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IMPACT OF *FAAH* GENOTYPE AND MARIJUANA USE ON BRAIN STRUCTURE AND NEUROPSYCHOLOGICAL PERFORMANCE IN EMERGING ADULTS

by

Skyler G. Shollenbarger

A Thesis Submitted in

Partial Fulfillment of the

Requirements for the Degree of

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in Psychology

at

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May 2014

ABSTRACT

IMPACT OF *FAAH* GENOTYPE AND MARIJUANA USE ON BRAIN STRUCTURE AND NEUROPSYCHOLOGICAL PERFORMANCE IN EMERGING ADULTS

by

Skyler G. Shollenbarger

The University of Wisconsin-Milwaukee, 2014

Under the Supervision of Professor Krista Lisdahl, Ph.D.

Introduction*:* Chronic MJ use may be associated with higher cognitive ability impairments (see Lisdahl et al., 2013). Regions undergoing later maturation (Gogtay 2004), may be at increased risk for MJ-induced alterations. Endogenous cannabinoid signaling (ECS) is modulated by the function the enzyme Fatty Acid Amide Hydrolase (see Ho & Hilard, 2005), thus the gene encoding for this enzyme (*FAAH*) impacts ECS (Sipe et al., 2002). Here, we examine the impact of MJ use and *FAAH* genotype on PFC complexity and underlying frontal white matter (WM) integrity in young adults.

Methods*:* Participants included 37 MJ users and 37 non-using young adults (ages 18-25). Of those, 27 were *FAAH* A carriers and 47 were homozygous (C/C) carriers. Exclusion criteria included co-morbid psychiatric and neurologic disorders and excessive other drug use. Brain complexity and WM integrity was measured using local gyrification index and Tracula programs. The Letter Number Sequencing, PASAT and D-Kefs c/w interference measured complex attention and inhibition. Multiple regressions and Pearson r correlations were used to predict LGI, WM integrity and cognitive performance indices from MJ use status, *FAAH* status, and MJ**FAAH* interactions controlling for demographic variables and comorbid drug use. ***Results***: MJ users demonstrated decreased LGI in bilateral vmPFC (RH: [*beta*=-.54, $p<.001$] and LH: [*beta*=-.55, $p<.001$]); bilateral mPFC (RH: [*beta*=-.48, $p=.001$] and LH: [*beta*=-.51, $p<.001$]); and bilateral frontal poles (RH: [*beta*=-.31, $p=.02$]; LH: [*beta*=-.43, $p=.004$]), with increased

LGI in LH DLPFC [*beta*=.40, *p*=.004]. Controlling for the same variables, reduced WM integrity was found in bilateral UCF (RH: [*beta*=.32, *p*=.03] and LH: [*beta*=.31, *p*=.03]) and fMinor [*beta*=.27, *p*=.05] tracts of MJ users. Significant interactions between MJ**FAAH* were seen predicting LGI in LH OFC [*beta*=-.24, *p*=.04] and WM integrity in fMinor [*beta*=.26, *p*=.04] and LH ATR [*beta*=.36, *p*=.003]. In MJ users, increased gyrification was associated with better LNS performance in RH mPFC [*r*=.51, *p*=.001], RH vmPFC [*r*=.41, *p*=.01], and RH frontal pole [*r*=.45, *p*=.005] and a negative correlation with gyrification and color-word completion time in LH vmPFC [*r*=-.32, *p*=.05]. In MJ users, decreased WM integrity was associated with greater PASAT performance in the RH UNC [*r*=.38, *p*=.02]. ***Discussion***: MJ use was associated with reduced LGI in several PFC regions with one region showing an opposite relationship. These results are consistent with Mata and colleagues (2010). We also found reduced WM integrity in fronto-temporal tracts, which may have important emotion regulation implications. These brain characteristics were also moderated by *FAAH* genotype. Additional implications of ECS and brain health will be discussed.

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Dedication

Life is a team effort and it is with great pride and gratitude that I share this experience with many wonderful people that seek to enhance the potential of others around them.

I dedicate this thesis to my multi-talented fiancé, Dr. Dyani Saxby who has provided profound perspective for appreciating the process of graduate school and forever changed my perspective on beauty. I also dedicate this project to my beautiful mother, Pamela Baden, whose hard work and unconditional love has shown me life's most valuable pleasures. I dedicate the work to my dancing granny, Christine Batdorf who has taught us all how to appreciate the humor in life. For this, I may remain present focused on many journeys to come.

I dedicate this thesis to my award-winning mentor, Dr. Krista Lisdahl who has provided the opportunity of a lifetime and who remains strikingly humble. Her dedication to improving the health of subsequent generations will remain timeless. I dedicate this project to my committee members, Dr. Christine Larson and Dr. Cecilia Hillard, who provided their time to help shape my research growth. I also dedicate this project to Dr. Jenessa Price who provided invaluable efforts for developing my scientific writing skills.

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I. INTRODUCTION

SIGNIFICANCE

Marijuana (MJ) use continues to be on the rise among youth populations, with up to 25% of adolescents reporting annual use, a nearly 4% significant increase from 2007 (Johnston, O'Malley, Bachman, 2011a). Additionally, over one third of college students reported past year use (Johnston, O'Malley, Bachman & Schulenberg, 2011b) and in young adults aged 21-22 almost 20% reported past month use with roughly 6% reporting daily use in 2012 (Johnston, O'Malley, Bachman, Schulenberg, 2013). Among chronic MJ-using youth, evidence suggests impairments in higher order cognition, such as complex attention and working memory (Harvey, Sellman, Porter, & Frampton, 2007; Hanson et al., 2010; Medina et al., 2007; Lisdahl & Price, 2012).

The central active ingredient in MJ, Δ^{9}- tetrahydrocannabinol (THC), binds to cannabinoid receptors (CB_1) in the brain. In-vivo human research indicates the presence of CB_1 receptors in several cortical regions, including the hippocampus and cerebellum, with increased densities in the prefrontal cortex (PFC) (Terry et al., 2009), a region associated with attention and executive functions (see Goldberg, 2009; see Yurgelun-Todd, 2007). The CB_1 receptor is part of a neurotransmitter system that responds to cannabinoids and this signaling, known as endocannabinoid signaling (ECS), is what causes the subjective experience of MJ use through retrograde regulation of monoamines, including dopamine (DA) (see Katona & Freund, 2012). Given that such processes may have an influence on addiction risk (Koob & Volkow, 2010) and executive functioning (EF) performance (for review see Egerton, Allison & Brett, 2006), it is plausible that variability in MJ-related neurocognitive consequences may be mediated by genes that

regulate ECS. One such candidate is fatty acid amide hydrolase (*FAAH*). To date, no studies have examined the impact of *FAAH* genotype on structural brain changes associated with adolescent and emerging adult MJ exposure. Consequently, there is great incentive to further understand the effects MJ has on the emerging adult brain.

NEUROCHEMISTRY

Endogenous cannabinoids are produced naturally in the brain and exogenous MJ administration mimics the typical chemical function. In reaction to calcium build-up in the post synaptic cell, endogenous cannabinoids (e.g. N-arachidonylethanolamide or AEA) indirectly affect glutamate (GLU) and γ-Aminobutyric acid (GABA) release by binding to G-protein coupled CB_1 receptors in pre-synaptic neurons (Gomez-Ruiz, Hernandez & Ramos, 2007; Howlett et al., 2004; Iversen, 2003; Kogan & Mechoulam, 2006). FAAH inactivates and degrades AEA into two elements arachidonic acid and ethanolamine, which prevents AEA from activating the CB_1 receptor (McKinney & Cravatt, 2005; Ho & Hillard, 2005). During MJ use, THC also binds to CB_1 receptors and similarly affects GLU and GABA release (Iverson, 2003). This has both excitatory (decrease in GABA) and inhibitory (decrease in GLU) effects on the post-synaptic neurons, including other monoamines (Szabo & Schlicker, 2005), which may induce behavioral consequences. Throughout adolescence, neurochemical changes in AEA regulation occur through increasing reliance on the action of FAAH in regions within the PFC (Long, Lind, Webster & Weickert, 2012). Additionally, chronic MJ using adults (ages 20-36) demonstrate significant, though reversible downregulation of CB_1 receptors in the PFC (Hirvonen et al., 2012). Thus, a continuum of FAAH activity may have

unique structural implications for adolescent and emerging adult MJ users, particularly in areas such as the PFC.

FAAH GENOTYPE AND ENDOCANNABINOID SIGNALING

Several genes contributing to individual variation in neurochemical responses may mediate ECS (Onaivi et al., 2002); recent data also suggest environmental influences on ECS response, specifically via unique fluctuations of endocannabinoids (Hill et al., 2010). Though CB_1 activation via AEA may be inhibited through AEA transport or FAAH activity, the latter was found to be the preferential constituent in the rat brain (Solinas et al., 2007). As previously mentioned, a potential biomarker of ECS is the gene encoding for the enzyme FAAH (*FAAH;* note: gene encoding for the FAAH enzyme is also called *FAAH* –all references to the gene will be *FAAH*) located on chromosome 1p35-34 in humans. Specifically, a single nucleotide polymorphism (SNP) from C to A at position 385 (rs324420) in the human *FAAH* gene results in a conversion of amino acid proline to threonine (P129T), which renders the enzyme instable as evidenced in immune cell examination (Sipe et al., 2002; Chiang, Gerber, Sipe, & Cravatt, 2004). Consequently, the three most common genotypes are as follows: C/C (63.19%), C/A (30.56%), A/A (6.25%), and those carrying the rare nucleotide 'A' demonstrate elevated levels of AEA in blood plasma levels (Sipe et al., 2010).

ECS has an important role in fetal and postnatal development, and FAAH activity is an important mediator in ECS regulation (Glaser et al., 2003; McFarland, Rakhshan, Wilson & Barker, 2004; Fernández-Ruiz, Berrendero, Hernández, Romero & Ramos 1999; Fride, 2008; Harkany, Keimpema, Barabás & Mulder, 2008). Maturational

disruption, as evidenced in animal models (Bernard et al., 2005), may negatively impact network activity.

ADOLESCENCE A SENSITIVE NEURODEVELOPMENTAL PERIOD?

In addition to ongoing development of the endocannabinoid system, there are also substantial neurodevelopmental changes present during adolescence through emerging adulthood, especially in the PFC (see Gogtay & Thompson, 2010; Gogtay et al., 2004). Underlying microstructural analysis demonstrate gray matter pruning in the PFC coincides with white matter (WM) tract development into early adulthood (Bava et al., 2010), producing increased axonal insulation. Dynamic changes in reward centers predate maturation in the PFC (Casey, Jones & Hare, 2008; Ernst, Pine & Harden, 2006; Galvan et al., 2006), suggesting fewer resources available for top-down executive control and heightened impulsivity behaviors (Kelley et al., 2004), including initiation of MJ and other drug use during adolescence (Bava & Tapert, 2010). Animal and human studies investigating the impact of adolescent MJ use suggests marked changes in cognition, structure and neural recruitment (Jager & Ramsey, 2008), as well as neuropsychological decline (Meier et al., 2012). Adolescents also demonstrate pronounced vulnerability to MJ exposure (see Trezza, Cuomo & Vanderschuren, 2008), thus determining the influence of MJ use on regions undergoing neural maturation is necessary.

In addition to gray matter pruning, underlying maturation also occurs in WM with changes in both volumetric and cohesiveness of axons (Giedd, 2004; Lenroot & Giedd, 2006; Schmithorst, Wilke, Dardzinski & Holland, 2002; Barnea-Goraly et al., 2005). Diffusion tensor imaging (DTI) provides in-vivo analysis of WM integrity through examining diffusion of water molecules. Quantification can be made on the direction,

which can be isotropic or anisotropic (fractional anisotropy; FA), and magnitude of diffusion (mean diffusivity; MD), and can be influenced by the geometric dimensions of the tissue (Beaulieu, 2002; Mamata et al., 2002; Pierpaoli, Jezzard, Basser, Barnett & Di Chiro, 1996). FA values range from 0-1,with greater values representing highly organized and cohesive tissue. Typically developing WM tracts demonstrate an inverse relationship between FA and MD. For example, during late adolescence and early adulthood WM cohesion increases, which causes increases in FA and decreases in MD within the PFC (Qiu, Li, Liu, Xie, & Wang, 2010) to support cognitive performance and guide increasingly complex behavior as we age (see Giedd, 2008; Bava et al., 2010). Increases in both FA and WM volume have been observed in healthy adolescent and emerging adults samples, particularly in PFC regions, which were associated with enhanced cognitive and intellectual abilities (Barnea-Goraly et al*.,* 2005; Bava et al., 2010; Tamnes et al., 2011).

Functional neuroimaging studies found increased brain activation abnormalities in early-onset versus late-onset marijuana users (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup & Daumann, 2010; Gruber, Dahlgren, Sagar, Gönenc & Killgore 2012; Jager, Block, Lulten & Rarnsey, 2010). With critical changes in brain maturation occurring, human research must address MJ-induced cognitive and structural changes, particularly in later developing regions such as the PFC (Barnea-Goraly et al., 2005; Bava et al*.*, 2010; Gogtay et al*.*, 2004).

MARIJUANA COGNITIVE IMPACT IN ADOLECENTS AND EMERGING ADULTS

When examining neurocognition as it relates to MJ exposure, length of abstinence may impact behavior, especially for the chronic users, given traceable metabolites can be

detected 27 days following past use (Ellies, Mann, Judson, Schramm & Tashchian, 1985). Though there is no evidence that metabolites can impact behavior, this aligns with subjective withdrawal symptoms persisting up to 28 days following abstinence (Kouri & Pope, 2000).

Studies requiring between 7 and 28 days of abstinence have found significantly slower processing speed, poorer complex attention, and cognitive inhibition (Lisdahl & Price, 2012); verbal memory, planning and sequencing ability (Medina et al., 2007); memory (Bartholomew, Holroyd & Heffernan, 2010); attention/executive performance (Tapert, Baratta, Abrantes & Brown, 2002); perseverative errors in problem-solving (Lane et al., 2007), and altered decision-making (Whitlow et al., 2004). In a non-abstinent group of poly-substance using teens, neuropsychological performance was not associated with MJ use, though the group was also diagnosed with conduct disorder (Teichner, Donohue, Crum, Azrin & Golden, 2000). Despite the impairments listed above, functional neuroimaging studies suggest adolescent MJ use may cause heightened activation of PFC regions while completing spatial working memory (Schweinsburg et al., 2010), executive attention (Abdullaev et al., 2010), and inhibitory processing (Tapert et al., 2007) tasks.

In general, chronic MJ use appears to negatively impact behavioral (Fergusson et al., 2003; Iversen, 2005) and cognitive functioning (see Schweinsburg, Brown & Tapert, 2008, see Lisdahl et al., 2012); though, neuropsychological impairments may be dependent upon initiation age of first usage (Ehrenreich et al., 1999; Huestegge et al., 2002; Pope et al., 2003; Fontes et al., 2011; Solowij et al., 2012; Meier et al., 2012), and gender (Pope, Jacobs, Mialet, Yurgelun-Todd & Gruber, 1997; Lisdahl & Price, 2012).

Indeed, preliminary evidence suggests some deficits may be reversible following a discontinuation of use (Fried, Watkinson & Gray, 2005; Hanson et al., 2010; Tait, Mackinnon & Christensen, 2011).

MARIJUANA STRUCTURAL CONSEQUENCES IN ADOLESCENCE

As the neocortex continues to mature throughout adolescence and emerging adulthood (Gogtay & Thompson, 2010; Gogtay et al., 2004), research highlighting the effects of MJ use on neural architecture has indicated abnormalities in regional gray matter volumes subserving memory and executive functioning, such as bilateral hippocampus, right amygdala, cerebellum and PFC regions (Cousijn et al., 2012; McQueeny et al., 2011; Medina, Nagel & Tapert, 2010; Medina et al., 2009). In light of the scope of this paper, structural consequences will focus on PFC and underlying PFC WM disparities between controls and MJ using emerging adults.

PREFRONTAL CORTEX – STRUCTURAL FINDINGS

Animal models offer evidence for heightened PFC vulnerability to MJ exposure in adolescents (Ellgren et al., 2008). In humans, structural imaging studies also suggest that MJ use may impact typical neurodevelopment, particularly in later developing regions. For example, MJ users did not differ from controls in total PFC volume, although a marginal gender by group interaction was observed. Female MJ users demonstrated larger posterior PFC volumes, including the orbitofrontal cortex, than same-gendered controls and smaller PFC volume was associated with better performance (Medina et al., 2009). In a group of heavy MJ-using adolescents reduced cortical thickness was found within frontal regions (Lopez-Larson et al., 2011), with age of onset negatively correlated with the right superior frontal gyrus. Additionally, another study found reduced medial

orbital frontal volume (mOFC) (Churchwell, Lopez-Larson, Yurgelun-Todd, 2010) in adolescent MJ-users. Our lab has also confirmed reductions in the mOFC as well as inferior parietal lobe in young adult MJ-users (Price et al., under review). Extensive exclusion criteria were implemented for these studies, suggesting that chronic MJ use in otherwise healthy youth can impact the structure and maturation processes of gray matter. Additional PFC characteristics aside from volume or cortical thickness, such as gyrification indices, may serve to elucidate the impact of MJ use on cortical changes.

PREFRONTAL CORTEX- WHITE MATTER FINDINGS

Containing both myelin and oligodendrocytes, WM is responsible for efficient communication between different cortical regions and demonstrates a functional role in orchestrating brain networks (see Fields, 2008; see Fields & Stevens-Graham, 2002). Of note, CB_1-rs are typically located on axons (see Mackie, 2005) although oligodendrocytes have also been found to contain CB_1 receptors in the rat brain (Molina-Holgado et al., 2002; Moldrich & Wenger, 2000), suggesting that cannabinoids may impact myelination. Further, adult animal studies examining repeated exposure to cannabinoid agonists found enhanced remyelination regulated through CB_1 activation and agonist treatment may reduce oligodendrocyte progenitor apoptosis (i.e. programmed cellular death; Sun et al., 2013; Molina-Holgado et al., 2002). Nonetheless, CB_1 agonist exposure during adolescence may not parallel adult findings.

Given continued PFC development (see Toga, Thompson & Sowell, 2006), with increased CB_1 receptor density localized within the PFC (Terry et al., 2009), MJ-induced changes in WM may be heightened during this sensitive period. With once exception (DeLisi et al., 2006, see below), converging lines of evidence suggest that chronic MJ use

during adolescence results in reduced WM integrity in the corpus collosum (CC) (Arnone et al., 2008; Abou-Saleh, 2010; Zalesky et al., 2012), front-temporal tracts (Ashtari, Cervellione, Cottone, Ardekani & Kumra, 2009), and other PFC regions (Bava et al., 2009; Yücel et al., 2010; Clark, Chung, Thatcher, Pajtek & Long, 2012). These WM differences have been linked with negative cognitive performance or behavioral outcomes in adolescent users (Bava, Jacobus, Mahmood, Yang & Tapert, 2010; Medina, Nagel, Park, McQueeny & Tapert, 2007). While current less infrequent use (i.e. not current regular users but used either 2-3 times to daily > 1 year during adolescence) in young adults aged 17-30 has been associated with increased FA/integrity compared to non-users (DeLisi et al., 2006), there are concerns regarding methodological limitations (e.g. comorbid drug/alcohol use, neurological insult history, handedness etc.), thus confounding variables may have driven the results. In summary, there is evidence of dynamic alterations in PFC microstructure are being reflected in MJ using adolescents and emerging adults, suggestive of heightened infrastructural vulnerabilities in early commencing users. Taking into consideration the later myelination of the PFC (Bava et al., 2010) and discovery of CB_1 receptors on myelinating glial cells (Molina-Holgado et al., 2002; Moldrich & Wenger, 2000), WM may prove to be more interactive with ones' environment and reflect dynamic structural changes concomitant with our behavior (Ullén, 2009).

CORTICAL GEOMETRY

Cortical folding (gyrification) patterns may be quantified and serve as another method to examine surface-based dimensions that reflect underlying organization (Schaer et al., 2008; 2012). Whether gyrification results from tensions propagated by amount of

connectivity and tension of WM (Van Essen, 1997) or differential cortical expansion (Richman et al., 1975; Ronan et al., 2013), cortical surface complexity increases between ages 6-16 in typically developing youth, most especially within the PFC (Blanton et al., 2001). Evidence suggests increased gyrification may be associated with enhanced vocabulary in typically developing youth (Wallace et al*.,* 2013). To our knowledge, no studies to date have examined local gyrfication in adolescent MJ users.

Mata and colleagues (2010) examined cortical curvature, a similar measure to gyrification, in young adults (mean age of 25.7). MJ users demonstrated significant decreases in sulcal concavity compared to controls in regions of the frontal lobe, with significant reductions found in sulci thickness of the right frontal lobe in users (Mata et al*.,* 2010). Given that global cortical comparisons were not found to be distinct between groups, the authors suggested sulcal curvature may be dependent upon WM tensions (Mata et al., 2010; Van Essen, 1997). As such, there is a need to examine PFC WM integrity among MJ-using adolescents and emerging adults.

FAAH & MJ USE

Initial evidence suggests *FAAH* genotype may indeed moderate the effects of MJ use in youth. In young adult daily MJ users (ages 18-25), those with C/C genotype reported significantly increased craving (Haughey, Marshall, Schacht, Louis & Hutchison, 2008), and increased withdrawal symptoms and happiness following use (Schatch, Selling & Hutchinson, 2009). Adults with *FAAH* A/A genotype have demonstrated significantly reduced risk for developing MJ dependence compared to C/C or C/A carriers (Tyndale, Payne, Gerber & Sipe, 2007) and failed to demonstrate an

association with methamphetamine dependence (Morita et al., 2005), alcoholism (Iwasaki et al., 2007), or heroin (Proudnikov et al., 2010).

Neuroimaging research has focused on adults and is mixed with regard to genotype and limbic reactivity. *FAAH* C/C genotype has been linked to increased reward sensitivity (Filbey et al., 2010), while other studies have found non-substance using adult A carriers to have heightened startle activation (Conzelmann et al., 2012) and increases in reward activation coupled with decreased threat-related reactivity (Hariri et al., 2009) Of note, Hariri and colleagues (2009) did not exclude for current substance use, which may impact functional activation patterns (Gruber & Yurgelun-Todd, 2005; Yurgelun-Todd et al. 1998) and Conzelmann and colleagues (2012) did not confirm abstinence with objective measures and relied on self-report. Thus far, preliminary research suggests a functional relationship with *FAAH* polymorphism and behavioral phenotypes, which necessitates the need to examine PFC structural differences between genotypes.

AIMS & HYPOTHESES

The current study examined whether the *FAAH* gene or MJ use independently or interactively predict PFC cortical gyrification (Schaer et al., 2012) and underlying WM integrity (via FreeSurfer; Desikan et al., 2006; Yendiki et al., 2011) (see Figure 1). Further, the study will examine whether relationships exist between executive functioning (EF) and gray matter gyrification or WM regions that significantly differ between MJ users and controls (see Figure 2) in 18 to 25-year old healthy young adults without comorbid psychiatric or neurologic disorders.

Insert Figures 1 & 2 Here

Primary Aim 1: To examine the independent and interactive effects of MJ group status and *FAAH* genotype on dimensions of PFC gyrification.

Hypothesis 1. MJ users (based on previous findings; Mata et al., 2010) will have reduced gyrification compared to controls. Due to potential risk in MJ-using youth (Haughey et al., 2008; Schatch et al., 2009), individuals homozygous for C/C *FAAH* allele will have significantly less gyrification compared to A carriers. Further, MJ users that are C/C carriers of *FAAH* will demonstrate the least curvature in the PFC compared to MJ-using A allele carriers.

Primary Aim 2: To examine the independent and interactive effects of MJ group status and *FAAH* genotype on WM integrity in the PFC.

Hypothesis 2. MJ users will have significantly poorer WM integrity (increased MD or decreased FA values) in the PFC compared to controls. Individuals with the C/C *FAAH* allele will have significantly poorer WM integrity in the PFC compared to A allele carriers. MJ users with the C/C *FAAH* allele will have significantly poorer WM integrity compared to the other genotype subgroups.

Primary Aim 3: Examine ROI's that significantly differ between MJ users and controls to determine the association between PFC gyrification and WM integrity and EF performance.

Hypothesis 3. Regions that significantly differ will be positively associated with performance and gyrification, such that better performance will be associated with

increased gyrification. In WM, a negative association with MD and performance will be observed, whereas a positive association with FA values and performance will be observed.

II. METHODS AND MATERIALS

PARTICIPANTS

Participants included 74 healthy emerging adults between the ages of 18-25 (41 male, 33 female; 28 homozygous CC & 13 A carrying males, 19 homozygous CC & 14 A carrying females) from a larger parent study examining genetic moderations of drugs in youth (PI: Lisdahl, NIH R03 DA027457). All participants were required to be fluent in English and right-handed. Exclusion criteria included MRI contraindications (pregnancy, claustrophobia, weight over 250 lbs., ferromagnetic implants of any kind, pacemakers or other devices in body); history of chronic medical or neurologic illness or injury (meningitis, HIV, epilepsy, brain tumor, traumatic brain injury, injury resulting in >2 minutes of unconsciousness and concussion symptoms, stroke, cerebral palsy, Parkinson's disease, Huntington's disease, high blood pressure, diabetes, consistent migraines); history of a learning disability; substantial complications during birth or premature birth; known prenatal exposure to alcohol (>4 drinks/day or >7 drinks/week) or illicit drugs (>10); current use of psychoactive medication; preexisting DSM-IV Axis I disorders independent of substance use (including major depressive disorder, bipolar disorder, attention deficit hyperactivity disorder, conduct disorder, social phobia, agoraphobia, panic disorder, generalized anxiety disorder, obsessive compulsive disorder, anorexia, and bulimia); and refusal to remain abstinent from all drugs and alcohol for at least seven days.

Eligible participants were chosen if they fit into of two groups: MJ users (> 10 uses in past year and > 50 lifetime uses) or non-using controls (<1 past year and < 5 lifetime uses) and had usable MRI data. In order to minimize the impacts of comorbid alcohol use across both groups, heavy binge drinkers were excluded; this was assessed using past year Cahalan criteria and "very heavy" drinkers were excluded. Participants were also matched as closely as possible on age, education, ethnicity, gender, and verbal IQ. For the current analysis, 37 controls and 37 MJ users met proposed inclusion and exclusion criteria.

PROCEDURES

The Institutional Review Board at the University of Cincinnati approved all aspects of this study and the same institution has approved ongoing analysis. Participants were recruited through advertisements in a local free newspaper and fliers distributed throughout the community and local universities. Interested participants were then screened by phone. After individuals provided oral informed consent, trained research assistants screened prospective participants over the phone for inclusion/exclusion criteria (mentioned above), including questions regarding past year drug use in order to assess matching into a particular drug use group. In addition, screeners utilized a semi-structured interview based on DSM-IV-TR criteria for Axis I psychotic, anxiety, and mood disorders. Those who had positive responses to the screening questions were discussed in committee; if clear decisions could not be reached then they were re-contacted and administered additional diagnostic questions based on the SCID I/P (determined by Dr. Lisdahl; First, Spitzer, Gibbon, & Williams, 2001).

Following the phone screen, eligible participants completed either one or two sessions. Those with considerable drug or alcohol use completed a first session three to four days prior to the second session, during which they were informed of the purpose of the study, procedures, potential risks and benefits, and confidentiality before providing written informed consent. They then provided a urine sample for a drug toxicology screen and completed questionnaires for background and demographic information and trait-specific psychological measures. During the second session (lasting approximately 5 to 6 hours), abstinence was once again verified through a urine drug screen and breathalyzer test, psychological measures were completed, a drug use interview and neuropsychological battery were administered, and participants underwent a high-resolution MRI scan. Control participants who endorsed less frequent drug use completed all tasks during one session (approximately 4-5 hours). Participants were paid $160 for two sessions or $110 for one session, reimbursed for parking, and received local drug and alcohol treatment resources and images of their brain.

SCREENING INVENTORIES AND QUESTIONNAIRES

Biological Samples. Participants were administered a urine toxicology screen using the One Step Drug Screen Test, a breathalyzer test, and a pregnancy test. Those who tested positive for drugs and/or alcohol except MJ and nicotine were excluded, and pregnant women were excluded as effects of MRI scans on fetuses are unknown. Additionally, urine samples were sent for further analysis to provide THC-COOH (THC metabolite) levels to assess abstinence-related decreases from session one.

Demographic Information. Participants completed a Background Questionnaire outlining demographic variables including age; gender; ethnicity (coded for Caucasian

vs. minority status); self and parents' educations, incomes, and employments; marital status; number of biological and/or step/half siblings; history of medical or neurologic illness, psychological disorders or use of psychiatric medication, and learning disability; involvement in extracurricular activities or hobbies, gambling frequency, and smoker status. Height and weight were also collected to calculate body mass index [BMI; (weight in kilograms/(height in meters)^2].

Drug Use. Drug use frequency was recorded to exclude for very heavy users as well as to control for possible variance in cognition based on amount used. A modified version of the Time-Line Follow-Back (Sobell, Maisto, Sobell, & Cooper, 1979) interview was conducted, using memory cues such as holidays and personal events recorded on a calendar to measure past year drug use. Drug categories assessed were as follows: nicotine cigarettes, chewing tobacco/snuff/pipe, cigars/hookah, alcohol, MJ, and 'other' drug use, which was a total including all of the following categories: ecstasy, sedatives (barbiturates, valium, Xanax, Ativan, ketamine, GHB), stimulants (cocaine, crack cocaine, amphetamine, and methamphetamine), hallucinogens (PCP, LSD, DMT, peoyote, acid, mushrooms), opioids (heroin, opium, pain pills), inhalants (paint, glue, household cleaners, nitrous oxide, gas), and other (anything else not mentioned). The participants' drug use was measured by the number of standard units (cigarettes, hits, cigars for nicotine; standard drinks for alcohol; joints for MJ; tablets for ecstasy; grams for stimulants; number of hits or pills for inhalants, hallucinogens, and opioids; and pills or hits for sedatives). Participants were administered the Customary Drinking and Drug Use Record (CDDR), measuring lifetime and past 3-month substance use, withdrawal

symptoms, DSM-IV abuse and dependence criteria, and substance-related difficulties (Brown et al., 1998; Stewart & Brown, 1995).

Psychological Tests. Participants were administered the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), which assess current depressive symptomology.

NEUROPSYCHOLOGICAL ASSESSMENTS

Premorbid Intelligence. The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest (Wechsler, 1999) and the Wide Range Achievement Test-4th edition (WRAT-4) Reading subtest (Wilkinson, 2006) measured estimates of verbal intelligence and quality of education for group comparison purposes (see Manly, Jacobs, & Touradji, 2002).

Complex Attention. Complex attention was assessed using the total correct responses in the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Letter Number Sequencing (LNS) and the Paced Auditory Serial Attention Test (PASAT). The LNS is a subscale of the WAIS-III Working Memory Index, which measures a person's ability to retain numbers and letters (ranging from two to eight bits of information over 7 separate trials) and perform a manipulation to organize the information according to a rule in order to provide a response (Wechsler, 1997). The PASAT is a working memory task in which requires participants to retain two consecutive numbers that are presented in a serial manner and perform a summation roughly every 2 seconds for a total of 60 numbers (Gronwall, 1977). Total scores on the LNS and PASAT were used for the current study.

Cognitive Inhibition. The D-KEFS Color Word Interference Test Inhibition total completion time assessed inhibitory ability (Delis & Kaplan, 2000). For this task, participants were presented with stimuli cards containing words (red, blue or green), colors (blocks made of red, blue, or green), and words printed in a different color (e.g. the word "blue" printed in green ink). During each of the three stimuli presentations, participants were asked to first read the words on the word card, name the colors on the color card and name the color on the mixed word/color ink card.

GENOTYPING

FAAH. The *FAAH* variant were genotyped using the TaqMan (fluorogenic 5' nuclease) assay (for example see Egan et al., 2003). The primers and the probes were obtained from Applied Biosystems. PCR was conducted with both primers and probes added in an ABI 9700 thermocycler and the endpoint results were scored using the ABI 7900HT Sequence Detection System.

MRI DATA ACQUISITION

Parameters. High-resolution anatomical images were optimized on a 4T Varian Unity INOVA MRI scanner at the Center for Imaging Research (CIR). T1-weighted, 3-D SPGR anatomical brain scan was obtained (about 30 minutes of scan time) using a modified driven equilibrium Fourier transform (MDEFT) sequence (FOV=25.6 cm, 256x256x192 matrix, slice thickness=1 mm, in- plane resolution=1x1 mm, TR=13 ms, TE=5.3 ms, flip angle=22˚). Diffusion Tensor Imaging (DTI) was obtained using 12 diffusion directions with b ≈ 600s/mm^2 (FOV= 25.6 cm, 64x64x30 matrix, resolution=4x4x4 mm^3, TR = 8,000 ms, TE = 88.8 ms, flip angle 90˚. Geometric and ghost distortion corrections were implemented using multi-echo reference scans. A

neuroradiologist at CIR reviewed anatomical scans and reported neurologic abnormalities. No participants with abnormalities were included in this sample.

MRI PROCESSING

PFC Local Gyrification Analysis. Images were preprocessed using FreeSurfer's 3D reconstruction pipeline (http://surfer.nmr.mgh.harvard.edu; Dale, Fischl, & Sereno, 1999). First, segmentation discerned type of tissue, resulting in segmented WM volume indicating location of gray-white boundary. After automatic correction for topology errors, a second surface was created reflecting the pial-gray boundary. Next, pial smoothing was applied via: [(l/r)h.pial-outer-smoothed]; which was followed by specifying regions of interest on the smoothed inflated surface and corresponding pial surface. PFC local gyrification indices (LGI) were also created using FreeSurfer software version 5.3 with a radius set to 20mm (Schaer et al., 2008; 2012), which quantified a ratio of the smoothed surface to the pial surface for each vertex and selected ROI (see Figure 3). ROI's were determined using an individual cortical surface-based anatomical atlas (Destrieux, Fischl, Dale, & Halgren, 2010). Similar to cortical thickness, each subject's LGI was entered for the following ROIs: [including the PFC; dorsal lateral PFC (DLPFC); medial PFC (mPFC); orbital frontal PFC (OFC), which was further broken down into: ventral medial PFC (vmPFC) and ventral lateral PFC (vlPFC); and frontal pole for both right (RH) and left (LH) hemispheres].

PFC Underlying WM Integrity. WM pathways were reconstructed via diffusion tensor imaging (DTI) using voxel based 3x3 symmetric tensor matrices differentiating both direction and magnitude, assuming direction was uniformly linear within each voxel. Fractional anistoropy (FA) was obtained through eigenvalue variance for a given

voxel, which determines isotropic versus anisotropic movement represented by a scalar value between 0 and 1. ROI-based comparison was computed through FreeSurfer version 5.3 tractography software TRACULA (Yendiki et al., 2011), which reconstructed WM pathways (trac-all -path). For ROI-based analysis, participant's DTI was registered to their individual T1 weighted image obtained through FreeSurfer cortical parcellation and subcortical segmentation (recon-all –path).

DATA ANALYSIS

Preliminary Analysis. All analyses were conducted using SPSS version 22.0.0. ANOVAs and Chi-square tests were run to examine potential demographic differences as well as differences in past year drug use histories between MJ users and controls by genotype. Variables that either differed between groups or may impact neural architecture were entered as covariates, such as mood symptoms (Medina et al., 2007), alcohol use (Medina et al., 2008) or nicotine use (Paul et al., 2008). Covariates included WRAT-4 Reading scaled score, age, gender, ethnicity (coded for Caucasian vs. minority status), past year alcohol use, recent nicotine use (cotinine levels), depressive symptoms, and *FAAH* genotype (when examining MJ group status).

Primary Analysis. **AIM 1.** General linear modeling (GLM) in SPSS was used to examine whether MJ group status, *FAAH* genotype, or an interaction between MJ group status**FAAH* genotype were significantly associated with each PFC gyrification indices for each ROI [PFC, DLPFC, mPFC, OFC (which was further broken down into: vmPFC and vlPFC), and frontal pole for both RH and LH. Standard least squares multiple regression was used; block one included covariates (see preliminary analysis), block two included MJ group status, and block three included the interaction between MJ group

status and *FAAH* genotype. If the interaction (MJ**FAAH* genotype) was not significant, only block two was interpreted. Significance was determined if $p<.05$.

Primary Analysis. AIM 2. Average FA and MD were extracted from the underlying WM tracts [corpus callosum forceps minor (fMinor), anterior thalamic radiation (ATR), and uncinate fasciculus (UNC)] in the PFC utilizing FreeSurfer 's TRACULA (Yendiki et al., 2011). Standard least squares multiple regression was used; block one included covariates (see preliminary analysis), block two included MJ group status, and block three included the interaction between MJ group status and *FAAH* genotype. If the interaction (MJ**FAAH* genotype) was not significant, only block two was interpreted. Significance was determined if $p<.05$.

Primary Analysis. AIM 3: Pearson correlations were run between cognitive performance (complex attention and cognitive inhibition; see Price et al., under review) in MJ users and both gyrification and WM variables that significantly differed between MJ users and controls. Significance was determined if $p<.05$.

III. RESULTS

DEMOGRAPHIC & MOOD INFORMATION

ANOVAs and chi-squares tested whether MJ users and non-using controls differed in demographic variables (see Table 1). Significant differences were found between MJ users and controls in BDI-II depressive symptoms with MJ users reporting more than controls [$F(1,72)=4.10$, $p=.05$]. MJ users and controls did not differ in ethnicity [64.9% Caucasian for MJ users and controls, $x^2(4)3.43$, $p=.49$], gender [$x^2(1)2.68$, $p=.10$], past year Cahalan criteria [$x^2(5)4.62$, $p=.46$], age [$F(1,72)=.41$,

p=.52], WRAT-4 Reading standard score [F(1,72)=.36, *p*=.55], education [F(1,72)=1.43, *p*=.24], annual income [F(1,72)=.09, *p*=.76], or body mass index [F(1,71)=.08, *p*=.77].

ANOVAs and chi-squares tested whether *FAAH* genotype differences between C/C carriers and A carriers (see Table 1). Significant differences were found between C/C and A carriers in ethnicity (76.6% of C/C carriers were Caucasian and 44.4% of A carriers were Caucasian) [x^2(4)12.56, *p*=.01], age [F(1,72)=5.85, *p*=.02], WRAT-4 Reading standard score [F(1,72)=6.6, *p*=.01], and BDI-II depressive symptoms [F(1,72)=6.23, *p*=.02]. No differences were found between genotypes in gender [x^2(1).91, *p*=.34], education [F(1,72)=.09, *p*=.77], income [F(1,72)=2.2, *p*=.14], or body mass index [F(1,71)=.08, *p*=.78].

Insert Table 1 Here

ALLELE FREQUENCIES

FAAH allele frequencies for 74 subjects were: 47 C/C carriers status and 27 A carriers status (see Table 1). A marginal difference was found between MJ users and controls in *FAAH* genotype [63% of MJ users were A carriers and 37.4% of controls were A carriers, [x^2(1)2.86, *p*=.09].

DRUG USE INFORMATION

As expected, MJ users differed from controls in lifetime nicotine use [x^2(6)22.75, *p*=.001], lifetime alcohol use x^2(5)13.89, *p*=.02], lifetime MJ use x^2(5)63.41, *p*=.001], lifetime other drug use (although this was limited) [x^2(4)34.97, *p*=.001], cotinine level [F(1,71)=20.98, *p*=.001], past year nicotine use [F(1,72)=8.03, *p*=.006], past year alcohol

use [F(1,72)=6.37, *p*=.014], and past year MJ use [F(1,72)=15.94, *p*=.001] (see Table 1). No difference between past year other drug use existed between MJ users and controls [F(1,72)=3.49, *p*=.07].

C/C carriers and A carriers did not differ in past year Cahalan criteria [x^2(5)8.94, *p*=.11], lifetime nicotine use [x^2(6)4.56, *p*=.60], lifetime alcohol [use x^2(5)5.72, *p*=.34], lifetime MJ use [x^2(5)3.06, *p*=.69], lifetime other drug use [x^2(4)2.59, *p*=.63], cotinine level, [F(1,71)=2.58, *p*=.11], past year nicotine use [F(1,72)=.95, *p*=.33], past year alcohol use [F(1,72)=.003, *p*=.96], past year MJ use [F(1,72)=.42, *p*=.52], or past year other drug use [F(1,72)=1.32, *p*=.26] (see Table 1).

MULTIVARIATE RELATIONSHIPS

Aim 1 Regression Analysis: Gyrification: *MJ Group Status*. After controlling for WRAT-4 Reading scaled score, age, gender, ethnicity, past year alcohol use, cotinine levels, depressive symptoms, and *FAAH* genotype, MJ users demonstrated significantly increased gyrification in the LH DLPFC [*t* (63) = 3.0, *beta*=.40, *p*=.004] in comparison to controls (see Table 2). In contrast, MJ users demonstrated reduced gyrification in bilateral OFC (RH: [*t* (63) =-2.3, *beta*=-.32, *p*=.02] and LH: [*t* (62) = -1.97, *beta*=-.28, *p*=.05]), specifically, bilateral vmPFC (RH: [*t* (63) = -4.1, *beta*=-.54, *p*<.001] and LH: [*t* (63) = -4.1, *beta*=-.55, *p*<.001]); bilateral mPFC (RH: [*t* (63) = -3.6, *beta*=-.48, *p*=.001] and LH: [*t* (63) = -3.8, *beta*=-.51, *p*<.001]); and bilateral frontal poles (RH: [*t* (63) = -2.3, *beta*=-.31, *p*=.02]; LH: [*t* (63) = -2.998, *beta*=-.43, *p*=.004]). ***FAAH Genotype*.** *FAAH* genotype significantly predicted local gyrification index in the LH DLPFC [*t* (63) = -1.998, *beta*=-.25, *p*=.05], with C/C genotypes demonstrating increased gyrification compared to A carriers. **MJ****FAAH* **Interaction.** *FAAH* genotype interacted with MJ

group status to significantly predict gyrification in the LH OFC [*t* (62) = -2.1, *beta*=-.24, *p*=.04] in that the MJ users with CC genotype had increased gyrification while A carriers had decreased, the controls demonstrated no significant difference in gyrification between genotypes (see Figure 4). **Covariates**. Increased depressive symptoms predicted decreased gyrification in the LH DLPFC [*t* (63) = -3.1, *beta*=-.37, *p*=.003]. Gender predicted gyrification in bilateral PFC RH: [*t* (63) = -2.9, *beta*=-.37, *p*=.005] and LH: [*t* (63) = -3.6, *beta*=-.43, *p*=.001]; bilateral OFC RH: [*t* (63) = -2.7, *beta*=-.33, *p*=.009] and LH: [*t* (63) = -3.1, *beta*=-.39, *p*=.003], specifically bilateral vlPFC RH: [*t* (63) = -2.2, *beta*=-.28, *p*=.03] and LH: [*t* (63) = -2.3, *beta*=-.29, *p*=.03]; bilateral mPFC RH: [*t* (63) = -3.3, *beta*=-.38, *p*=.002] and LH: [*t* (63) = -2.4, *beta*=-.28, *p*=.02]; bilateral vmPFC RH: [*t* (63) = -3.5, *beta*=-.41, *p*=.001] and LH: [*t* (63) = -2.3, *beta*=-.28, *p*=.02]; and bilateral frontal pole RH: [*t* (63) = -2.95, *beta*=-.35, *p*=.004] and LH: [*t* (63) = -2.1, *beta*=-.27, *p*=.04], such that women demonstrated reduced gyrification in each area mentioned. Ethnicity minority status predicted gyrification in the LH PFC [*t* (63) = -2.0, *beta*=-.25, *p*=.05], such that reduced gyrification was found for ethnic minorities compared to Caucasians. Age predicted gyrification in OFC (LH) [*t* (62) = -3.0, *beta*=-.37, *p*=.004], such that older age was associated with decreased gyrfication in this region.

Insert Table 2 Here

Aim 2 Regression Analysis: White Matter Integrity: *MJ Group Status*. After controlling for WRAT-4 Reading scaled score, age, gender, ethnicity (coded for Caucasian vs. minority status), past year alcohol use, cotinine levels, depressive

symptoms, and *FAAH* genotype, MJ users demonstrated increased MD in fminor [*t* (62) = 1.96, *beta*=.27, *p*=.05], bilateral UNC (RH: [*t* (62) = 2.3, *beta*=.32, *p*=.03] and LH: [*t* (62) = 2.2, *beta*=.31, *p*=.03]) (see Table 3). ***FAAH Genotype.*** *FAAH* genotype did not demonstrate any significant contributions. **MJ**FAAH* Interaction.** *FAAH* genotype interacted with MJ Group status to significantly predict FA in fMinor [*t* (61) = 2.1, *beta*=.26, *p*=.04] and LH ATR [*t* (61) = 3.1, *beta*=.36, *p*=.003]. In the fMinor MJ users with C/C genotype demonstrated reduced integrity (FA), whereas the A carrier controls demonstrated reduced integrity (FA) (see Figure 5). In LH ATR, MJ users with C/C genotype demonstrated reduced integrity (FA) (see Figure 6).

Insert Figures 5 & 6 Here

Covariates. WRAT-4 Reading Standard Score predicted MD in the RH ATR [*t* (62) = -2.1, *beta*=-.28, *p*=.04], MD in the LH ATR [*t* (62) = -2.9, *beta*=-.37, *p*=.005], such that higher scores were associated with decreased MD. Ethnicity predicted MD in the RH ATR [*t* (62) = -2.3, *beta*=-.28, *p*=.02], such that ethnic minorities demonstrated reduced MD compared to Caucasians. Cotinine levels predicted decreased FA in the RH ATR [*t* (62) = -1.97, *beta*=-.24, *p*=.05], such that higher cotinine levels were associated with a decrease in FA. Increased depressive symptoms predicted increased MD in the LH ATR [*t* (62) = 2.8, *beta*=.34, *p*=.006]. See Table 3 for mean DTI values by group.

Insert Table 3 Here

Aim 3 Correlation Analysis: Brain-Behavior Relationships:

MJ Group. Pearson *r* correlation revealed a positive correlation with gyrification and LNS performance in the RH mPFC [r=.51, n=37, p=.001], RH vmPFC [r=.41, n=37, p=.01], and RH frontal pole [r=.45, n=37, p=.005], with high degree of gyrification associated with better performance. Additionally, there was a negative correlation with gyrification and color-word inhibition completion time in the LH vmPFC [r=-.32, n=37, p=.05], with increased gyrification associated with faster response times.

Within the WM, a positive correlation was observed in MD and PASAT total correct in the RH UNC [r=.38, n=37, p=.02], with higher MD associated with better performance time. Overall, both increased gyrification and increased MD were associated with improved working memory and faster response time on an inhibitory task.

Controls. Positive correlations were found with gyrification and complex attention in bilateral OFC: RH /PASAT: [r=.35, n=36, p=.04], RH /LNS: [r=.34, n=37, p=.04], and LH/PASAT: [r=.36, n=36, p=.03], with increased gyrification associated with better performance. A positive correlation was found between gyrification and PASAT correct in the RH frontal pole [r=.35, n=36, p=.04], with greater gyrification associated with better performance. No significant relationships were demonstrated for controls in WM tracts examined (fMinor and bilateral UNC). See Table 4 for mean neuropsychological performances by group and genotype.

Insert Table 4 Here

DISCUSSION

This study examined the relationship between the *FAAH* genotype, MJ group status, and brain structure (gyrification and WM integrity) in a sample of 18-25 year old emerging adults with and without chronic MJ use. Follow-up analyses assessed the brain-behavior relationships between significant structural findings and executive abilities, including complex attention and inhibition. Consistent with the predicted hypotheses, MJ users had reduced gyrification and poorer WM integrity in several PFC regions in comparison to matched controls. We also found that *FAAH* genotype mediated the impact of MJ use on structural characteristics. The primary results revealed significantly reduced gyrification in MJ users in comparison to controls in several PFC regions (bilateral OFC, bilateral mPFC and bilateral frontal poles), while one region showed an opposite relationship, with increased gyrification for MJ users (LH DLPFC). WM findings indicate an increase in MD for MJ users in the corpus callosum fMinor and bilateral UNC, suggesting poorer microstructural integrity in MJ using young adults. *FAAH* genotype findings indicate that A carriers, including both control and MJ users, had reduced gyrification in the LH DLPFC. MJ users with A genotype demonstrated reduced gyrification in the LH OFC; however, MJ users that were C/C carriers had reduced WM integrity in the fMinor and LH ATR. In controls, A carriers demonstrated reduced WM integrity in the fMinor. Therefore, the current study found abnormal gray matter and WM structure in emerging adult MJ users, and reduced gyrification was associated with poorer executive functioning, specifically complex attention and inhibition.

We found decreased gyrification in the MJ users in several PFC regions. This is consistent with prior research demonstrating aberrant PFC characteristics in MJ using

youth (Churchwell et al., 2010; Gruber et al., 2011; Lopez-Larson et al., 2011; Medina et al., 2009; Price et al., under review; Wilson et al., 2000). Findings were also consistent with Mata and colleagues (2010), who found reduced sulcal concavity in frontal lobes of young adult MJ users in comparison to non-users. We found greater gyrification in the DLPFC LH of MJ users. This particular PFC region is the last to develop (Gogtay et al., 2004), and the mean age of this sample was 21.4. Thus, MJ users may have not undergone maturation in this region and evidence suggests asymmetries in maturation rates (see Toga & Thompson, 2003). Though the mechanisms driving gyrification are unclear, whether predominant influence is attributed to amount of connectivity and tension (Van Essen, 1997) or differential expansion of cortical layers (Richman et al., 1975; Ronan et al., 2013), both perspectives may be influenced by interruptions in myelination refinement, which may be related to poorer WM integrity in our sample (see WM section). Twin studies reveal that environmental stimuli or non-genetic influences greatly influence gyrification patterns (Bartley, Jones, & Weinberger, 1997), particularly within the PFC (Hasan et al., 2011). As PFC changes in sulcal and gyral complexity continue to extend into late adolescents (Blanton et al., 2001), environmental influences, including regular MJ use, during this developmental period may be detrimental to brain development and functioning (Becker et al., 2010; Gruber, Dahlgren, Sagar, Gönenc & Killgore 2012; Jager et al., 2010; see Lisdahl et al., 2013; Meier et al., 2012). During adolescence, neurotrophins involved in neuronal growth and pruning, play a key role in nervous system maturation (see Reichardt, 2006) and may be reduced in adult MJ users (Angelucci et al., 2008; D'Souza, Pittman, Perry, & Simen 2009). The impact of MJ use on in-vivo adolescent neurotrophin levels is unknown; however, divergent inter-cortical

growth rates and changes in connectivity are thought to impact gyrification patterns (Van Essen, 1997; Richman et al., 1975; White & Hilgetag, 2008; Ronan et al., 2013), which may be interrupted with adolescent MJ use increasing risk factors. For example, neurotrophic transcription may be altered as a result of physical activity (see Gomez-Pinilla, 2008; Trejo, Llorens-Martin, & Torres-Alemain, 2008) and adolescent MJ use has demonstrated an inverse relationship with physical activity (Winnail & Valois, 1995).

Among gray matter regions where MJ users differed from controls in gyrification indices [LH DLPFC, bilateral OFC, bilateral vmPFC, bilateral mPFC, and bilateral frontal poles], increased gyrification in right hemisphere: mPFC, vmPFC and frontal pole was associated with better performance on LNS total scores in MJ users. In controls, increased OFC gyrification and RH frontal pole was associated with better complex attention scores. The OFC has an important role in inhibiting reward-driven behavior and may be compromised in addicted individuals (Lubman, Yucel, & Pantelis, 2004). Ultimately, for both groups, increased gyrification was associated with better performance scores suggesting that functional benefit is gained with greater gyrification. Phylogeny of gyrification exposes an increase in surface area with minimal increases in cortical thickness (Welker, 1990), which serves to reduce volume expansion and maximize computational potential (see White et al., 2010).

In WM, we found increases in MD for MJ users in the fMinor and bilateral UNC, suggesting poorer microstructural integrity in MJ using young adults compared to non-users. This is consistent with previous research indicating WM degradation in young MJ users (Arnone et al., 2008; Bava et al., 2009; Abou-Saleh, 2010; Yücel et al., 2010; Clark et al., 2012; Zalesky et al., 2012) and in a group with comorbid alcohol use (Ashtari et

al., 2009). Additionally, the UNC may play an integral role in emotion regulation, as it serves to connect the amygdala with the PFC (see Stuss, 2002). Previous research reflects that greater FA in the UNC predicted lessened amygdala activation in adolescents, while increased amygdala activation to sad faces was associated with greater internalization of symptoms (Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014), suggesting potential difficulties with emotional regulation. Thus, reduced WM integrity in fronto-limbic regions of MJ users, as seen with this study, may indicate disruption of WM refinement impacting executive control and affective regulation. Further, here we found evidence that supports a relationship between surface geometry and underlying WM integrity. MJ users demonstrated specific reductions in medial and ventral aspects of the PFC in addition to decreased WM integrity tracts that project directly to these cortical regions, offering additional support for the potential role of WM connectivity on gyrification (Van Essen, 1997).

There has been conflicting evidence relating *FAAH* genotype to behavioral outcomes (Tyndale et al., 2007; Filbey et a., 2010; Haughey et al., 2008; Schatch et a., 2009; Conzelmann et al., 2012; Hariri et al., 2009), however our study suggests that genotype may impact gray matter and WM differently. We found reduced gyrification for *FAAH* A carriers compared to C/C carriers in the left hemisphere DLPFC. We also found a significant MJ by *FAAH* interaction such that reduced gyrification was found in A carrying MJ users for the left hemisphere OFC. Genotype did not affect gyrification in this region for controls. Within WM, a significant interaction between *FAAH* genotype and MJ group status exposed relationships with FA measures of WM cohesion in fMinor and left hemisphere ATR. Reduced fMinor integrity in MJ users was observed in C/C

carriers; however, we found an opposite relationship in controls where A carriers had reduced WM integrity in this tract. We also found C/C carrying MJ users demonstrated reduced WM integrity in the left hemisphere of the ATR. Genotype did not impact the impact of WM integrity in the LH ATR for controls.

In youth, C/C genotype may increase risk associated with MJ use (Haughey et al., 2008; Schatch et a., 2009). Chronic MJ use may cause functional PFC changes in ECS (Hirvonen et al., 2012); for example, adolescent MJ users demonstrate reduced GLU levels within the PFC (Prescot, Locatelli, Renshaw, & Yurgelun-Todd, 2011). Reduced GLU may weaken neurons' ability to retain synaptic connections, as evidenced in animals (Won Chan, Hill, Zito, 2013). Further, animal models suggest that THC exposure during adolescence may increase abnormalities in several proteins related to cellular structure and oxidative state compared to adulthood (Quinn et al., 2008) and changes in CB1/G-protein coupling and CB_1 receptor densities extending into adulthood (Rubino et al., 2008), which may underlie performance deficits and behavioral changes depending on the developmental stage of exposure (Schneider & Koch, 2003; Schneider & Koch, 2005; O'Shea, Singh, McGregor & Mallet, 2004). Therefore, in MJ users, the C/C genotype, associated with lower AEA (Sipe et al., 2010), may confer additional risk for neurocognitive consequences. However, the current results are mixed (MJ-using A carriers demonstrated reduced gyrification in DLPFC and OFC while C/C genotype was associated with poorer fMinor and ATR WM integrity). Therefore, additional research is needed to help clarify the relationship between *FAAH* genotype, MJ exposure and brain structure in youth.

In non-MJ using youth, A carrier status, which is associated with increased AEA levels (Sipe et al., 2010) may be detrimental to underlying structural complexity. CB_1 receptors undergo somatodendritic recycling and trafficking targeting axons (Leterrier et al., 2006), and agonist-induced desensitization may lower CB_1 receptor mobility (Mikasova, Groc, Choquet, & Manzoni, 2008). Therefore, chronic MJ use during youth may interrupt this process. ECS may also play a key role in myelination, which may be regulated via communication between oligodendrocytes and neurons (gray matter) (Simons & Trajkovic, 2006). We found A carrying controls had reduced WM integrity, the opposite of MJ-users. Increased cannabinoid signaling may enhance myelination in populations suffering myelination loss, as evidenced by animal models (Webb, Luo, Ying Ma, & Tham, 2008); however, in young adult controls enhanced ECS may be associated with poorer WM cohesiveness. In sum, aberrant ECS during emerging adulthood either through MJ use or genotype, may be associated with poorer brain characteristics and *FAAH* genotype may moderate the impact of adolescent MJ use on brain development and be tissue specific.

Insert Figure 7 Here

Among WM regions that differed between MJ users and controls [fMinor and bilateral UNC], there was one significant relationship that found reduced integrity in the right hemisphere UNC to be associated with increased performance on a working memory task. Though typical performance data suggests that increases in WM integrity are associated with improved performance (Tamnes et al., 2011), we found this untrue for

one tract in MJ users only. This finding may be related to reduced affective interference during a demanding and stress-provoking task. Additionally, in controls, WM integrity was not associated with better or worse performance.

Chronic MJ use during adolescence and emerging adulthood appears to have negative influence on brain structure. Young adult users reflect demonstrate aberrant brain characteristics that are consistent with neuropsychological (Lisdahl & Price, 2012). Extensive cortical remodeling is occurring during adolescence (see Crews, He, & Hodge, 2007), and the current study found that MJ use during this time was associated with reduced PFC gyrification and poorer underlying WM integrity. ECS appears to be important for brain maturation and reliance on CB_1 binding may increase in adulthood (Verdurand et al., 2011). Consequently, chronic emerging adult MJ use may interfere with brain maturation.

Limitations. Alcohol and MJ remain highly comorbid (Johnston et al., 2011b). Although the current study statistically controlled for alcohol and excluded "very heavy" drinkers (according to Calahan criteria), it is possible that some of the findings are associated with combined or *simultaneous* MJ and alcohol use. For example, WM integrity differences have been found in samples combining MJ and alcohol use may impact WM tracts in adolescents and young adults (Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Bava, Jacobus, Thayer, & Tapert, 2013; Jacobus, Squeglia, Bava, & Tapert, 2013; Bava, et al., 2010; Bava et al., 2009), though combined MJ and alcohol use may be less detrimental on WM integrity than binge-drinking alone (Jacobus et al., 2009). Future studies may want to investigate differences in simultaneous MJ and alcohol use versus separate occasion uses of each substance.

Another potential limitation of the current study is that it is difficult to determine what results are due to premorbid differences that may have been present prior to MJ exposure. For example, one longitudinal study suggests that smaller OFC predicts MJ use during adolescence, although this sample included current or past psychiatric diagnoses (Cheetham et al., 2012). Conversely, prospective longitudinal findings have demonstrated a decline in intellectual and neuropsychological functioning among adolescent-onset (before age 18) even after cessation of 1 or more years (Meier et al., 2012), indicating that early MJ use may affect the developing brain such that individuals never achieve their estimated intellectual performance even with sustained abstinence. This aligns with marked neuronal changes in animal models when exposure occurs during adolescence (Schneider & Koch, 2003; O'Shea et al., 2004; Cha, White, Kuhn, Wilson, & Swartzwelder, 2006; Quinn et al., 2008; Rubino, & Parolaro, 2008). In general, some recovery in functioning may be experienced with discontinued use (Schwartz et al., 1989; Fried et al., 2005; Hanson et al., 2010; Tait et al., 2011); however, full IQ potential may not be reached with adult abstinence (Meier et al., 2012).

Conclusions. Overall, this study demonstrates that regular MJ use impacts brain structure in adolescents and young adults. Specifically, we found general decreases in gray matter gyrification and decreased WM integrity in adolescent MJ users, which was moderated in some regions by *FAAH* genotype. Therefore, it is an important public health priority to delay the onset of regular MJ use until neuronal maturation has been reached (see Lisdahl et al., 2013).

Figure 1: Study Design (Aims 1 & 2) –Impact of MJ, *FAAH* Genotype, and MJ x FAAH on Gyrification and WM Integrity).

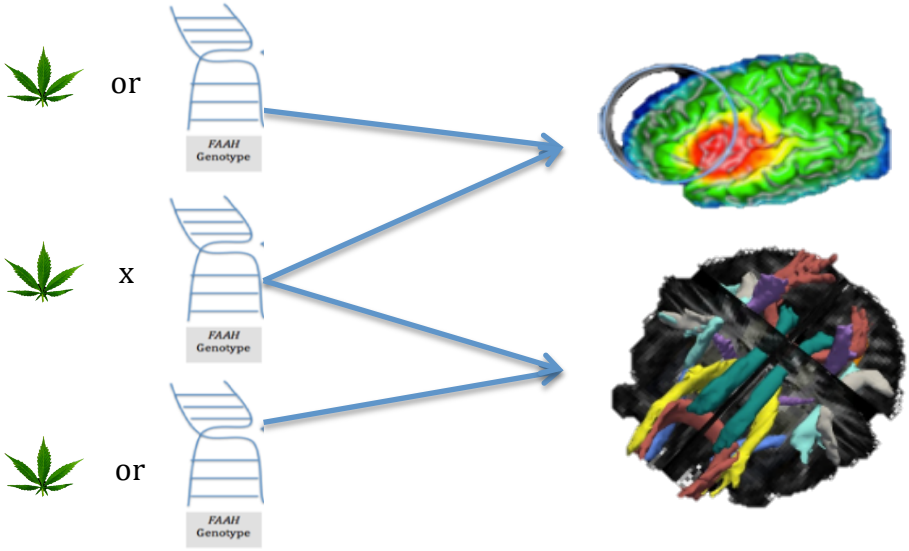

Figure 2: Study Design (Aim 3) –Correlation of Significantly Divergent Regions Between MJ Users and Controls and Executive Functioning Performance.

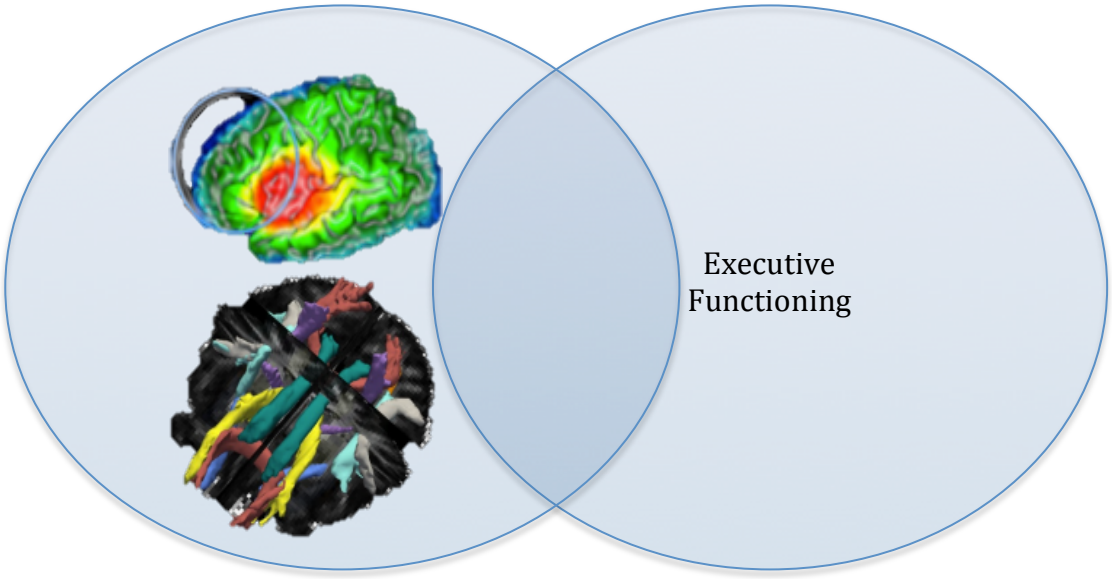

Figure 3: Gyrification Analysis Pipeline.

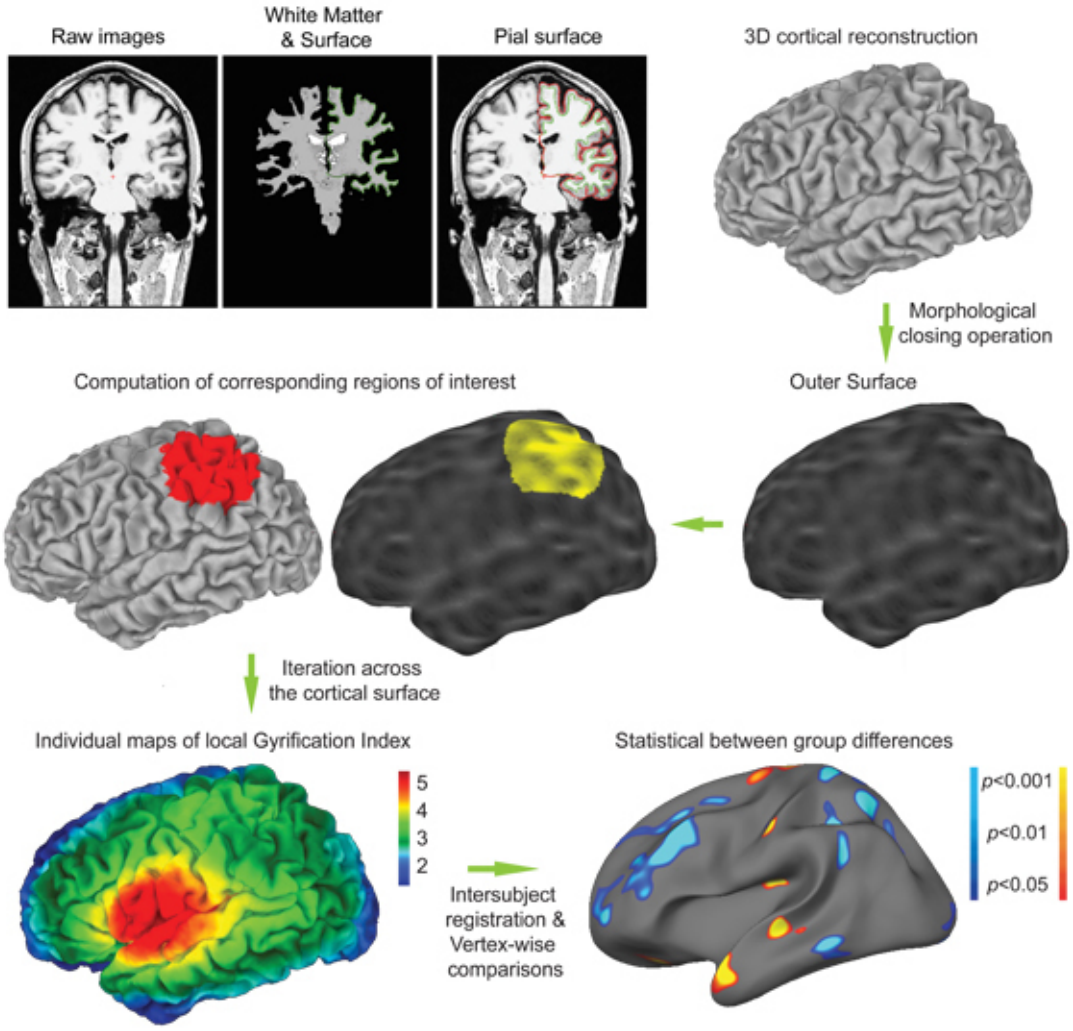

Image obtained from Schaer and colleagues (2012). NOTE: For this study, LGI was obtained and analyzed using SPSS and did not use FreeSurfer's statistical program.

Figure 4: Mean Gyrification for OFC (LH) varies by *FAAH* genotype in MJ users.

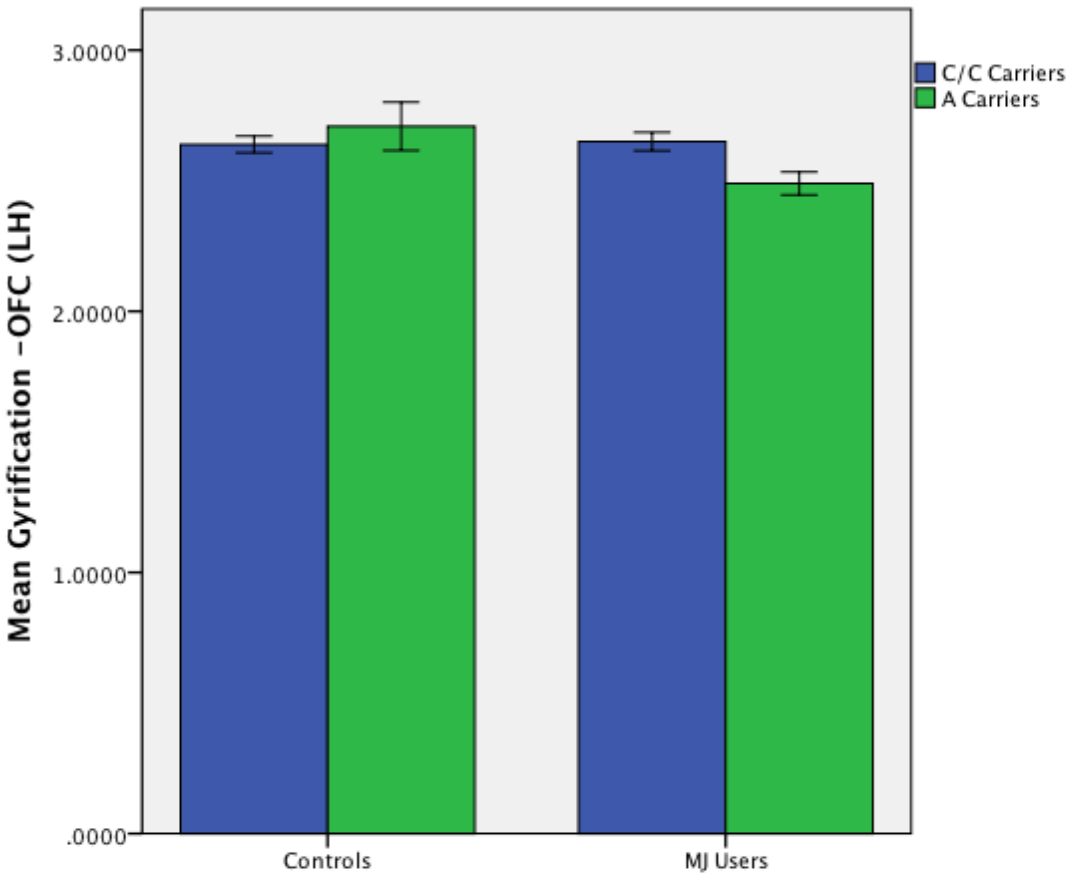

Figure 5: Mean FA for fMinor varies by group and *FAAH* genotype.

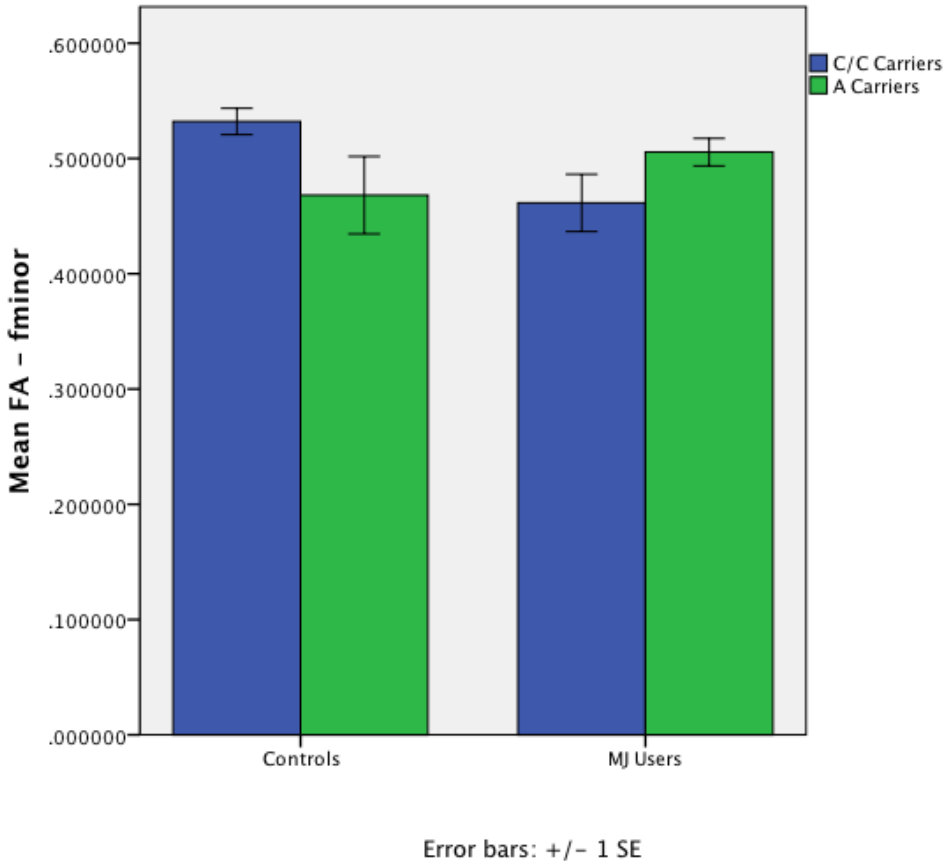

Figure 6: Mean FA for ATR (LH) varies by *FAAH* genotype in MJ users.

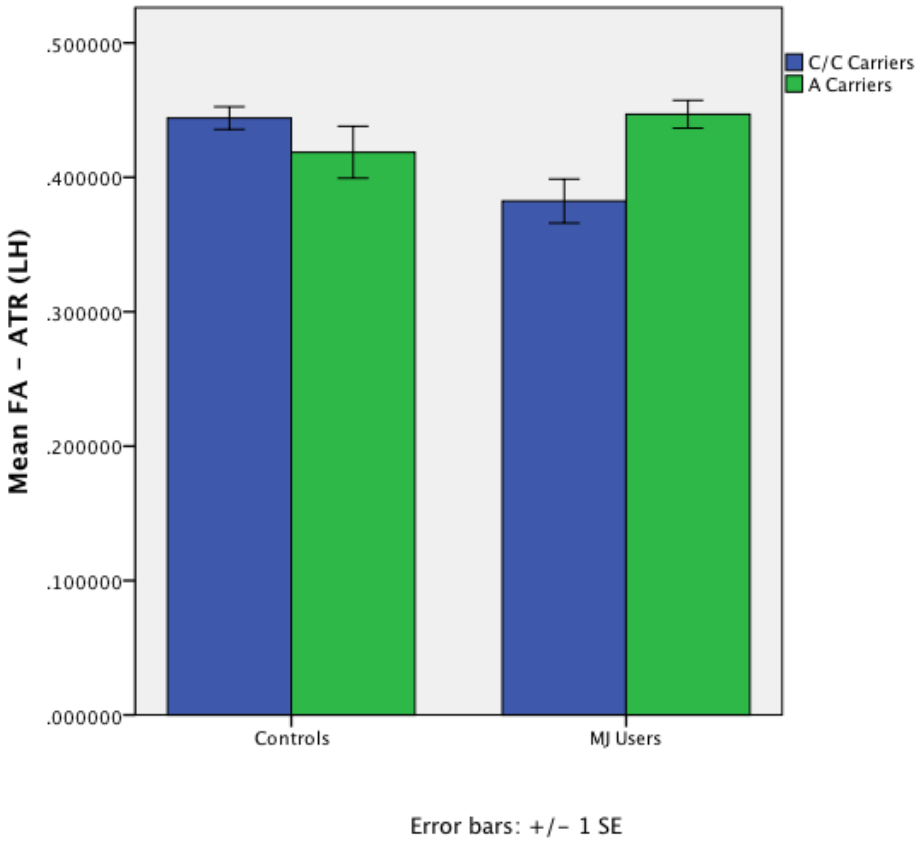

Figure 7. Theoretical Influence of ECS on Brain Complexity.

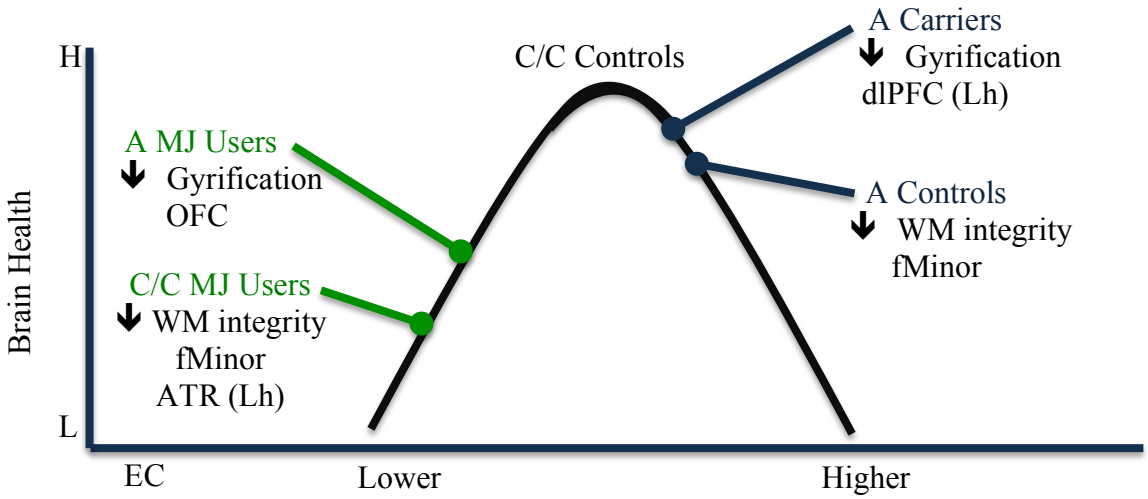

Table 1. Demographic & Substance Use Information According to Group & Genotype.

	MJ Users (n = 37)	Controls (n = 37)	*FAAH* Carrier of A (n = 27)	*FAAH* C/C (n = 47)
Age	21.4 (2.42) [18 – 25]	21.1 (2.3) [18 – 25]	22.07 (2.25)* [18 – 25]	20.74 (2.29)* [18 – 25]
% Female	35.1%	54.1%	51.9%	40.4%
% Caucasian	64.9%	64.9%	44.4%**	76.6% **
FAAH genotype C/C%	42.6%	57.4%		
WRAT-4 Reading Standard Score	102.92 (15.66) [73 – 134]	101.08 (9.97) [81 – 120]	97.04 (10.05)** [80 – 120]	104.85 (13.83)** [73 – 134]
Education	13.32 (1.97) [9–19]	13.84 (1.71) [11 – 18]	13.67 (2.08) [9 – 19]	13.53 (1.73) [11 – 18]
Beck Depression Inventory Total-2	5.11 (3.75)* [0 – 17]	3.43 (3.35)* [0 – 14]	2.93 (2.46)* [0 – 8]	5.04 (3.98)* [0 – 17]
Past year nicotine use	1696.92 (2459.63)** [0 – 7350]	448.35 (1065.31)** [0 – 3680]	775.37 (1182.83) [0 – 3680]	1243.40 (2318.90) [0 – 7350]
Cotinine levels	3.83 (2.4)** [0 – 6]	1.41 (2.11)** [0 – 6]	3.22 (2.53) [0 – 6]	2.24 (2.53) [0 – 6]
Past year alcohol use	277.73 (363.56)** [0 – 1724]	111.43 (168.67)** [0 – 878]	192.26 (331.80) [2 – 1724]	195.91 (273.13) [0 – 1238]
Past year marijuana use	490.62 (746.17)** [4 – 3895]	.84 (2.23)** [0 – 10]	303.19 (445.17) [0 – 1662]	212.72 (645.87) [0 – 3895]
Past year other drug use	8.92 (28.70) [0 – 171]	.12 (.52) [0 – 3]	.89 (2.4) [0 – 12]	6.6 (25.7) [0 – 171]

Notes:* p<.05; ** p<.01.

Table 2. Descriptive Statistics of Local Gyrification Indices According to Group.

	Marijuana Users (n = 37)		Controls (n = 37)	
LGI	M (SD)	Range	M (SD)	Range
Prefrontal Cortex (RH)	2.94 (0.23)	2.63-3.94	3.03 (0.50)	2.48-5.24
Prefrontal Cortex (LH)	2.89 (0.18)	2.56-3.36	2.89 (0.17)	2.47-3.22
DLPFC (RH)	3.58 (0.32)	2.61-4.80	3.44 (0.65)	2.46-6.06
DLPFC (LH)	3.58 (0.30)**	2.69-4.23	3.32 (0.41)**	2.62-4.05
OFC (RH)	2.64 (0.26)*	2.02-3.54	2.80 (0.43)*	2.39-4.80
OFC (LH)	2.58 (0.18)*	2.17-2.93	2.66 (0.21)*	2.39-3.47
mPFC (RH)	2.19 (0.21)**	1.93-2.91	2.55 (0.61)**	1.85-4.58
mPFC (LH)	2.09 (0.19)**	1.82-2.84	2.37 (0.43)**	1.79-3.33
vmPFC (RH)	2.11 (0.23)**	1.72-2.98	2.45 (0.54)**	1.80-4.20
vmPFC(LH)	1.99 (0.17)**	1.76-2.67	2.31 (0.47)**	1.83-3.85
vlPFC (RH)	2.79 (0.28)	2.11-3.65	2.91 (0.46)	2.47-4.93
vlPFC (LH)	2.79 (0.22)	2.34-3.20	2.79 (0.19)	2.41-3.32
Frontal Pole (RH)	2.23 (0.18)*	1.92-2.87	2.42 (0.44)*	1.89-3.81
Frontal Pole (LH)	2.07 (0.16)**	1.74-2.47	2.23 (0.29)**	1.88-2.91

Notes: * p<.05; ** p<.01.

Table 3. Descriptive Statistics of Diffusion Tensor Imaging Values According by Group.

	Marijuana Users (n = 37)		Controls (n = 37)	
DTI	M (SD)	Range	M (SD)	Range
ATR- MD (RH)	0.0008 (0.00007)	0.0007-0.001	0.0008 (0.0001)	0.0003-0.0009
ATR- FA (RH)	0.41 (0.06)	0.26-0.50	0.44 (0.05)	0.28-0.55
ATR- MD (LH)	0.0008 (0.00007)	0.0007-0.001	0.0008 (0.0001)	0.0004-0.001
ATR- FA (LH)	0.41 (0.07)	0.27-0.53	0.44 (0.049)	0.29-0.57
UNC- MD (RH)	0.0009 (0.00008)*	0.0007-0.001	0.0008 (0.0001)*	0.0003-0.001
UNC- FA (RH)	0.38 (0.07)	0.20-0.51	0.40 (0.06)	0.23-0.52
UNC- MD (LH)	0.0009 (0.0001)*	0.0008-0.001	0.0008 (0.0001)*	0.0004-0.001
UNC- FA (LH)	0.36 (0.07)	0.19-0.48	0.40 (0.06)	0.24-0.50
fMinor- MD	0.0009 (0.0001)*	0.0007-0.001	0.0008 (0.0001)*	0.0004-0.001
fMinor- FA	0.48 (0.09)	0.27-0.62	0.51 (0.08)	0.28-0.66

Notes: ATR-Anterior Thalamic Radiation; UNC- Uncinate Fasciculus; fMinor- Corpus Callosum Forceps Minor; * $p<.05$; ** $p<.01$

Table 4. Descriptive Statistics of Neuropsychological Performance by Group & Genotype.

	Neuropsychological Performance		
Group	LNS total M (SD) [range]	PASAT total M (SD) [range]	D-KEFS Color-Word time M (SD) [range]
Marijuana Users	11.68 (2.82) [6-16] (n=37)	36.7 (10.1) [15-57] (n=37)	45.8 (9.77) [27-70] (n=37)
Controls	11.7 (2.72) 8-18 (n=37)	35.6 (12.9) 11-59 (n=36)	47.5 (9.6) 27-73 (n=37)

	Neuropsychological Performance		
FAAH genotype	LNS total M (SD) [range]	PASAT total M (SD) [range]	D-KEFS Color-Word time M (SD) [range]
A carriers	11 (2.11) [7-15] (n=27)	34.4 (12.5) [11-57] (n=26)	50.3 (10.4) [34-70] (n=27)
C/C carriers	12.1 (3.00) [6-18] (n=47)	37.1 (10.9) [15-59] (n=47)	44.6 (8.7) [27-43] (n=47)

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