Developmental Cognitive Neuroscience 16 (2015) 101–109

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood

Joanna Jacobus[a,b], Lindsay M. Squeglia[c], Alejandro D. Meruelo[b], Norma Castro[b], Ty Brumback[b], Jay N. Giedd[b], Susan F. Tapert[a,b,*]

[a] Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA
[b] University of California San Diego, Department of Psychiatry, La Jolla, CA, USA
[c] Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Charleston, SC, USA

ARTICLE INFO

Article history:
Received 2 January 2015
Received in revised form 17 April 2015
Accepted 18 April 2015
Available online 27 April 2015

Keywords:
Adolescence
Brain
Alcohol
Marijuana
Imaging
Cortical thickness

ABSTRACT

Studies suggest marijuana impacts gray and white matter neural tissue development, however few prospective studies have determined the relationship between cortical thickness and cannabis use spanning adolescence to young adulthood. This study aimed to understand how heavy marijuana use influences cortical thickness trajectories across adolescence. Subjects were adolescents with heavy marijuana use and concomitant alcohol use (MJ + ALC, $n = 30$) and controls (CON, $n = 38$) with limited substance use histories. Participants underwent magnetic resonance imaging and comprehensive substance use assessment at three independent time points. Repeated measures analysis of covariance was used to look at main effects of group, time, and Group × Time interactions on cortical thickness. MJ + ALC showed thicker cortical estimates across the brain (23 regions), particularly in frontal and parietal lobes ($ps < .05$). More cumulative marijuana use was associated with increased thickness estimates by 3-year follow-up ($ps < .05$). Heavy marijuana use during adolescence and into young adulthood may be associated with altered neural tissue development and interference with neuromaturation that can have neurobehavioral consequences. Continued follow-up of adolescent marijuana users will help understand ongoing neural changes that are associated with development of problematic use into adulthood, as well as potential for neural recovery with cessation of use.

1. Introduction

Adolescence is a unique developmental period characterized by major physiological, psychological, and neurodevelopmental changes. These changes typically coincide with escalation of alcohol and marijuana use (Brown et al., 2008), which continues into early adulthood (Sartor et al., 2007). The comorbid use of alcohol and marijuana among teens continues to subtly rise as perception of harm declines. Fifty-eight percent of alcohol drinking adolescents report using alcohol and marijuana simultaneously, (Agosti et al., 2002), 45% of youth endorse a lifetime prevalence of marijuana use by the 12th grade, and 22% of these youth endorse use in the past 30 days (Johnston et al., 2015).

The adolescent brain undergoes considerable maturation, including changes in cortical volume and refinement of cortical connections (Huttenlocher and Dabholkar, 1997). These neural transformations (e.g., maturing neural circuitry, cortical thinning and fiber projections) leave the adolescent brain more susceptible to potential neurotoxic effects of substances (Brown et al., 2000; Spear, 2000; Spear and Varlinskaya, 2005; Squeglia et al., 2009; Tapert et al., 2002). Although overall brain volume remains largely unchanged after puberty, ongoing synaptic refinement and myelination results in reduced gray matter and increased white matter volume by late adolescence (Casey et al., 2008; Giedd, 2004; Sowell et al., 2003; Yakovlev and Lecours, 1967).

Cortical gray matter follows an inverted U-shaped developmental course, with cortical volume peaking around ages 12–14 (Giedd, 2004; Giedd et al., 2009; Gogtay et al., 2004; Sowell et al., 2003). The mechanisms underlying the decline in cortical volume and thickness are suggested to involve pruning and elimination of weaker synaptic connections, decreases in neuropil, increases in intra-cortical myelination, or changes in the cellular organization of the cerebral cortex (Huttenlocher and Dabholkar, 1997; Paus et al.,

* Corresponding author at: VA San Diego Healthcare System, Psychology Service (116B), 3350 La Jolla Village Drive, San Diego, CA 92161, USA. Tel.: +1 858 552 8585; fax: +1 858 552 7414.
E-mail address: stapert@ucsd.edu (S.F. Tapert).

http://dx.doi.org/10.1016/j.dcn.2015.04.006

2008; Tamnes et al., 2009). In contrast, white matter development generally is characterized by linear volume increases driven by progressive axonal myelination (Giedd et al., 2009; Gogtay et al., 2004; Simmonds et al., 2014). These processes refine motor functioning, higher-order cognition, and cognitive control (Bava et al., 2010).

Marijuana use during adolescence is associated with altered brain structure. Studies show alterations in white matter integrity in adolescent marijuana users compared to non-users, particularly in fronto-parietal circuitry and pathways connecting the frontal and temporal lobes (Bava et al., 2009). Altered cortical morphometry has also been observed in adolescent marijuana users, with marijuana-using adolescents having larger cerebellar volumes than non-users (Medina et al., 2010), thinner cortices in prefrontal and insular regions, and thicker cortices in posterior regions when compared to controls (Lopez-Larson et al., 2011). Structural neuroimaging studies have also examined whether structural brain alterations were present before onset of marijuana use (Cheetham et al., 2012). Notably, orbitofrontal cortex (OFC) volumes at age 12 predicted initiation of marijuana use at age 16 when controlling for other substance use. Regional volume vulnerabilities may increase risk for initiation and maintenance of marijuana misuse.

This study builds on previous work by our laboratory examining the acute and longer-term impact of adolescent marijuana use on cortical thickness pre- and post 28-days of monitored abstinence from marijuana (Jacobus et al., 2014). We found increased temporal lobe thickness estimates in adolescent heavy marijuana users (age 17), and negative associations with cortical thickness and lifetime marijuana use both acutely and following prolonged abstinence from marijuana. It is unclear if such structural alterations of the cerebral cortex persist into young adulthood. The aim of this prospective study was to identify differences in cortical thickness between adolescent heavy marijuana users and control adolescents with minimal substance use histories assessed at three independent time points (~ages 18, 19 and 21 respectively). We hypothesized that those individuals who initiated heavy marijuana use during adolescence would show thicker cortices over time compared to our control teens by young adulthood in frontal and temporal brain regions.

2. Methods

2.1. Participants

Adolescents were recruited from local San Diego schools and followed for three years, which included a baseline assessment (ages 16–19 at enrollment) and subsequent 1.5, and 3-year in-person follow-up visit (see Table 1). Participants underwent neuroimaging and substance use assessment at all three time points. Study design invited individuals back every 18-months in order to capture relationships between substance use and neuroimaging estimates spanning adolescence to young adulthood (i.e., repeated assessment over 3 years beginning at ages 16–19). Inclusion in the present study required valid neuroimaging data at all three time points ($N = 68$) to avoid asymmetrical processing in the longitudinal cortical thickness processing approach. 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. Marijuana and control groups were selected based on lifetime marijuana use episodes at baseline (>100 lifetime marijuana use episodes for users and <10 for controls), and alcohol use was limited to <150 lifetime drinking episodes for both groups at enrollment. Adolescents were then classified at baseline as marijuana users who also use alcohol regularly (MJ + ALC, $n = 30$; ≥120 lifetime marijuana use episodes and ≥22 lifetime alcohol use episodes at study entry) or control teens with limited marijuana use histories (CON, $n = 38$; ≤9 lifetime marijuana use episodes, and ≤20 lifetime alcohol use episodes, on average). Average days of marijuana use per month ranged from 13 to 15 days over the course of three years for the substance users (see Fig. 1). The vast majority of substance users, MJ + ALC, met criteria for marijuana abuse/dependence over the course of the three-year study (97%) and approximately 87% met criteria for alcohol abuse/dependence. Approximately 55% of controls met criteria for alcohol abuse/dependence over the course of the study; six participants (15%) in the control group met abuse criteria for marijuana use at 3-year follow-up. See Fig. 1 for frequency and cumulative alcohol and marijuana use reported over the course of three years for the sample.

Table 1
Demographic characteristics at baseline ($N = 68$), unless otherwise noted.

	CON $n = 38$ *M* (SD)	MJ + ALC $n = 30$ *M* (SD)
Age, baseline	17.7 (0.9)	18.2 (0.8)
Age, Year 1.5	19.1 (0.9)	19.6 (0.8)
Age, Year 3	20.8 (1.0)	21.2 (0.7)
% Male	76%	63%
% Caucasian	63%	66%
Grade point average	3.4 (0.6)	3.1 (0.7)
Annual household income	127.4 (77.6)	136.8 (106.9)
% Family History positive for substance use disorder	58%	68%
Vocabulary *T*-score	59.5 (9.1)	56.4 (8.5)
Body Mass Index, baseline	22.9 (3.2)	23.8 (4.6)
Body Mass Index, Year 1.5	23.1 (3.0)	23.9 (4.5)
Body Mass Index, Year 3	23.6 (3.1)	24.8 (4.8)
Beck Depression Inventory total, baseline	2.4 (2.7)	3.1 (3.6)
Beck Depression Inventory total, Year 1.5	2.8 (4.6)	3.6 (3.7)
Beck Depression Inventory total, Year 3	2.3 (4.1)	3.5 (5.4)
Spielberger State Anxiety *T*-score, baseline	37.4 (7.2)	40.2 (8.2)
Spielberger State Anxiety *T*-score, Year 1.5	37.6 (6.2)	36.2 (4.7)
Spielberger State Anxiety *T*-score, Year 3	36.4 (6.6)	39.1 (8.3)
Lifetime MJ use episodes, baseline to Year 3*	125.5 (246.4)	1100.3 (698.8)
Lifetime alcohol use episodes, baseline to Year 3*	247.5 (247.0)	604.8 (418.0)
Lifetime other drug use episodes, baseline to Year 3*	12.6 (32.0)	77.0 (113.9)
Average # cigarettes per day, baseline*	0.1 (0.2)	0.8 (2.2)
Average # cigarettes per day, Year 1.5*	0.1 (0.5)	1.0 (2.4)
Average # cigarettes per day, Year 3	0.3 (1.4)	0.8 (1.8)
Days since last MJ use, baseline	–	65.3 (113.4)
Days since last MJ use, Year 1.5	158.6 (456.3)	85.2 (160.9)
Days since last MJ use, Year 3	142.0 (336.9)	97.8 (189.1)
Days since last alcohol use, baseline	114.4 (168.9)	61.2 (98.6)
Days since last alcohol use, Year 1.5	65.7 (242.4)	44.1 (131.5)
Days since last alcohol use, Year 3*	34.5 (69.0)	15.1 (15.7)
Age of onset, regular marijuana use[a]	–	15.3 (2.0)
Age of onset, regular alcohol use[a,*]	17.9 (0.9)[b]	16.5 (2.0)[c]

[a] Defined as >1x/week for 52+ weeks.
[b] $n = 24$.
[c] $n = 26$.
* $p < .05$.

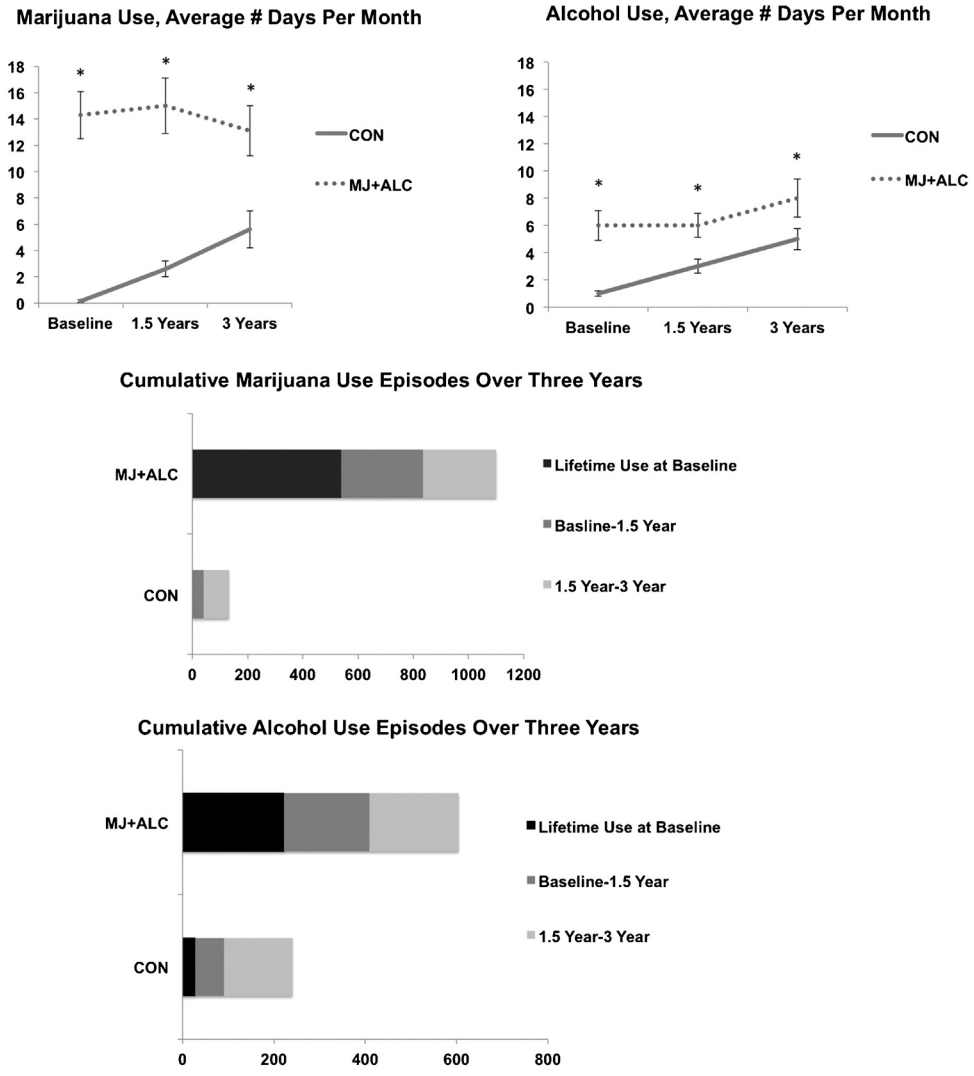

Fig. 1. Substance use characteristics of sample ($N = 68$), $^{*}p < .05$.

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 min; 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.

Participants underwent weekly toxicology screening for four weeks prior to their neuroimaging session to confirm abstinence from marijuana at each time point (monitored abstinence at baseline, 1.5, and 3-year follow-up). Decreasing 11-nor-9-carboxy-tetrahydrocannabinol (THCCOOH) metabolite ratios confirmed completion of the marijuana abstinence protocol at each visit and helped ensure the longer-term adverse alterations in cortical thickness were being captured, as compared to acute effects of recent use. Compliance at each visit was determined for each positive test result by dividing each THCCOOH normalized collection by the previous collected specimen (urine 2/urine 1), per Huestis and Cone recommendations for determining new cannabis use as a function of time (Huestis and Cone, 1998; Smith et al., 2009). Notably, positive THCCOOH/creatinine ratios ranged from 0.0 to 10.6 ng/mg on the day of the scan session across all three time points (baseline, Year 1.5, and Year 3), which falls below the commonly used confirmation cutoff <15 ng/mL.

2.2. Measures

2.2.1. 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 (Brown et al., 1998), defined as cumulative use (e.g., alcohol, marijuana) episodes (i.e., number of days) reported at study entry (baseline), the interval from baseline to Year 1.5, and the interval from Year 1.5 to Year 3. 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 and Sobell, 1992).

2.2.2. 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 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 prior to the baseline imaging session. The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest was included

as an estimate of premorbid intellectual functioning (Wechsler, 1999).

2.3. Procedures

2.3.1. Cortical thickness acquisition and processing

All scans were acquired on the same 3.0 T 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 (SPGR) scan was acquired (TE/TR = min full, field of view = 24 cm, resolution = 1 mm^3, 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 et al., 1999; Fischl et al., 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 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 strenghts has been shown using these standardized procedures (Han et al., 2006; Reuter et al., 2012).

Following cross-sectional processing of all three 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 three cross-sectionally processed time points (baseline and follow-ups) 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).

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 mater 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.

2.4. Data analysis

2.4.1. 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 Fig. 1 for substance use characteristics of this sample).

2.4.2. Cortical thickness 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 between-group and interaction effects were followed-up post hoc to determine what time point was driving the statistically significant between-group differences ($\alpha = .05$). Intracranial volume (ICV) and lifetime alcohol use was included as a covariate given the high rate of alcohol use reported by the marijuana users in this sample.

2.4.3. Secondary correlational analysis

Partial correlations (controlling for lifetime alcohol and marijuana use given associations between both substances and the outcome variable cortical thickness) (Jacobus et al., 2014)) were run in our MJ + ALC group ($n = 30$) and CON group ($n = 38$) to explore unique substance use associations (e.g., cumulative alcohol and marijuana use, recency of alcohol and marijuana use, and age of marijuana use onset) with cortical thickness at 3-year follow-up.

3. Results

3.1. Demographics

No demographic differences were observed (see Table 1). Group differences in substance use were observed, consistent with inclusion criteria and recruitment efforts for heavy marijuana users and controls (see Table 1, Fig. 1).

3.2. Cortical thickness measurement

Examination of 34 independent cortical regions in each hemisphere revealed significant group and Group by Time effects consistent with findings of thicker cortices in the MJ + ALC group across the brain ($ps < .05$). No main effects of time were identified. Findings within each lobe of the brain are presented below (see Table 2). Lifetime alcohol use and ICV were identified *a priori* as covariates for each ANCOVA; all significant findings were re-run controlling for lifetime other drug use and results remain unchanged ($ps < .05$).

3.2.1. Frontal lobe cortical thickness

In the right hemisphere, the group main effect significantly predicted cortical thickness in the right precentral gyrus ($F(1,64) = 6.54$, $p = .01$) and right paracentral lobule ($F(1,64) = 6.4$, $p = .01$). Follow-up analysis for the right hemisphere revealed statistically significant between group differences at baseline and 3-year follow-up for the right precentral gyrus ($ps < .02$) and 1.5 and 3-year follow-up for the right paracentral lobule ($ps < .02$) (see Fig. 2) in which MJ + ALC showed thicker estimates compared to CON.

In the left hemisphere, the group main effect significantly predicted cortical thickness estimates in the left precentral gyrus ($F(1,64) = 12.21$, $p < .01$), left pars opercularis ($F(1,64) = 4.90$,

Table 2
Cortical thickness estimates across time points for between-group differences identified. Means below are *adjusted* for lifetime alcohol use and ICV. Cohen's *d* reflects between-group differences (CON < MJ+ALC) at each time point.

	CON ($n = 38$) *M* (SE)			MJ + ALC ($n = 30$) *M* (SE)			Cohen's *d*[a] Baseline	Cohen's *d*[a] 1.5 Years	Cohen's *d*[a] 3 Years
	Baseline	1.5 Years	3 Years	Baseline	1.5 Years	3 Years			
Frontal lobe									
RH precentral Gyrus	2.68 (.02)	2.66 (0.02)	2.64 (0.02)	2.75 (0.02)	2.72 (0.02	2.71 (0.02)	**0.47***	ns	**0.47***
RH paracentral lobule	2.55 (0.02)	2.54 (0.02)	2.54 (0.02)	2.62 (0.02)	2.63 (0.02)	2.62 (0.02)	ns	**0.46***	**0.41**
LH precentral gyrus	2.72 (0.02)	2.70 (0.02)	2.67 (0.02)	2.79 (0.02)	2.79 (0.02)	2.77 (0.02)	**0.47***	**0.60***	**0.67***
LH pars opercularis	2.73 (0.02)	2.69 (0.02)	2.65 (0.02)	2.78 (0.03)	2.78 (0.03)	2.73 (0.03)	ns	**0.43***	**0.38**
LH frontal pole	2.98 (0.05)	2.91 (0.05)	2.87 (0.05)	3.13 (0.05)	3.08 (0.05)	3.03 (0.05)	**0.33***	**0.37***	**0.35***
LH paracentral lobule	2.60 (0.02)	2.53 (0.02)	2.52 (0.02)	2.60 (0.03)	2.59 (0.03)	2.59 (0.03)	ns	ns	**0.33***
LH superior frontal gyrus	2.94 (0.02)	2.85 (0.02)	2.81 (0.02)	2.95 (0.03)	2.92 (0.03)	2.90 (0.03)	ns	ns	**0.41***
Parietal lobe									
RH superior parietal cortex	2.34 (0.02)	2.30 (0.02)	2.29 (0.02)	2.40 (0.02)	2.37 (0.02)	2.36 (0.02)	**0.40***	**0.47***	**0.47***
RH inferior parietal cortex	2.66 (0.02)	2.60 (0.02)	2.58 (0.02)	2.70 (0.02)	2.67 (0.02)	2.64 (0.02)	ns	**0.39***	**0.33***
RH supramarginal gyms	2.76 (0.02)	2.73 (0.02)	2.70 (0.02)	2.83 (0.02)	2.80 (0.02)	2.77 (0.02)	**0.39***	**0.39***	**0.39***
RH postcentral gyrus	2.18 (0.02)	2.17 (0.02)	2.14 (0.02)	2.25 (0.02)	2.23 (0.02)	2.23 (0.02)	**0.44***	**0.37***	**0.56***
RH precuneus	2.55 (0.02)	2.53 (0.02)	2.54 (0.02)	2.62 (0.02)	2.64 (0.02)	2.62 (0.02)	**0.41***	**0.65***	**0.47***
LH superior parietal cortex	2.35 (0.02)	2.29 (0.02)	2.28 (0.02)	2.39 (0.02)	2.37 (0.02)	2.33 (0.02)	ns	**0.53***	ns
LH supramarginal gyrus	2.77 (0.02)	2.74 (0.02)	2.70 (0.02)	2.81 (0.02)	2.82 (0.02)	2.77 (0.02)	ns	**0.44***	**0.39***
LH postcentral gyrus	2.21 (0.02)	2.20 (0.02)	2.18 (0.02)	2.28 (0.02)	2.27 (0.02)	2.24 (0.02)	**0.44***	**0.44***	**0.38***
Temporal lobe									
RH transverse temporal cortex	2.61 (0.03)	2.61 (0.03)	2.60 (0.04)	2.75 (0.04)	2.76 (0.04)	2.77 (0.04)	**0.44***	**0.47***	**0.53***
Occipital lobe									
LH pericalcarine cortex	1.71 (0.03)	1.72 (0.03)	1.71 (0.03)	1.82 (0.03)	1.81 (0.03)	1.80 (0.03)	**0.48***	**0.39***	**0.39***

* $p < .05$ bold and asterisk reflects significant between group difference.
[a] CON < MJ + ALC.

$p = .03$), and left frontal pole ($F(1,64) = 4.62$, $p = .03$). The group by time interaction predicted cortical thickness in the left paracentral lobule ($F(2,63) = 4.72$, $p = .01$), left superior frontal gyrus ($F(1.7,110.35) = 3.60$, $p = .03$), and left pars orbitalis $F(2,63) = 4.21$, $p = .01$) (see Table 2).

Follow-up analysis for the main effect of group in the left hemisphere revealed significant differences at all three time points for left precentral gyrus ($ps \leq .01$) and left frontal pole ($ps \leq .04$); and 1.5 and 3-year follow-up for left pars opercularis ($ps \leq .03$) in which MJ + ALC showed thicker estimates compared to CON. Significant interaction effects revealed thicker estimates for MJ + ALC at 3-year follow-up only in the left paracentral lobule ($p = .04$); and while CON decreased in thickness from baseline to 3-year follow-up in this region ($ps < .01$), no statistically significant decline was observed for MJ + ALC. The between-group effect was only significant at 3-year follow-up in the left superior frontal gyrus ($p = .02$, MJ + ALC > CON), and both groups decreased over time ($ps < .02$). While no between-group differences were identified in left par orbitalis, decreasing thickness estimates ($ps < .01$) were identified across time points, with the exception of baseline to 1.5-year follow-up for MJ + ALC (see Table 2).

3.2.2. Parietal lobe cortical thickness

In the right hemisphere, the group main effect significantly predicted cortical thickness estimates in the right superior parietal cortex ($F(1,64) = 7.83$, $p < .01$), right inferior parietal cortex ($F(1,64) = 4.05$, $p = .04$), right supramarginal gyrus ($F(1,64) = 5.38$, $p = .02$), right postcentral gyrus ($F(1,64) = 8.00$, $p < .01$), and right precuneus cortex ($F(1,64) = 9.78$, $p < .01$). Follow-up analysis revealed significant between group differences at all three time points for the right superior parietal cortex ($ps \leq .02$), right supramarginal gyrus ($ps < .05$), right postcentral gyrus ($ps < .05$), right precuneus cortex ($ps < .02$), and 1.5 and 3-year follow-up for right inferior parietal cortex ($ps < .05$) (see Table 2, Fig. 2).

In the left hemisphere of the parietal lobe, the group main effect significantly predicted thickness estimates in the left superior parietal cortex ($F(1,64) = 7.03$, $p = .01$), left supramarginal gyrus ($F(1,64) = 4.28$, $p = .04$), and the left postcentral gyrus ($F(1,64) = 6.32$, $p = .01$). Follow-up analysis revealed significant differences at 1.5-year follow-up in the left superior parietal cortex ($p = .01$), 1.5 and 3-year follow-up in the left supramarginal gyrus ($ps \leq .03$), and all three time points in the left postcentral gyrus ($ps \leq .03$) (see Table 2, Fig. 2).

3.2.3. Temporal lobe cortical thickness

The group main effect significantly predicted cortical thickness estimates in the right transverse temporal cortex ($F(1,64) = 9.44$, $p < .01$), and follow-up analysis revealed significant between group differences at all three time points ($ps < .01$) (see Table 2).

3.2.4. Occipital lobe cortical thickness

No main or interaction effects were found to predict cortical thickness estimates in the right hemisphere. However, the main effect of group predicted cortical thickness in the left pericalcarine cortex ($F(1,64) = 7.39$, $p < .01$). Follow-up analysis revealed between group differences at all three time points ($ps < .03$) (see Table 2).

3.3. Associations with substance use severity and cortical thickness at 3-year follow-up

3.3.1. Marijuana use

Positive partial correlations ($n = 30$, MJ + ALC only), between cumulative marijuana use and cortical thickness controlling for lifetime alcohol use, were identified in the left inferior temporal cortex ($pr = .39$, $p = .03$) and right entorhinal cortex ($pr = .39$, $p = .03$) (see Fig. 3).

3.3.2. Alcohol use

Negative association between lifetime alcohol use and cortical thickness (controlling for lifetime marijuana use) were identified in the left hemisphere, including the left paracentral lobule ($pr = -.40$, $p = .03$); left pericalcarine cortex ($pr = -.42$, $p = .02$); left postcentral gyrus ($pr = -.43$, $p = .02$); and left precentral gyrus ($pr = -.39$, $p = .03$). Similarly, negative associations with lifetime alcohol use were also

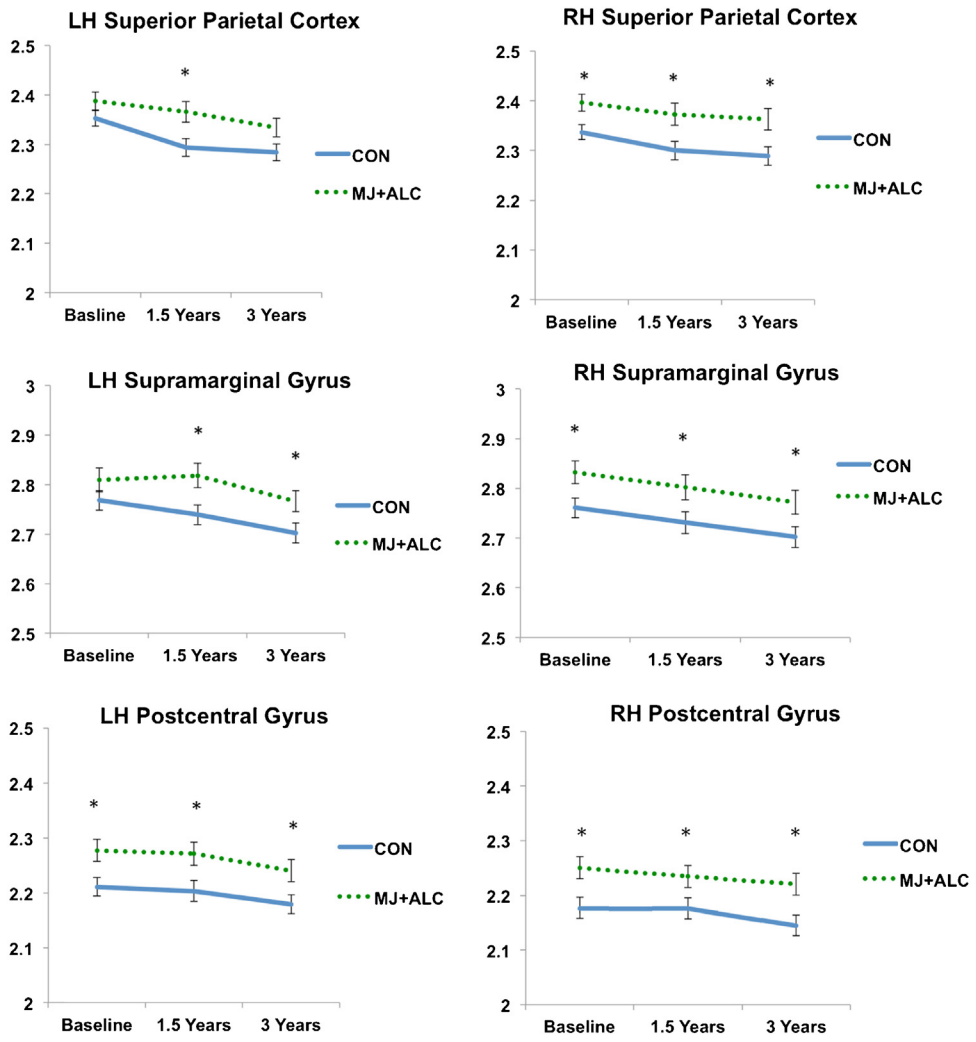

Fig. 2. Parietal lobe cortical thickness estimates over three years for select regions, measured in millimeters and controlling for lifetime alcohol use and ICV, ($N = 68$) (left (LH) and right (RH) hemisphere); $^{*}p < .05$.

identified in the right hemisphere, including the right caudal anterior cingulate ($pr = -.39$, $p = .03$); right fusiform gyrus ($pr = -.433$, $p = .01$); right lingual gyrus ($pr = -.37$, $p = .04$); right postcentral gyrus ($pr = -.37$, $p = .04$); right precentral gyrus ($pr = -.47$, $p = .01$).

Age of onset of regular marijuana use was negatively associated with cortical thickness in the right entorhinal cortex, controlling for lifetime alcohol use ($pr = -.46$, $p = .01$). There were no associations between age of onset of regular alcohol use ($ps > .10$) and recency of marijuana and alcohol use ($ps > .05$) and cortical thickness at follow-up. No significant partial correlations were identified within the CON group ($ps > .05$).

4. Discussion

This study looked at cortical thickness estimates at three independent time points (ages 18, 19, and 21, respectively) in adolescent marijuana and alcohol users compared to controls with limited substance use histories. We found significant between-group differences in cortical thickness estimates after controlling for lifetime alcohol use. MJ + ALC demonstrated increased cortical thickness estimates in all four lobes of the brain, bilaterally. Notably, 18 of 23 regions in which differences were observed were in the frontal and parietal cortex. Positive dose-dependent associations were identified in temporal brain regions, as cumulative marijuana use from ages 16 to 22 was associated with thicker cortices in inferior temporal and entorhinal cortex. Several negative associations were observed with lifetime alcohol use, as more alcohol use reported was associated with thinner cortical estimates in all four lobes.

It is important to detail how these findings compare to our previous work with a similar sample, as we found both similarities and differences from our cortical thickness study in which adolescent marijuana users were observed pre- and post 28-days of monitored abstinence (Jacobus et al., 2014). In Jacobus et al. (2014), *increased* thickness estimates in our marijuana users (controlling for alcohol use) was found in the entorhinal cortex compared to matched controls. Similarly, the present study found *increased* thickness estimates in our user group compared to our controls, and findings were more widespread and noted in all four lobes of the brain. The present study also found more lifetime marijuana use was associated with increased thickness in the entorhinal cortex, a region rich in cannabinoid 1 (CB1) receptors and important for learning and memory (Battistella et al., 2014; Iversen, 2003; Tsou et al., 1998).

However, dose-dependent bivariate correlations were different in that previously (Jacobus et al., 2014) we saw increased marijuana use associated with thinner cortices and increased alcohol use associated with thicker cortical estimates at age 17, pre- and post monitored abstinence. Our dose-dependent associations in the present study suggest otherwise. We found *increased* lifetime

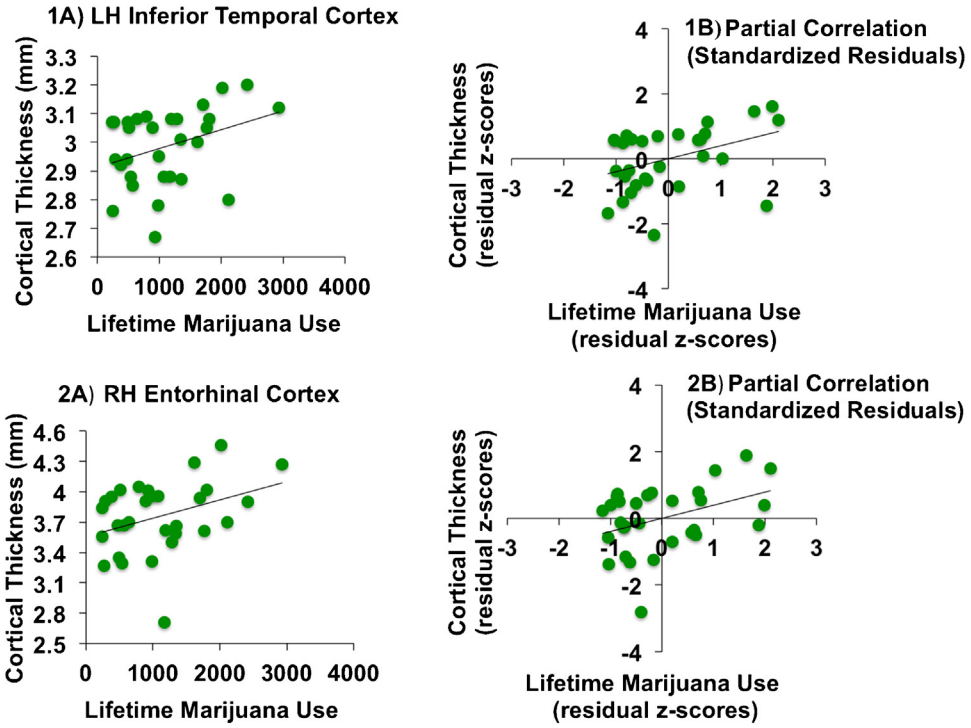

Fig. 3. Bivariate relationships (A) and corresponding partial correlations (B) with lifetime marijuana use and cortical thickness, measured in millimeters (mm) (left (LH) and right (RH) hemisphere), controlling for lifetime alcohol use ($n = 30$).

marijuana use reported associated with *thicker* cortical estimates and *increased* lifetime alcohol use reported associated with *thinner* cortices (at age ~21). This may reflect several points recently discussed by Filbey and colleagues (2014) in the literature, including (1) methodological issues, the present study assessed substance independently over the course of three years compared to 28-days at age 17; (2) age and maturational bias, correlations in the present study reflect associations following many years of substance use and potential for interference with complex neurodevelopmental processes; (3) changes in marijuana and alcohol use patterns, as individuals in the present study remain relatively chronic in their marijuana use over time but subtly increase in their alcohol use; and (4) possible interactions with pre-existing vulnerabilities that are present at age 17 (near initiation), but likely changes as the individual continues to chronically use substances and increase in age (Cheetham et al., 2012; Filbey et al., 2014; Jacobus et al., 2013a; Squeglia et al., 2014)

Lopez-Larson and colleagues (2011) cross-sectionally investigated cortical thickness in adolescents 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. The present study found increases in thickness in parietal, temporal, and occipital cortices, consistent with work by this team. The mechanism by which marijuana may alter the neural architecture and plasticity of the brain is undetermined. The endocannabinoid system plays a role in neuromaturational processes (e.g., pruning) and modulates neurotransmission for several neurotransmitter systems (Berghuis et al., 2007; Iversen, 2003; Rubino and Parolaro, 2008; Stella, 2013). Interference with this system due to marijuana, or tetrahydrocannabinol (THC) administration, likely causes a cascade of neuronal events (Kim and Thayer, 2001; Kim et al., 2008) that changes brain structure and function (Batalla et al., 2013), and thereby neurocognitive processing (Meier et al., 2012), emotional regulation and reward processing (Cousijn et al., 2011), and propensity for psychiatric comorbidities and addiction (Hall, 2014).

It is unclear how associations with marijuana use and cortical thickness remodeling may be unique compared to alterations in macrostructural volume (e.g., volume comprised of cortical area and thickness). Studies suggest that volume changes are driven by changes in surface area (Im et al., 2008; Pakkenberg and Gundersen, 1997) whereas others suggest thickness as one ages (Storsve et al., 2014), however relationships between these metrics are likely dynamic across the lifespan and represent different neuromaturational mechanisms at different stages of life and disease (e.g., myelination, quantity of cortical columns, cellular organization of cortical columns, dendrites, synapses) (Mountcastle, 1997; Ostby et al., 2009; Rakic, 1988; Storsve et al., 2014). Changes in regional brain volume associated with marijuana use have varied, as some have observed decreased volume (Ashtari et al., 2011; Demirakca et al., 2011; Schacht et al., 2012) and others have identified macrostructural volume increases in CB1-dense brain regions such as neocortex, amygdala, striatum, hippocampus, and cerebellum (Cousijn et al., 2012; Gilman et al., 2014; McQueeny et al., 2011; Medina et al., 2010).

In reward-network regions specifically, such as the orbitofrontal cortex (OFC), a recent examination by Filbey and colleauges, found decreased orbitofrontal cortex (OFC) volume in heavy marijuana users compared to controls, and increased structural and functional connectivity within the OFC network. Lorenzetti and collages (2014), did not find OFC differences in their sample of heavy marijuana users, but did see smaller hippocampus and amygdala volumes. Cheetham et al. (2012) found that smaller OFC volume pre-initiation of marijuana use (age 12) predicted progression into use four years later (age 16). Taken together, findings underscore that alterations in cortical metrics are likely dynamic and influenced by age, pre-existing vulnerabilities, and exogenous factors such as marijuana use. Continuing to study associations between cortical metrics and substance use is important given estimates have been linked to cognitive functioning in several studies in our laboratory and others (Ashtari et al., 2011; Jacobus et al., 2014; Squeglia et al., 2012).

Alcohol likely has similar deleterious consequences on the brain. The present dose-dependent associations are consistent with our previous findings, as Squeglia et al., found decreases in cortical thickness estimates associated with heavy episodic alcohol use in males (Squeglia et al., 2012), and accelerated declining brain volume trajectories in a large prospective investigation examining individuals (ages 12–24) who transitioned to heavy drinking (Squeglia et al., in press). Alcohol likely interferes with neural development of the cerebral cortex, and thinner cortices observed with more cumulative use reported may represent non-beneficial pruning and/or inhibition of cell generation or cell death (Crews and Nixon, 2009).

Limitations of the present study include self-report of substance use, which can introduce measurement error. Further, while this study was prospective, participants were not assessed prior to initiation of substance use. However, previous work in our laboratory finds marijuana-related associations with white matter integrity in a sample of individuals assessed pre- and post-initiation of substance use (Jacobus et al., 2013b). Nevertheless, future work should determine the influence of pre-existing differences on cortical metrics. The current investigation included users of both marijuana and alcohol, and despite controlling for alcohol use, it remains unclear what is precisely the result of marijuana as compared to the combination of co-occurring marijuana and alcohol use. Our sample was predominately male (70%), however gender should be evaluated and future studies will focus on differential gender effects on brain morphometry in adolescent marijuana users. Group did not statistically differ on days since last use of marijuana and alcohol use, likely influenced by the monitored abstinence period, therefore acute effects may not have been captured in our reported findings. A statistically significant within-subjects effect was not widely observed (e.g., decreasing cortical thickness estimates), which may be attributed to the smaller sample size combined with a more restricted age range. We tried to reduce the number of correlational analysis that were conducted, however given that effects were modest, future work should replicate findings.

Studies should continue to follow existing adolescent cohorts to understand neural and behavioral changes that occur into young adulthood. Understanding how co-occurring marijuana and alcohol use influences both macrostructural and microstructural brain development, along with structural and functional connectivity, will help clinical interventions target neural vulnerabilities to develop novel and effective interventions to reduce marijuana misuse as prevalence rates of marijuana continue to increase (Johnston et al., 2015).

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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

References

Agosti, V., Nunes, E., Levin, F., 2002. Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. Am. J. Drug Alcohol Abuse 28 (4), 643–652.

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K.L., Roofeh, D., Cook, P., Kumra, S., 2011. Medial temporal structures and memory functions in adolescents with heavy cannabis use. J. Psychiatr. Res. 45 (8), 1055–1066, http://dx.doi.org/10.1016/j.jpsychires.2011.01.004

Batalla, A., Bhattacharyya, S., Yucel, M., Fusar-Poli, P., Crippa, J.A., Nogue, S., Martin-Santos, R., 2013. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS ONE 8 (2), e55821, http://dx.doi.org/10.1371/journal.pone.0055821

Battistella, G., Fornari, E., Annoni, J.M., Chtioui, H., Dao, K., Fabritius, M., Giroud, C., 2014. Long-term effects of cannabis on brain structure. Neuropsychopharmacology 39 (9), 2041–2048, http://dx.doi.org/10.1038/npp.2014.67

Bava, S., Frank, L.R., McQueeny, T., Schweinsburg, B.C., Schweinsburg, A.D., Tapert, S.F., 2009. Altered white matter microstructure in adolescent substance users. Psychiatry Res. 173 (3), 228–237, http://dx.doi.org/10.1016/j.pscychresns.2009.04.005

Bava, S., Jacobus, J., Mahmood, O., Yang, T.T., Tapert, S.F., 2010. Neurocognitive correlates of white matter quality in adolescent substance users. Brain Cogn. 72 (3), 347–354, http://dx.doi.org/10.1016/j.bandc.2009.10.012

Beck, A., 1978. Beck Depression Inventory (BDI). Psychological Corporation, San Antonio, TX.

Berghuis, P., Rajnicek, A.M., Morozov, Y.M., Ross, R.A., Mulder, J., Urban, G.M., Harkany, T., 2007. Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science 316 (5828), 1212–1216, http://dx.doi.org/10.1126/science.1137406

Brown, S.A., McGue, M., Maggs, J., Schulenberg, J., Hingson, R., Swartzwelder, S., Murphy, S., 2008. A developmental perspective on alcohol and youths 16 to 20 years of age. Pediatrics 121 (Suppl. 4), S290–S310, http://dx.doi.org/10.1542/peds.2007-2243D

Brown, S.A., Myers, M.G., Lippke, L., Tapert, S.F., Stewart, D.G., Vik, P.W., 1998. Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): a measure of adolescent alcohol and drug involvement. J. Stud. Alcohol 59 (4), 427–438.

Brown, S.A., Tapert, S.F., Granholm, E., Delis, D.C., 2000. Neurocognitive functioning of adolescents: effects of protracted alcohol use. Alcohol. Clin. Exp. Res. 24 (2), 164–171.

Casey, B.J., Jones, R.M., Hare, T.A., 2008. The adolescent brain. Ann. N. Y. Acad. Sci. 1124, 111–126, http://dx.doi.org/10.1196/annals.1440.010

Cheetham, A., Allen, N.B., Whittle, S., Simmons, J.G., Yucel, M., Lubman, D.I., 2012. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. Biol. Psychiatry 71 (8), 684–692, http://dx.doi.org/10.1016/j.biopsych.2011.10.029

Cousijn, J., Goudriaan, A.E., Wiers, R.W., 2011. Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. Addiction 106 (9), 1667–1674, http://dx.doi.org/10.1111/j. 1360-0443.2011.03475.x

Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2012. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. Neuroimage 59 (4), 3845–3851, http://dx.doi.org/10.1016/j.neuroimage.2011.09.046

Crews, F.T., Nixon, K., 2009. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol. 44 (2), 115–127, http://dx.doi.org/10.1093/alcalc/agn079

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9 (2), 179–194, http://dx.doi.org/10.1006/nimg.1998.0395

Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., Hermann, D., 2011. Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol. Drug Alcohol Depend. 114 (2–3), 242–245, http://dx.doi.org/10.1016/j.drugalcdep.2010.09.020

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31 (3), 968–980, http://dx.doi.org/10.1016/j.neuroimage.2006.01.021

Filbey, F.M., Aslan, S., Calhoun, V.D., Spence, J.S., Damaraju, E., Caprihan, A., Segall, J., 2014. Long-term effects of marijuana use on the brain. Proc. Natl. Acad. Sci. U. S. A., http://dx.doi.org/10.1073/pnas.1415297111

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97 (20), 11050–11055.

Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis. II. Inflation, flattening, and a surface-based coordinate system. Neuroimage 9 (2), 195–207, http://dx.doi.org/10.1006/nimg.1998.0396

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Dale, A.M., 2004. Automatically parcellating the human cerebral cortex. Cereb. Cortex 14 (1), 11–22.

Giedd, J.N., 2004. Structural magnetic resonance imaging of the adolescent brain. Ann. N. Y. Acad. Sci. 1021, 77–85, http://dx.doi.org/10.1196/annals.1308.009

Giedd, J.N., Lalonde, F.M., Celano, M.J., White, S.L., Wallace, G.L., Lee, N.R., Lenroot, R.K., 2009. Anatomical brain magnetic resonance imaging of typically developing children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 48 (5), 465–470, http://dx.doi.org/10.1097/CHI.0b013e31819f2715

Gilman, J.M., Kuster, J.K., Lee, S., Lee, M.J., Kim, B.W., Makris, N., Breiter, H.C., 2014. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J. Neurosci. 34 (16), 5529–5538, http://dx.doi.org/10.1523/JNEUROSCI. 4745-13.2014

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101 (21), 8174–8179, http://dx.doi.org/10.1073/pnas.0402680101

Hall, W., 2014. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction, http://dx.doi.org/10.1111/add.12703

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., Fischl, B., 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32 (1), 180–194, http://dx.doi.org/10.1016/j.neuroimage.2006.02.051
Huestis, M.A., Cone, E.J., 1998. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J. Anal. Toxicol. 22, 445–454.
Huttenlocher, P.R., Dabholkar, A.S., 1997. Regional differences in synaptogenesis in human cerebral cortex. J. Comp. Neurol. 387 (2), 167–178.
Im, K., Lee, J.M., Lyttelton, O., Kim, S.H., Evans, A.C., Kim, S.I., 2008. Brain size and cortical structure in the adult human brain. Cereb. Cortex 18 (9), 2181–2191, http://dx.doi.org/10.1093/cercor/bhm244
Iversen, L., 2003. Cannabis and the brain. Brain 126, 1252–1270.
Jacobus, J., Squeglia, L.M., Bava, S., Tapert, S.F., 2013a. White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. Psychiatry Res. 214 (3), 374–381, http://dx.doi.org/10.1016/j.pscychresns.2013.07.014
Jacobus, J., Squeglia, L.M., Infante, M.A., Bava, S., Tapert, S.F., 2013b. White matter integrity pre- and post marijuana and alcohol initiation in adolescence. Brain Sci. 3 (1), 396–414, http://dx.doi.org/10.3390/brainsci3010396
Jacobus, J., Squeglia, L.M., Sorg, S.F., Nguyen-Louie, T.T., Tapert, S.F., 2014. Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. J. Stud. Alcohol Drugs 75 (5), 729–743.
Johnston, L.D., O'Malley, P.M., Miech, R.A., Bachman, J.G., Schulenberg, J.E., 2015. Monitoring the Future National Survey Results on Drug Use: 1975-2014: Overview, Key Findings on Adolescent Drug Use. Institute for Social Research, The University of Michigan, Ann Arbor.
Kim, D., Thayer, S.A., 2001. Cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture. J. Neurosci. 21 (10), RC146.
Kim, H.J., Waataja, J.J., Thayer, S.A., 2008. Cannabinoids inhibit network-driven synapse loss between hippocampal neurons in culture. J. Pharmacol. Exp. Ther. 325 (3), 850–858, http://dx.doi.org/10.1124/jpet.107.131607
Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60 (9), 878–888.
Lopez-Larson, M.P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J.B., Terry, J., Yurgelun-Todd, D., 2011. Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav. Brain Res. 220, 164–172.
Lorenzetti, V., Solowij, N., Whittle, S., Fornito, A., Lubman, D.I., Pantelis, C., Yucel, M., 2014. Gross morphological brain changes with chronic, heavy cannabis use. Br. J. Psychiatry, http://dx.doi.org/10.1192/bjp.bp.114.151407
Lucas, C.P., Zhang, H., Fisher, P.W., Shaffer, D., Regier, D.A., Narrow, W.E., Friman, P., 2001. The DISC Predictive Scales (DPS): efficiently screening for diagnoses. J. Am. Acad. Child Adolesc. Psychiatry 40 (4), 443–449, http://dx.doi.org/10.1097/00004583-200104000-00013
McQueeny, T., Padula, C.B., Price, J., Medina, K.L., Logan, P., Tapert, S.F., 2011. Gender effects on amygdala morphometry in adolescent marijuana users. Behav. Brain Res. 224 (1), 128–134, http://dx.doi.org/10.1016/j.bbr.2011.05.031
Medina, K.L., Nagel, B.J., Tapert, S.F., 2010. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res. 182 (2), 152–159, http://dx.doi.org/10.1016/j.pscychresns.2009.12.004
Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R.S., Moffitt, T.E., 2012. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc. Natl. Acad. Sci. U. S. A., http://dx.doi.org/10.1073/pnas.1206820109
Mountcastle, V.B., 1997. The columnar organization of the neocortex. Brain 120, 701–722.
Ostby, Y., Tamnes, C.K., Fjell, A.M., Westlye, L.T., Due-Tonnessen, P., Walhovd, K.B., 2009. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. J. Neurosci. 29 (38), 11772–11782, http://dx.doi.org/10.1523/JNEUROSCI. 1242-09.2009
Pakkenberg, B., Gundersen, H.J., 1997. Neocortical neuron number in humans: effect of sex and age. J. Comp. Neurol. 384 (2), 312–320.
Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9 (12), 947–957, http://dx.doi.org/10.1038/nrn2513
Rakic, P., 1988. Specification of cerebral cortical areas. Science 241 (4862), 170–176.
Reuter, M., Rosas, H.D., Fischl, B., 2010. Highly accurate inverse consistent registration: a robust approach. Neuroimage 53 (4), 1181–1196, http://dx.doi.org/10.1016/j.neuroimage.2010.07.020
Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61 (4), 1402–1418, http://dx.doi.org/10.1016/j.neuroimage.2012.02.084
Rice, J.P., Reich, T., Bucholz, K.K., Neuman, R.J., Fishman, R., Rochberg, N., Begleiter, H., 1995. Comparison of direct interview and family history diagnoses of alcohol dependence. Alcohol. Clin. Exp. Res. 19 (4), 1018–1023.
Rosas, H.D., Liu, A.K., Hersch, S., Glessner, M., Ferrante, R.J., Salat, D.H., Fischl, B., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58 (5), 695–701.
Rubino, T., Parolaro, D., 2008. Long lasting consequences of cannabis exposure in adolescence. Mol. Cell. Endocrinol. 286, S108–S113, http://dx.doi.org/10.1016/j.mce.2008.02.003
Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 14 (7), 721–730.
Sartor, C.E., Lynskey, M.T., Heath, A.C., Jacob, T., True, W., 2007. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. Addiction 102 (2), 216–225.
Schacht, J.P., Hutchison, K.E., Filbey, F.M., 2012. Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users. Neuropsychopharmacology 37 (11), 2368–2376, http://dx.doi.org/10.1038/npp.2012.92
Shaffer, D., Fisher, P., Dulcan, M.K., Davies, M., Piacentini, J., Schwab-Stone, M.E., Regier, D.A., 1996. The NIMH diagnostic interview schedule for children version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA Study. Methods for the epidemiology of child and adolescent mental disorders study. J. Am. Acad. Child Adolesc. Psychiatry 35 (7), 865–877.
Simmonds, D.J., Hallquist, M.N., Asato, M., Luna, B., 2014. Developmental stages and sex differences of white matter and behavioral development through adolescence: a longitudinal diffusion tensor imaging (DTI) study. Neuroimage 92, 356–368, http://dx.doi.org/10.1016/j.neuroimage.2013.12.044
Smith, M.L., Barnes, A.J., Huestis, M.A., 2009. Identifying new cannabis use with urine creatinine-normalized THCCOOH concentrations and time intervals between specimen collections. J. Anal. Toxicol. 33, 185–189.
Sobell, L.C., Sobell, M.B., 1992. Timeline Follow Back. A Technique for Assessing Self-Reported Alcohol Consumption. Humana Press, New York, NY.
Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., 2003. Mapping cortical change across the human life span. Nat. Neurosci. 6 (3), 309–315, http://dx.doi.org/10.1038/nn1008
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24 (4), 417–463.
Spear, L.P., Varlinskaya, E.I., 2005. Adolescence. Alcohol sensitivity, tolerance, and intake. Recent Dev. Alcohol. 17, 143–159.
Spielberger, C., Gorsuch, R., Lushene, R., 1970. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA, USA.
Squeglia, L.M., Jacobus, J., Brumback, T., Meloy, M.J., Tapert, S.F., 2014. White matter integrity in alcohol-naive youth with a family history of alcohol use disorders. Psychol. Med. 44 (13), 2775–2786, http://dx.doi.org/10.1017/S0033291714000609
Squeglia, L.M., Sorg, S.F., Schweinsburg, A.D., Wetherill, R.R., Pulido, C., Tapert, S.F., 2012. Binge drinking differentially affects adolescent male and female brain morphometry. Psychopharmacology (Berl) 220 (3), 529–539, http://dx.doi.org/10.1007/s00213-011-2500-4
Squeglia, L.M., Spadoni, A.D., Infante, M.A., Myers, M.G., Tapert, S.F., 2009. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol. Addict. Behav. 23 (4), 715–722.
Squeglia, L.M., Tapert, S.F., Sullivan, E.V., Jacobus, J., Meloy, M.J., Rohlfing, T., Pfefferbaum, A., 2015. Brain development in heavy drinking adolescents. Am. J. Psychiatry (in press).
Stella, N., 2013. Chronic THC intake modifies fundamental cerebellar functions. J. Clin. Invest., http://dx.doi.org/10.1172/JCI70226
Storsve, A.B., Fjell, A.M., Tamnes, C.K., Westlye, L.T., Overbye, K., Aasland, H.W., Walhovd, K.B., 2014. Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. J. Neurosci. 34 (25), 8488–8498, http://dx.doi.org/10.1523/JNEUROSCI. 0391-14.2014
Tamnes, C.K., Ostby, Y., Fjell, A.M., Westlye, L.T., Due-Tonnessen, P., Walhovd, K.B., 2009. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb. Cortex 20 (3), 534–548.
Tapert, S.F., Granholm, E., Leedy, N.G., Brown, S.A., 2002. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. J. Int. Neuropsychol. Soc. 8, 873–883.
Tsou, K., Brown, S., Sanudo-Pena, M.C., Mackie, K., Walker, J.M., 1998. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83 (2), 393–411.
Wechsler, D. (Ed.), 1999. Manual for the Wechsler Abbreviated Scale of Intelligence. Psychological Corporation, San Antonio, TX.
Yakovlev, P.I., Lecours, A.R., 1967. The myelogenetic cycles of regional maturation of the brain. In: Mikowski, A. (Ed.), Regional Development of the Brain in Early Life. Blackwell Scientific, Oxford, England, pp. 3–70.