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Review article

Reprint of "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 ($ps < 0.05$). 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 that contribute to morphological differences in young adulthood that are often observed in cross-sectional studies of heavy marijuana users.

Contents

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1. 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 26% to 64% between 8th and 12th grade, with reports of 10% of 8th graders and 35% of 12th graders having used in the past 30 days (Johnston et al., 2016). 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., 2016). 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 and Dabholkar, 1997; Paus et al., 2008; Tamnes et al., 2009). The adolescent brain undergoes dynamic neurodevelopment and is likely more susceptible to neurotoxins that could potentially affect higher-order cognitive functions (Bava et al., 2010; Casey and 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 and Tapert, 2013). Squeglia et al. (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 et al. (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 et al., 2015). Utilizing a longitudinal approach, Epstein and Kumra (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 and Kumra, 2015).

As previously mentioned, most adolescents who engage in marijuana use also consume high levels of alcohol simultaneously. Jacobus et al. (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 et al., 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 et al. (2015b) also examined cortical thickness in heavy marijuana and concomitant alcohol users ($n = 30$) ages 16 to 22. When compared to their non-using 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 et al., 2015b). 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.