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

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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.,

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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<br>$n = 38$<br>*M* (SD) | MJ + ALC<br>$n = 30$<br>*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] $n = 26$.
* $p < .05$.