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Impact of cannabis use on prefrontal and parietal cortex gyrification and surface area in adolescents and emerging adults

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ABSTRACT

Background: Regions undergoing maturation with CB1 receptors may be at increased risk for cannabis-induced alterations. Here, we examine the relationships between cannabis use and prefrontal (PFC) and inferior parietal gyrification and surface area (SA) in youth.
Methods: Participants included 33 cannabis users and 35 controls (ages 18–25). Exclusions included co-morbid psychiatric/neurologic disorders and heavy other drug use. Multiple regressions and Pearson r correlations examined the effects of cannabis use on gyrification, SA and cognition.
Results: Cannabis use was associated with decreased gyrification in: ventral-medial PFC (RH: [FDR corrected $p = .02$], LH: [FDR corrected $p = .02$]); medial PFC (RH: [FDR corrected $p = .02$], LH: [FDR corrected $p = .02$]); and frontal poles (RH: [FDR corrected $p = .02$], LH: [FDR corrected $p = .02$]). No differences were observed in bilateral hemispheres, PFC, dorsolateral, ventrolateral, or inferior parietal ROIs. Cannabis use was associated with marginally decreased SA in left: medial PFC [FDR corrected $p = .09$], and ventral lateral PFC: [FDR corrected $p = .09$]. In cannabis users, increased gyrification was associated with improved working-memory performance in right medial ($p = .003$), ventral-medial ($p = .03$), and frontal pole ROIs ($p = .007$).
Conclusions: Cannabis use was associated with reduced gyrification in PFC regions implicated in self-referential thought and social cognition. Results suggest that these gyrification characteristics may have cognitive implications.

1. Introduction

Cannabis is the second most used drug after alcohol, with 22.9% of high school seniors and 20% of college students using in the past month, and perhaps most alarmingly, one in every 15 seniors reporting daily use (Johnston et al., 2014). Cannabis legislation changes are sweeping across the United States. Policy experts predict that increased access and reduced price will lead to increased usage, especially in young adults who are the heaviest users (Caulkins et al., 2012). Late adolescence and emerging adulthood is a period of ongoing neurodevelopment, with pruning of inefficient gray matter connections (Gogtay et al., 2004; Gogtay and Thompson, 2010). Healthy adult rats demonstrate enhanced binding of cannabinoid (CB_1) receptors within areas such as the prefrontal cortex (PFC) (Verdurand et al., 2011) in comparison to juveniles, suggesting increased reliance upon the cannabinoid system with age. Indeed, converging lines of animal and human evidence have suggested that this is a sensitive period that may be particularly vulnerable to cannabis-induced neurocognitive effects (Jager and Ramsey, 2008; Meier et al., 2012; see Lisdahl et al., 2013 for review).

Preclinical animal models suggest that endogenous endocannabinoid signaling in the PFC influences executive functioning (EF) performance (for review see Egerton et al., 2006). In humans, significant CB_1 receptor density has been measured in the PFC, a region associated with mood regulation and EF, and throughout the cortex (Goldberg, 2009; Terry et al., 2009; see Yurgelun-Todd, 2007). Therefore, disruption of the endogenous cannabinoid system during adolescence may particularly impact the integrity later developing regions, such as the PFC and parietal lobes (Gogtay et al., 2004; Gogtay and Thompson, 2010). Indeed, daily cannabis users demonstrate significant, though reversible, downregulation of the CB_1 density in PFC and other cortical regions including

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the parietal lobes (Hirvonen et al., 2012). Further, cannabis-using youth demonstrate impairments in executive functioning, including complex attention, inhibitory control, and working memory (Harvey et al., 2007; Hanson et al., 2010; Medina et al., 2007; Lisdahl and Price, 2012).

Previous structural magnetic resonance imaging (MRI) research has demonstrated that regular (weekly or more) cannabis using adolescents demonstrate larger PFC (including orbitofrontal cortex) volume in female cannabis users (Medina et al., 2009) and reduced medial orbitofrontal volumes in a primarily male sample (Churchwell et al., 2010). Our group has found reduced medial orbitofrontal (mOFC) and inferior parietal volumes in this same sample of young adults (Price et al., 2015) compared to controls, and other groups have found that earlier age of onset significantly predicted decreased right superior PFC thickness (Lopez-Larson et al., 2011). Recent MRI advances have yielded new measurements of cortical architecture that may be more sensitive to drug effects than volume or cortical thickness. One such candidate is local gyrification index, or a 3-dimensional ratio representing the degree of folding on the outer surface relative to buried cortex within neighboring sulci, which may also be calculated for regions of interest (Schaer et al., 2008, 2012). Several candidate theories attempt to explain the primary driving mechanisms of gyrification development, including cortico-cortical mechanical tension, morphogenetic, and differential cortical expansion rate influences (Richman et al., 1975; see Van Essen, 1997; Toro and Burnod, 2005; Ronan et al., 2013; Tallinen et al., 2014; see Kriegstein et al., 2006; Hilgetag and Barbas, 2006; White et al., 2010 for reviews). Another measure is cortical surface area (SA), which is a reflection of the amount of area on the cortical surface represented in mm^2 (Dale et al., 1999).

Age-related changes in cortical surface area (SA) and other surface characteristics, including gyral and sulcal shape, have been noted in several preliminary studies. Schnack et al. (2015) measured SA changes between MRI scans in 504 subjects. Results from the study found age-related changes in SA such that adolescence is a period in which the cortex is greatly expanding and reaches the maximum individual peak in SA during this time. Further, the same study found that those with the highest IQ had the greatest rate of cortical SA change during this period. Magnotta et al. (1999) found a significant relationship between age with gyral and sulcal shape in a sample of 148 participants aged 18–82. A more recent two-year longitudinal study with 52 participants found overall decreases in gyrification index in youth who were between the ages of 11 and 17 at baseline, with significant widening of sulci and loss of SA within the frontal cortex (Alemán-Gómez et al., 2013). Other samples have found reduced PFC surface complexity in teens compared to children (Su et al., 2013), and reduced PFC gyrification in young adults compared to early teens (Klein et al., 2014). Further, increased gyrification has been associated with enhanced vocabulary knowledge in typically developing youth (Wallace et al., 2013). In a large cohort of 322 healthy adults spanning ages 20–85, SA decreases were most robust within the dorsomedial frontal, and PFC gyrification decreases were observed with older age (Hogstrom et al., 2012). Sex differences in folding have also been noted with females demonstrating greater gyrification in PFC compared to males (Luders et al., 2004; Mutlu et al., 2013). Lastly, a large longitudinal study in 647 participants found an inverted-U shaped trajectory of SA maturation between the ages of 3 and 30 (Raznahan et al., 2011). Changes in SA appeared to peak later than cortical thickness in the large cohort. The same study found that gyrification index (*note*: this index differs from the Schaer et al., 2008 LGI measure) and convex hull area influence SA changes during early to late adolescents; however, late adolescent changes in SA may be most attributed by reductions in gyrification in comparison to reduced convex hull area. Further, SA may peak at later developmental periods compared to other cortical measures such as volume (Wierenga et al., 2014). Preliminary evidence suggests that later developing regions, such as the PFC (Gogtay et al., 2004), continue to undergo gyrification, cortical surface shape, and SA changes during adolescents and young adulthood.

While several studies have demonstrated a great degree of genetic influences on cortical thickness, gray, and white matter volume (see Douet et al., 2014), studies of gyrification or surface characteristics among small samples of monozygotic (MZ) twins demonstrate observable differences (Bartley et al., 1997; Biondi et al., 1998; Mohr et al., 2004; White et al., 2002), suggesting that environmental factors may influence the shape of the cortical surface (see White et al., 2010) especially in secondary and tertiary sulci (Lohmann et al., 1999). For example, Hasan et al. (2011) found that PFC gyrification was no more similar in MZ twins compared to dizygotic twins. Therefore, compared to other brain characteristics, such as gray and white matter volume, surface morphometry values (including gyrification) appear to be significantly influenced by environmental factors compared to genetics, although this needs to be confirmed in larger sample sizes.

Therefore, gyrification may reflect changes sensitive to repeated behavioral or environmental influences, such as substance use, although additional research in emerging adults is needed. To our knowledge, only one study has examined surface morphology in a sample of young cannabis users (Mata et al., 2010). Mata et al. (2010) examined sulcal concavity, a measure similar yet distinct from a 3-dimensional gyrification value. The study noted decreased sulcal concavity in the left PFC and bilateral temporal lobes of young adult cannabis users compared to controls (Mata et al., 2010). The study also failed to find any significant differences in global SA after controlling for potential confounds, suggesting a unique characteristic of sulcal curvature differences in regions undergoing neuromaturation in young cannabis users (Mata et al., 2010). The same study did not examine sub-regional differences in SA or how sulcal differences between cannabis users and non-users relate to downstream behavioral phenotypes, such as neuropsychological function.

Because cannabis use has an age of onset (SAMHSA, 2014) that overlaps with continued PFC gyrification development (Su et al., 2013; Klein et al., 2014), examining the impact of cannabis use on gyrification remains an important area to investigate. The current study examined whether cannabis use status predicted PFC or parietal gyrification in a sample of adolescents and emerging adults. Surface morphology may be related to cortical thickness and volume (Alemán-Gómez et al., 2013). Given that both reductions in cortical thickness and volume (Lopez-Larson et al., 2011; Price et al., 2015) and reductions in PFC sulcal concavity (Mata et al., 2010) were previously found in young cannabis users, we predicted that cannabis users would demonstrate reduced gyrification and SA in PFC and parietal regions. Reduced SA and gyrification may be most pronounced in both inferior frontal and parietal regions that show reductions in volume (Churchwell et al., 2010; Price et al., 2015) Within regions that differed between cannabis users and controls, follow-up analyses examined brain–behavior relationships in both groups.

2. Materials and methods

2.1. Participants

Participants included 68 (33 cannabis-users, 35 controls) right-handed adolescents and emerging adults between the ages of 18–25 (21 male and 12 female cannabis-users; 15 male and 20 female controls) from a larger imaging genetics study (PI: Lisdahl, NIH R03 DA027457). Exclusion criteria included MRI