	39.1%
Alcohol, lifetime use days, baseline (SD; range)	0.04 (0.2)	0.04 (0.2; 0-1)	0.4 (0.4; 0-5)
Alcohol, days use over follow-up (SD; range) *	0.34 (0.8)	127.2 (119.8; 20-523)	217.0 (228.6; 29-929)
Binge drinking episodes use over follow-up *	0.0 (0.0)	55.8 (76.2)	89.0 (118.2)
Peak drinks on an occasion (lifetime) *	0.7 (1.9)	11.3 (3.6)	10.6 (3.0)
Marijuana, lifetime use days at baseline (SD; range)	0.0 (0.0)	0.0 (0.0)	0.2 (0.7; 0-3)
Marijuana, days use over follow-up (SD; range) *	0.0 (0.0)	9.4 (11.1; 0-37)	426.0 (475.9; 53-1720)
Other drug use, lifetime use at baseline (SD; range)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Other drug use, days use over follow-up (SD; range) *	0.0 (0.0)	5.1 (13.3; 0.0-62.0)	90.0 (131.5; 0.0-356.0)
Beck Depression Inventory, baseline	0.9 (1.7)	0.6 (0.9)	1.1 (2.0)
Beck Depression Inventory, follow-up *	1.3 (1.8)	2.0 (2.7)	6.9 (7.7)
State Trait Anxiety Inventory, baseline	24.9 (4.9)	23.9 (4.6)	26.8 (7.2)
State Trait Anxiety Inventory T-Score, follow-up	24.1 (3.6)	25.4 (5.9)	29.0 (9.8)

	Controls (CON) <i>n</i> = 23, Mean (SD)	Alcohol initiators (ALC) <i>n</i> = 23, Mean (SD)	Marijuana initiators (ALC+MJ) <i>n</i> = 23, Mean (SD)
Vocabulary <i>T</i> -score, baseline	58.0 (8.11)	56.0 (7.5)	55.2 (9.1)
Child Behavior Checklist Externalizing <i>T</i> -score, baseline *	39.5 (7.7)	39.0 (6.8)	44.4 (7.6)
Youth/Adult Self-Report Externalizing <i>T</i> -score, follow-up *	39.4 (10.1)	45.4 (6.9)	53.9 (10.1)
Child Behavior Checklist Internalizing <i>T</i> -score, baseline	41.6 (8.7)	42.2 (7.4)	43.9 (7.1)
Youth/Adult Self-Report Internalizing <i>T</i> -score, follow-up *	40.5 (9.2)	42.7 (10.2)	50.0 (10.9)

* *p* < 0.05

Table 2

Neuropsychological performance on subtests administered. Means below are presented as scaled scores unless noted.

	CON M(SE)		ALC M(SE)		ALC+MJ M(SE)		Cohen's <i>d</i>
	Age 13	Age 19	Age 13	Age 19	Age 13	Age 19	
Complex Attention							
CVLT ^a Trial 1 Raw Score	7.7 (0.4)	7.8 (0.4)	7.3 (0.4)	7.4 (0.3)	7.3 (0.4)	7.4 (0.4)	ns
CVLT ^a Trials 1-5 Total Recall Raw Score	55.9 (1.6)	62.0 (1.9)	55.5 (1.4)	58.1 (1.8)	52.9 (1.6)	56.3 (1.9)	0.4 [*]
WAIS-III ^b Arithmetic Scaled Score	12.7 (0.7)	12.3 (0.6)	13.1 (0.6)	11.5 (0.6)	11.0 (0.7)	10.5 (0.6)	0.2 [*]
WAIS-III ^b Digit Span Total Scaled Score	10.7 (0.5)	10.3 (0.5)	10.5 (0.5)	11.1 (0.5)	11.0 (0.5)	11.0 (0.5)	ns
WAIS-III ^b Digit Span Forward, Raw Total Score	9.6 (0.4)	10.3 (0.4)	10.0 (0.4)	11.2 (0.4)	10.6 (0.4)	11.7 (0.4)	ns
WAIS-III ^b Digit Span Backward, Raw Total Score	6.4 (0.3)	7.5 (0.5)	6.1 (0.3)	8.0 (0.5)	6.3 (0.3)	7.3 (0.5)	ns
Processing Speed							
WAIS-III ^b Digit Symbol Scaled Score	10.0 (0.7)	10.3 (0.5)	10.7 (0.7)	11.1 (0.5)	10.9 (0.7)	10.8 (0.5)	ns
D-KEFS TMT Visual Scanning Scaled Score	9.5 (0.6)	11.3 (0.4)	9.7 (0.5)	12.2 (0.3)	10.1 (0.6)	12.0 (0.4)	ns
D-KEFS TMT Number Sequencing Scaled Score	11.0 (0.6)	12.0 (0.5)	11.2 (0.5)	12.7 (0.4)	11.5 (0.6)	13.0 (0.4)	ns
D-KEFS TMT Letter Sequencing Scaled Score	11.5 (0.4)	12.7 (0.5)	11.7 (0.3)	13.0 (0.4)	11.2 (0.4)	12.3 (0.4)	ns
D-KEFS TMT Motor Speed Scaled Score	12.0 (0.3)	13.2 (0.2)	12.1 (0.3)	13.6 (0.2)	12.0 (0.3)	13.3 (0.2)	ns
Verbal Memory							
CVLT ^a Short Delay Free Recall Raw Score	11.9 (0.4)	13.7 (0.6)	11.6 (0.4)	12.2 (0.6)	11.5 (0.4)	12.5 (0.6)	ns
CVLT ^a Short Delay Cued Recall Raw Score	11.9 (0.4)	14.2 (0.6)	12.0 (0.4)	12.9 (0.5)	11.7 (0.4)	13.0 (0.6)	ns
CVLT ^a Long Delay Free Recall Raw Score	12.0 (0.4)	14.0 (0.5)	12.1 (0.4)	13.1 (0.5)	12.0 (0.4)	12.6 (0.5)	ns
CVLT ^a Long Delay Cued Recall Raw Score	12.4 (0.4)	14.6 (0.5)	12.3 (0.3)	13.0 (0.5)	12.4 (0.4)	13.2 (0.5)	ns
Visuospatial Functioning							
Complex Figure Copy Accuracy Raw Score	29.2 (0.7)	32.2 (0.8)	28.3 (0.6)	30.9 (0.7)	28.6 (0.7)	30.5 (0.8)	ns
Complex Figure Delay Accuracy Raw Score	18.8 (1.1)	23.3 (1.3)	16.3 (1.0)	20.0 (1.2)	18.2 (1.0)	21.3 (1.3)	ns
WASI Block Design <i>T</i> -Score	59.2 (2.0)	61.7 (2.1)	56.7 (1.8)	55.8 (1.9)	59.0 (1.9)	58.1 (2.0)	ns

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	CON M(SE)		ALC M(SE)		ALC+MJ M(SE)		Cohen's <i>d</i>
	Age 13	Age 19	Age 13	Age 19	Age 13	Age 19	
Executive Functioning							
D-KEFS TMT Number-Letter Switching Scaled Score							ns
D-KEFS Color Word Interference Color Naming Scaled Score							ns
D-KEFS Color Word Interference Word Reading Scaled Score							ns
D-KEFS Color Word Interference Inhibition Scaled Score							ns
D-KEFS Color Word Interference Inhibition/Switching Scaled Score							ns

* Cohen's *d* reflects between group differences (CON, ALC > ALC+MJ) (*N*=69).

^a Includes CVLT-C at baseline and CVLT-II at follow-up;

^b Includes WISC-III at baseline