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Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry

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ABSTRACT

A recent shift in legal and social attitudes toward marijuana use has also spawned a surge of interest in understanding the effects of marijuana use on the brain. There is considerable evidence that an adolescent onset of marijuana use negatively impacts white matter coherence. On the other hand, a recent well-controlled study demonstrated no effects of marijuana use on the morphometry of subcortical or cortical structures when users and non-users were matched for alcohol use. Regardless, most studies have involved small, carefully selected samples, so the ability to generalize to larger populations is limited. In an attempt to address this issue, we examined the effects of marijuana use on white matter integrity and cortical and subcortical morphometry using data from the Human Connectome Project (HCP) consortium. The HCP data consists of ultra-high resolution neuroimaging data from a large community sample, including 466 adults reporting recreational marijuana use. Rather than just contrasting two groups of individuals who vary significantly in marijuana usage as typifies prior studies, we leveraged the large sample size provided by the HCP data to examine parametric effects of recreational marijuana use. Our results indicate that the earlier the age of onset of marijuana use, the lower was white matter coherence. Age of onset also also affected the shape of the accumbens, while the number of lifetime uses impacted the shape of the amygdala and hippocampus. Marijuana use had no effect on cortical volumes. These findings suggest subtle but significant effects of recreational marijuana use on brain structure.

1. Introduction

Previous epidemiological studies have revealed strong negative impacts of marijuana use, suggesting that marijuana has similar potential for abuse as other illicit substances (e.g., cocaine), is associated with respiratory illnesses, and leads to cognitive impairment (for a review see ref. Volkow et al., 2014). However, several focused empirical studies have countered these results, finding instead no significant effect of marijuana use on subcortical brain morphometry and only an uncertain effect on cognition (e.g., Block et al., 2000; Pope et al., 2003; Weiland et al., 2015). The past two decades have seen shifts in legal and societal attitudes toward marijuana use, with 23 states and the District of Columbia legalizing medical marijuana and four states legalizing recreational marijuana (Marijuana Resource Center: State Laws Related to Marijuana, 2016); moreover, perceptions of the risk of regular marijuana use have decreased, even amongst adolescents, particularly in Colorado, recreational marijuana is now legal (Schuermeyer et al., 2014). As increases in the potency of marijuana have accompanied these shifts in attitudes (Volkow et al., 2014), it is becoming increasingly important to understand the precise neural effects of long-term marijuana use and the impact of the age of first use.

Adolescence is a sensitive period for brain development with white matter myelination and gray matter pruning, and, critically, an increase in the number of cannabinoid receptors that respond to marijuana (Jacobus and Tapert, 2014). While preliminary studies of the effects of marijuana use on white matter integrity showed no significant effects in adolescents or adults (DeLisi et al., 2006; Gruber and Yurgelun-Todd, 2005), a growing body of research suggests that an adolescent onset of heavy marijuana use can have neurotoxic effects on developing white matter, reflected in decreased white matter coherence as assessed by measures of diffusivity, e.g., fractional anisotropy (FA) and radial diffusivity (RD) (Arnone et al., 2008; Bava et al., 2013; Filbey et al., 2014; Jacobus et al., 2009, 2013). Importantly, these effects have been observed longitudinally, suggesting a causation between marijuana use and white matter changes (Bava et al., 2013; Becker et al., 2015; Jacobus et al., 2013). However, most of these studies have relied on small sample sizes (i.e., between 10 and 50 marijuana users, with most below 20), so their ability to generalize to a broader population is limited. Moreover, the majority of these studies all examined the effects of heavy use (e.g., daily use), and much less is known about the

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effects of casual marijuana use on white matter integrity. As many white matter tracts continue to develop in adolescence and young adulthood (Lebel and Beaulieu, 2011), with maximal change in such development during this time frame (Simmonds et al., 2014), it is important to understand how the age of onset of marijuana use impacts neurodevelopment not only in heavy users but more casual users, especially considering that adolescence is often a time of experimentation with substances of abuse (Schuermeyer et al., 2014).

Studies of the effects of marijuana use on cortical and subcortical morphometrics in humans have typically focused on the amygdala and hippocampus (Rocchetti et al., 2013) and, to a lesser extent, the nucleus accumbens (e.g., Gilman et al., 2014) and orbitofrontal cortex(Churchwell et al., 2010; Filbey et al., 2014; Pagliaccio et al., 2015). These structures are known to have important roles in reward processing and their function/structure is known to be disrupted by drugs of abuse (Berridge and Robinson, 2003). At least some, but far from all, of the evidence suggests an influence of marijuana on brain structure. For example, marijuana users compared to nonusers have been found to have reduced amygdala volume (Churchwell et al., 2010; Schacht et al., 2012), and amygdala volume reductions have been correlated with increased levels of self-reported craving and relapse in consumption after 6-months from detoxification from alcohol dependence (Wrase et al., 2008). On the other hand, a recent meta-analysis of 14 studies of marijuana users compared to nonusers found no summary changes in amygdala volume, but did observe a consistent pattern of reduced hippocampal volume (Rocchetti et al., 2013). In addition, a large number of studies with animals and humans have shown that marijuana affects the structure of the nucleus accumbens (Gilman et al., 2014; Kolb et al., 2006). Hence, there is evidence in the existing literature to suggest the possibility that marijuana influences the structure of these regions, all of which are known to be affected in addiction (Koob and Volkow, 2010).

Nonetheless, a recent well-controlled study by Weiland et al. (2015) found no evidence of an effect of marijuana on the morphometry of these structures. They compared morphometry in a sample of adult and adolescent daily users of marijuana to nonusers (matching the groups for alcohol use), while controlling for other confounding variables of tobacco use, depression, impulsivity, age, and gender. Importantly, they found no group differences in measures of brain morphometry for the nucleus accumbens, amygdala, hippocampus, cerebellum, or 35 cortical regions in each hemisphere. Interestingly, when they simply controlled for the amount of alcohol use, rather than matching users and nonusers, they replicated several findings of Gilman and colleagues. Furthermore, when examining effect size across previous studies, they found that the literature demonstrates a mean lack of effect.

Given the discrepancies in the literature, we wanted to re-examine this issue using a large representative sample. To this end, we analyzed extremely high-quality multi-modal neuroimaging data from 466 participants in the Human Connectome Project (HCP) who reported using marijuana at least once during their lives (Van Essen et al., 2012). The participants in this sample consist of twins and their non-twin siblings who have no history of major psychiatric illness, but vary greatly in terms of race, education, income, BMI, and the degree of recreational drug use. A recent study used this HCP dataset to disentangle causal effects of marijuana use on regional brain volume from shared genetic effects and found that it was mainly shared genetic effects explained differences in bran volumes (Pagliaccio et al., 2015). However, this study did not investigate the effects of marijuana use on white matter integrity or the shape of subcortical regions, which was the focus of the current study. Rather than investigating extremes of marijuana use (i.e., heavy users vs. nonusers) like most previous studies, we leveraged the large sample size to take a parametric approach, examining marijuana use along a spectrum, so as to search more specifically for dose-dependent effects. Nevertheless, a comparison of users and nonusers was also performed as a replication of prior work.

2. Materials and methods

2.1. HCP participants

Data analyzed in the current study came from the most recent S900 Release (http://humanconnectome.org/documentation/S900/index.html) from the WU-Minn HCP Consortium (Van Essen et al., 2012). Data were only considered if they had structural (e.g., at least 1 T1w and T2w scan) and diffusion imaging scans, and had complete SSAGA and family information (see below), resulting in 857 possible participants. We further restricted analyses to individuals who had reported using marijuana at least once in their lifetime, resulting in 466 participants in the final sample. An overview of the participant recruitment strategy is described in detail elsewhere (Van Essen et al., 2012). In brief, the HCP aims to "recruit a sample of relatively healthy individuals free of a prior history of significant psychiatric or neurological illnesses. Our goal is to capture a broad range of variability in healthy individuals with respect to behavioral, ethnic, and socioeconomic diversity (p. 2224)." The sample is meant to be representative of the population at large and includes individuals who smoke, are overweight, have subclinical psychiatric symptoms, and—critical for the current study—use recreational drugs. HCP participants are human adult twins (MZ and DZ) and their non-twin siblings, aged 22–35 years.

The data included in this study consisted of individuals from 270 different families, ranging from 1 to 4 members per family, with a mean number of 1.7 members per family. Sibships with individuals having severe neurodevelopmental disorders, documented neuropsychiatric disorders, diabetes, or high blood pressure were excluded, as were twins born before 34 weeks gestation and non-twins born before 37 weeks (Van Essen et al., 2012). Demographic, medical, family history, personality, cognitive, and lifestyle information is collected from each subject over two weeks of phone and in-person interviews as well as through written assessments (e.g. the Semi-Structured Assessment for the Genetics of Alcoholism, SSAGA).

2.2. Marijuana use

Marijuana use was quantified with self-report measures assessed by the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA). Number of times used was quantified in the SSAGA as 0 (never used), 1 (1–5 uses), 2 (6–10 uses), 3 (11–100 uses), 4 (101–999 uses), or 5 (>1000 uses). Age of first use in the SSAGA was quantified as follows: 1 (first use at less than 15 years of age), 2 (15 to 17 years of age), 3 (18 to 20 years of age), 4 (≥21 years of age), or 5 (never used). Age of first use was reverse scored so that an earlier age of first use was scored more highly, in line with the times used measure.

2.3. Covariates

Age, gender, tobacco and alcohol usage, and years of education were included as covariates in all analyses. Many studies of substance use quantify tobacco use with a "packs per day" measure. As no equivalent measure is available in the SSAGA, we quantified tobacco use using a composite measure calculated from the average of the *Z*-scores for the following SSAGA measures: "Total times used/smoked ANY TOBACCO in past 7 days", "Cigarettes per day when smoking regularly", "Years since respondent smoked last cigarette", "Years smoked." In this manner, the cumulative effect of recent and/or past tobacco use could be controlled for. In a similar manner, we quantified alcohol use as a composite measure reflecting frequency of recent and past drinking, calculated from the average of the *Z*-scores for the following SSAGA measures: "Total drinks in past 7 days", "Drinks per drinking day in past 12 months", "Frequency of any alcohol use in past 12 months", "Drinks per day in heaviest 12-month period", and "Frequency of any alcohol use, heaviest 12-month period". Where appropriate, scores were reverse scored