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Abnormal cerebellar morphometry in abstinent adolescent marijuana users

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Abstract

Background—Functional neuroimaging data from adults have, in general, found frontocerebellar dysfunction associated with acute and chronic marijuana (MJ) use (Loeber & Yurgelun-Todd, 1999). One structural neuroimaging study found reduced cerebellar vermis volume in young adult MJ users with a history of heavy polysubstance use (Aasly et al., 1993). The goal of this study was to characterize cerebellar volume in adolescent chronic MJ users following one month of monitored abstinence.

Method—Participants were MJ users (*n*=16) and controls (*n*=16) aged 16-18 years. Extensive exclusionary criteria included history of psychiatric or neurologic disorders. Drug use history, neuropsychological data, and structural brain scans were collected after 28 days of monitored abstinence. Trained research staff defined cerebellar volumes (including three cerebellar vermis lobes and both cerebellar hemispheres) on high-resolution T1-weighted magnetic resonance images.

Results—Adolescent MJ users demonstrated significantly larger inferior posterior (lobules VIII-X) vermis volume ($p<.009$) than controls, above and beyond effects of lifetime alcohol and other drug use, gender, and intracranial volume. Larger vermis volumes were associated with poorer executive functioning ($p's<.05$).

Conclusions—Following one month of abstinence, adolescent MJ users had significantly larger posterior cerebellar vermis volumes than non-using controls. These greater volumes are suggested to be pathological based on linkage to poorer executive functioning. Longitudinal studies are needed to examine typical cerebellar development during adolescence and the influence of marijuana use.

Keywords

Adolescents; MRI; Cerebellum; Vermis; Cannabis; Alcohol; Drug Effects

1. INTRODUCTION

Marijuana (MJ) (active ingredient *delta*-9-tetrahydrocannabinol or THC) continues to be the most popular illicit drug used among teens, with almost half of 12th graders having tried MJ (Johnston et al., 2008). Early use of MJ, before the age of 15, is particularly problematic, as it increases the risk for developing a substance use disorder (SUD) in the future seven-fold

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(SAMHSA, 2004). Concomitant alcohol and MJ use is common, as 58% of adolescent drinkers also use MJ (Agosti et al., 2002; Martin et al., 1996). Given the high prevalence of MJ use during adolescence, a time of continued neurodevelopment (e.g., Giedd et al., 1996b; Gogtay et al., 2004; Lenroot and Giedd, 2006; Nagel et al., 2006; Pfefferbaum et al., 1994; Sowell et al., 2004), the influence of chronic use of MJ on brain morphometry among teens is of great interest.

Animal and human studies have suggested that the cerebellum may be vulnerable to the effects of chronic MJ exposure (Chang & Chronicle, 2007; Loeber &Yurgelun-Todd, 1999; Quickfall & Crockford, 2006). THC affects the brain via the cannabinoid receptors (CB_1). Animal studies have shown high densities of the CB_1 in many brain regions, including the cerebellum, frontal lobes, basal ganglia, limbic forebrain, hypothalamus, and hippocampus (Iverson, 2003; Herkenham et al., 1990; Herkenham et al., 1991a; Herkenham et al., 1991b; Herkenham et al., 1992; Mackie, 2008; Yoshida et al., 2006), although non-human animals have greater cerebellar CB_1 density than humans (McPartland et al., 2007; Herkenham et al., 1990). Endogenous cannabinoids have inhibitory effects on both excitatory and inhibitory neurotransmitter release, and play an important role in control of neural circuits, such as in the cerebellum (Childers & Breivogel, 1998; Ghozland et al., 2002; Harkany et al., 2008 Iverson, 2003; Pazos et al., 2005; Pistis et al., 2004; Lau & Schloss, 2008; Suárez et al., 2008). More specifically, animal research has suggested a prominent role of the endogenous cannabinoid system as a retrograde messenger in Purkinje cell synapses, the principal cortical neuron in the cerebellum (Suarez et al., 2008; Yamasaki et al., 2006).

The cerebellum plays a pivotal roll in balance and psychomotor speed, as well as language generation, time estimation, rhythm production, inhibition, attention, and associative memory (Allen & Courchesne, 2003; Courchesne et al., 1994; Ivry & Keele, 1989; Leiner et al., 1993; Luna et al., 2001; Mathew et al., 1998; Timmann et al., 2002; Schmahmann & Sherman, 1998). Consistent with this, exposure to exogenous cannabinoids in animals result in motor abnormalities (Adams & Martin, 1996; Iverson, 2003; Rodriguez de Fonseca et al., 1998; Patel & Hillard, 2001) that are at least partially mediated by CB_1 receptor changes in the cerebellum (Casu et al., 2005; Dar, 2000; DeSanty & Dar, 2001).

These animal findings are supported by human neuroimaging studies using functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or single photon emission computed tomography (SPECT). Chronic MJ users have shown abnormal cerebellar or vermis functioning compared to controls (Amen & Waugh, 1998; Block et al., 2000; Block et al., 2002; Bolla et al., 2005; Chang et al., 2006; O'Leary et al., 2000; O'Leary et al., 2002; O'Leary et al., 2003; Sneider et al., 2008; Sneider et al., 2006; Volkow et al., 1996). Behavioral studies on MJ users have also found evidence of cognitive deficits that are thought to be associated with cerebellar functioning. For example, studies have found abnormal time estimation following acute (Hicks et al., 1984; Mathew et al., 1998; McDonald et al., 2003; Lieving et al., 2006) and chronic (Solowij et al., 2002) MJ exposure. Skosnik and colleagues (2008) found abnormalities in classical eyeblink conditioning, which is mediated by the cerebellum, in chronic adolescent and young adult MJ users. With few exceptions (Carlin & Trupin, 1977; Pope et al., 2002; Schaeffer, et al., 1981), studies of adult MJ users have demonstrated deficits in processing speed, attention, and executive functioning (Bolla et al., 2002; Croft et al., 2001; Ehrenreich et al., 1999; Fried et al., 2005; Lyons et al., 2004; Mathew et al., 1998; Messinis et al., 2006; Pope et al., 1997; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Varma et al., 1988; Wadsworth et al., 2006; Whitlow et al., 2004).

Despite behavioral abnormalities implicating the cerebellum, few studies have examined structural brain changes as a result of MJ exposure. One such study found reduced cerebellar vermis volume in young adult MJ users with a history of heavy polysubstance use; however,

these findings may have been due to substantial alcohol consumption in the sample (Aasly et al., 1993). Block and colleagues (2000) did not find significant differences in left or right cerebellar volumes in young adult MJ users as compared to non-using controls.

It is important to note that findings from adult studies may not generalize to youth. The endocannabinoid system continues to develop and modulate neurotransmitter systems during adolescent neurodevelopment (Belue et al., 1995; Viveros et al., 2005). Functional MRI studies have demonstrated differences in cerebellar activity across adolescence (e.g., Luna et al., 2001). Although numerous studies have demonstrated adolescent structural brain maturation in the cortex and subcortical regions (e.g., Giedd et al., 1996; Lenroot and Giedd, 2006; Nagel et al., 2006), including pruning of gray matter and myelination of white matter, comparatively few studies have specifically examined cerebellar development. Giedd and colleagues (1996) did not find significant changes in cerebellar size in boys and girls between the ages of 4-18. In contrast, a later report stated that the cerebellum was one of the latest structures to reach peak volume, at approximately age 16, in 36 mostly male healthy adolescents followed longitudinally from ages 8-19 (Mackie et al., 2007). Consistent with this finding, Castellanos et al (2002) found a slight increase in cerebellar volume from ages 10 to 20, although the changes in late adolescence were modest. Hill and colleagues (2007) found reduced gray matter volume in the cerebellum among older adolescents compared to younger adolescents, suggesting cerebellar gray matter pruning.

Clouding the developmental picture, the cerebellum may be particularly vulnerable to environmental impact. Wallace and colleagues (2006) examined the heritability of brain morphometry in several regions among 5 to 18 year-old monozygotic and dyzygotic twin pairs. The most distinct pattern was found in the cerebellum, which had an additive genetic factor of only.49 compared to .77-.89 in other areas of the cortex. Further, unlike the other brain regions, heritability of cerebellar morphometry did not differ according to age. Therefore, cerebellar development may be more environmentally influenced than other brain regions, possibly rendering the cerebellum vulnerable to environmental exposures such as chronic MJ use.

Despite heavy use during adolescence, few studies have examined the effects of chronic MJ use on the cerebellum during this developmental stage. In human adolescents (Medina et al., 2007), chronic MJ exposure has been associated with cerebellar-related cognitive functions, including slower psychomotor processing speed and poorer executive functioning. Our previous investigation indicated moderately larger prefrontal cortex volumes in MJ-using girls compared to non-using females (Medina et al., In Press). Further, our laboratory found that although adolescent MJ users did not significantly differ from controls in hippocampal volume, hippocampal volume was unrelated to verbal memory unlike in normal controls, and increased MJ use was associated with larger left hippocampal volume (Medina et al., 2007). Using voxel-based morphometry, Jarvis and colleagues (2008) found significantly larger gray matter volumes in the cerebellar vermis in 7 adolescents with bipolar disorder and cannabis use disorders compared to 7 with bipolar disorder alone. No studies to date have focused on cerebellar morphometry in adolescent MJ users without psychiatric comorbidities. Therefore, the goal of the current study was to characterize cerebellar morphometry and cerebellar-associated cognitive functioning in 32 adolescents with and without chronic MJ exposure. The secondary goal was to examine whether gender moderated the effects of MJ exposure on cerebellar morphometry, as was found to be the case for the prefrontal cortex (Medina et al., In Press).

2. METHODS

2.1 Participants

As part of an ongoing study, teens were recruited from local schools via flier distribution (e.g., Medina et al., 2007; Tapert et al., 2007). To assess study eligibility, a comprehensive telephone screen was administered to both adolescents and parents/guardians. Inclusion criteria required that youth were 16-18 years old, fluent in English, and had a parent or legal guardian available to consent (for those under 18) and provide historical data. Exclusionary criteria included: history of chronic medical illness, neurological condition, or head trauma with loss of consciousness >2 minutes; history of DSM-IV Axis I disorder (other than substance use disorder) or use of psychoactive medications; significant prenatal alcohol (≥4 drinks in a day or ≥7 drinks in a week) or drug exposure; complicated delivery or premature birth (<33 weeks gestation); learning disability or mental retardation; first-degree relative with history of bipolar I or psychotic disorders; left-handedness; and sensory problems. If at any time during the 28-day abstinence period a participant reported or tested positive for any substance use, he/she was excluded from study.

Teens were classified into two groups based on MJ use: a MJ using ("MJ user") or a drug-free ("control") group. Criteria for the MJ user group included >60 lifetime MJ experiences; past month MJ use at time of study enrollment; <25 lifetime uses of any drug other than MJ, alcohol, or nicotine; and not meeting criteria for heavy drinking status (Cahalan et al., 1969). Control group classification criteria were: <5 lifetime experiences with MJ (none in the past month), no previous use of any other drug except nicotine or alcohol, and not meeting criteria for heavy drinking status.

2.2 Measures

2.2.1 Detailed Screening Interview—The computerized *DISC Predictive Scales (DPS)* (Lucas et al., 2001) was administered to exclude participants with major psychiatric disorders, including DSM-IV Axis I mood, anxiety, attention deficit hyperactivity and conduct disorders. Parallel modules of the computerized *Diagnostic Interview Schedule* (C-DIS-IV; Robins et al., 1996) were used for 18-year-olds. The *Structured Clinical Interview* (*SCI*) measured psychosocial functioning, last menstruation (for females), health history, and handedness.

2.2.2 Parent Interview—If the teen continued to be eligible, their parent or guardian underwent a detailed screening interview using the parent version of the *SCI*, including information on prenatal, infant, and early childhood development, childhood behavior, medical history, parental socioeconomic status (Hollingshead, 1965), and family history of psychiatric and substance use disorders (Rice et al., 1995). For adolescents younger than 18, the parents/guardians were also administered the parent version of the *DPS*.

2.2.3 Substance Use Interview—Teens were administered the *Customary Drinking and Drug Use Record (CDDR)* to assess past 3-month and lifetime substance use, withdrawal symptoms, DSM-IV abuse and dependence criteria, and substance-related life problems (Brown et al., 1998; Stewart and Brown, 1995). The modified *Time-Line Followback* (TLFB; Sobell and Sobell, 1992) was administered to obtain detailed information regarding type, quantity, and frequency of drug use during the month prior to the monitored abstinence period. Teens were asked frequency of use for each of the following drugs: MJ, alcohol, nicotine, stimulants (cocaine, amphetamine, methamphetamine, ecstasy), opiates (heroin, narcotic pain relievers other than as prescribed), dissociatives/hallucinogens (PCP, mushrooms, LSD, ketamine), sedatives (GHB, barbiturates, benzodiazepines), and misuse of other prescription or over-the-counter medications. Parents were also administered a 28-day *TLFB* to assess youths' recent substance use.

2.2.4. Reading Ability—The Wide Range Achievement Test-3rd Edition Reading Subtest was administered to establish reading ability, which is an estimate of premorbid intelligence, which also reflects quality of education (Wilkinson, 1993).

2.2.5 Executive Functioning—As part of the larger study, all teens completed a neuropsychological battery. A composite variable comprised of executive functioning variables was calculated for the entire sample (*N*=32) using scores from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) Verbal Fluency total correct, Tower total achievement score, and Tower error scores (Medina et al., 2007a; Medina et al., In Press). A second composite variable reflected psychomotor processing speed, which comprised scores from the D-KEFS Trail Making Test Number Sequencing and Letter Sequencing subtest scores. Finally, a 60-second time estimation task was administered (scored as amount of deviation from 60 seconds).

2.3 Procedures

Eligible adolescents were scheduled to begin a monitored abstinence protocol, followed by neuropsychological testing and an MRI session. As part of the abstinence protocol, teens were monitored with supervised urine and Breathalyzer tests every 3-4 days for a period of 4 weeks. Youths with positive urine samples or breath alcohol concentrations or who appeared intoxicated were offered the option of restarting the abstinence procedure at a later time or to discontinue the study. If toxicology results indicated cessation and maintenance of abstinence, the adolescent completed the research battery. Upon completion of the study, youth and parents/guardians received financial compensation for participation.

High-resolution anatomical magnetic resonance images were collected on a 1.5 Tesla GE Signa LX (Milwaukee, WI) system using a sagittally acquired inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence (TR = 2000 ms, TE = 16 ms, FOV = 240 mm, voxel dimensions = 0.9375 × 0.9375 × 1.328 mm, 128 continuous slices, acquisition time = 8:36) (Wong, 2000). Each participant's high resolution anatomical image was manually AC-PC aligned and skull-stripped using a combination of a hybrid watershed and deformable surface semi-automated skull-stripping program (Segonne et al., 2004), followed by manual editing to calculate intracranial volume (ICV). Cerebellar and vermis regions of interest (ROI) were defined manually (see details below) in AFNI (Cox, 1996) by raters who attained high levels of inter-rater reliability (intraclass correlation coefficients >.95) prior to data collection.

2.4 Data Processing

As stated above, all ROIs were manually delineated on 1-mm sagittal 3D image slices. The cerebellar and vermis ROI protocol was developed by KLM based partly on previously published methods (DelBello et al., 1999; Piguet et al., 2006) and atlas boundaries as defined in Schmahmann and colleagues (1999). To delineate the vermis, tracers identified the midsagittal slice within the cerebellum. Three sections of the vermis were traced on a maximum of three slices in each lateral direction (totaling a maximum of 7 slides for each vermis) (similar to DelBello et al., 1999); if the vermis was no longer distinguishable from the cerebellar hemisphere in these three slices, tracing stopped. The vermis was separated into three sections (DelBello et al., 1999; Piquet et al., 2006; Schmahmann et al., 1999): 1) *anterior vermis* included lobules I-IV, the 2) *superior posterior vermis* included lobules VI-VII, and the 3) *inferior posterior vermis* included lobules VIII-X.

More specifically, the *anterior vermis* ROI boundaries included the apex of 4th ventricle, anterior limit of primary fissure (including most white matter), and superior/anterior boundaries of the vermis. The *superior posterior vermis* ROI boundaries included the posterior limit of primary fissure, superior limit of prepyramidal fissure, and the posterior boundary of

the vermis. The inferior posterior vermis ROI boundaries included the inferior limit of the prepyramidal fissure to the apex of 4th ventricle and excluded the cerebellar tonsil. Starting at the midsagittal slice, the *cerebellar hemispheres* were traced laterally; this included the tonsils and excluded the pons and middle cerebellar peduncle. The corpus medullare was included until it clearly became the peduncle. See Figure 1 for midsaggital, axial and coronal slices of these ROI boundaries. All volumes were analyzed as a ratio to overall ICV to control for individual variability in brain size (Giedd et al., 1996b).

2.5 Data Analysis

ANOVAs and chi-square tests compared groups on important demographic and drug use variables. Bivariate correlations between drug use variables, executive functioning, psychomotor speed, time estimation and cerebellar volumes were run. Interpretations of statistical significance were made if $p<.05$.

Because relatively little is known regarding cerebellar development, although substantial neurodevelopment is expected during adolescence, we used polynomial regressions to examine whether linear or quadratic relationships existed between age (centered age entered in block one, and centered age squared entered in block two) and the cerebellar and vermis ROI volumes, after controlling for gender, separately by group. This information was meant to help inform the interpretation of the effects of MJ on cerebellar volume. Due to the cross-sectional nature of the data, these results are viewed as preliminary and need to be replicated in longitudinal studies. Interpretations of statistical significance were made if $p<.05$.

To assess relationships between group status, gender-by-group interactions, and cerebellar volumes, ordinary least squares multiple regressions were run with each of the five cerebellar variables (left hemisphere, right hemisphere, anterior vermis, superior posterior vermis, inferior posterior vermis). The first block entered the following independent variables: group status (MJ-user vs. control), gender, lifetime alcohol use, and lifetime other drug use (any drugs besides alcohol, nicotine or MJ). A group x gender interaction term was entered in the second block. If the interaction term did not significantly contribute to the model, only results from the first block were reported. As a follow-up, regression analyses were run to assess the relationship between cerebellar volumes, group, and cerebellar-by-group interactions in predicting executive functioning, psychomotor processing speed, and time estimation after controlling for gender, lifetime alcohol use, and lifetime other drug use.

3. RESULTS

3.1 Descriptive Comparisons

ANOVAs and chi-squares assessed whether the MJ users and controls differed demographically (n=16/group). The MJ users and controls did not differ on age [average=18.0 years for both groups; $F(1,31)=.12$, $p=.74$]; reading ability [$F(1,31)=.14$, $p=.71$], gender [MJ users: 4 females, 12 males; controls: 6 females, 10 males; $x^2(1)=.52$, $p=.45$], family history of substance use disorders (SUD) [$x^2(2)=3.62$, $p=.16$], or parental total household income [$F(1,31)=.02$, $p=.90$], or ICV [$F(1,31)=.15$, $p=.71$]. While 75% of MJ users and 63% of controls were Caucasian, minority MJ users were 13% multiple ethnicities, 6% Pacific Islander, and 6% “other,” while minority controls were 37% Asian-American [$x^2(4)=10.18$, $p=.04$] (see Table 1).

Abstinence was monitored with urine toxicology screens and Breathalyzer tests, and participants were abstinent from all drugs for at least 30 days prior to scanning. Light to moderate alcohol use was permitted, but participants with self-reported binge drinking (≥4 drinks for females or ≥5 drinks for males within a day) or biological evidence of alcohol use

during this time were excluded. On average, MJ users had used marijuana for 3.4 years (±1.7, range= 0.8-6.7), and had greater lifetime MJ [$F(1,31)=50.0$, $p=.0001$] and alcohol use than controls [$F(1,31)=22.6$, $p=.0001$]. No control had used any drug besides alcohol or marijuana, but MJ users had used other drugs an average of 7 times in their lives [$F(1,31)=10.42$, $p=.003$] (see Table 1). The average abstinence from any alcohol use for MJ users was 44 days (±61, range=9-270 days) and 132 days (±130, range=30-365 days) for controls. Average other drug abstinence for the MJ users was 107 days (±33, range=30-300 days).

3.2 Cerebellar Morphometry

Among controls, girls had larger right [*beta* = −.58, $p < .02$] and total [*beta* = −.51, $p < .04$] cerebellar hemisphere volumes than boys after controlling for ICV, although it is important to note that there were only 4 girls in the sample. After controlling for gender, there was a significant quadratic [*beta* = .76, $p < .02$] relationship between age and right hemisphere cerebellar volume and significant linear [*beta* = .75, $p < .02$] and quadratic [*beta* = .76, $p < .02$] associations between age and left hemisphere cerebellar volume. Total cerebellar volume was significantly predicted by both linear [*beta* = .67, $p < .03$] and quadratic [*beta* = .78, $p < .02$] age terms. Age did not predict vermal volumes in the controls. Among MJ users, there were no significant linear or quadratic relationships between age and any of the regional cerebellar volumes. As seen in Figure 2; cerebellar volumes peaked around age 17.5-18.0.

3.3 Primary Findings: Predicting Cerebellar Volumes

After controlling for gender, lifetime alcohol and other drug use, group status (MJ users vs. controls) was associated with larger posterior inferior vermal volumes [*beta* = .66, $p < .009$], but not any other cerebellar or vermis region of interest (p's >.05) (see Figure 3). In contrast, increased alcohol use was associated with smaller posterior inferior vermal volumes [*beta* = −.51, $p < .04$]. (See Figure 4 for bivariate relationships between alcohol use and inferior posterior vermis volume by group.) There were no significant group-by-gender interactions in predicting cerebellar volumes (p's >.05). Gender significantly predicted anterior vermis [*beta* = −.46, $p < .02$], posterior superior vermis [*beta* = −.46, $p < .02$], and posterior inferior vermis [*beta* = −.47, $p < .02$]; in all cases being female was associated with larger vermal volumes. Other drug use was not associated with cerebellar volumes in this sample (p's >.05).

3.4 Brain-Behavior Relationships

3.4.1 Executive Functioning—Independent of group status, gender, alcohol and other drug use, smaller anterior [*beta* = −.39, $p < .04$] and posterior inferior [*beta* = −.60, $p < .001$] vermis volumes were associated with superior executive functioning in this sample of adolescents; there were no significant group-by-cerebellar volume interactions in predicting executive functioning (see Figure 5).

3.4.2 Psychomotor Speed—No significant relationships were seen between cerebellar volume and psychomotor speed. Group-by-cerebellar volume interactions were also non-significant.

3.4.3 Time Estimation—No main or interactive effects for cerebellar volumes were seen in predicting time estimation performance.

4. DISCUSSION

Marijuana (MJ) is the most commonly used drug during adolescence (Johnston et al., 2008). Chronic MJ exposure during this stage of ongoing neuromaturation (e.g., Giedd et al., 1996b; Gogtay et al., 2004; Lenroot and Giedd, 2006; Sowell et al., 2004) may result in abnormal brain structure. In human adolescents, chronic MJ exposure has been associated with

slower psychomotor processing speed and poorer executive functioning (Medina et al., 2007), two areas of cognition associated with cerebellar function. This is the first study to date to examine manually defined cerebellar regions of interest in adolescent MJ users and controls without comorbid psychiatric disorders. After one month of abstinence, adolescent MJ users demonstrated significantly larger inferior posterior (lobules VIII-X) vermis volumes than non-using controls. Larger vermal volumes were associated with poorer executive functioning, suggesting that the larger volumes seen in the MJ users may be an indicator of pathology. Gender did not moderate the effects of MJ use on cerebellar structure, although the girls generally demonstrated relatively larger cerebellar volumes compared to the boys.

These findings are consistent with Jarvis and colleagues (2008), who found increased gray matter vermis volumes in adolescents with comorbid bipolar disorder and cannabis use disorders compared to bipolar alone patients. Abnormalities in inferior posterior vermis have also been found in patients with multiple episodes of depression compared to first episode patients and healthy volunteers (DelBello et al., 1999) as well as in adolescents with attention deficit hyperactivity disorder (Berquin et al., 1998; Bussing et al., 2002; Hill et al., 2003; Mostofsky et al., 1998). Other studies have also linked the vermis lobes to affect regulation and attention (see Schahmann et al., 2000 for review). Given the increased sub-clinical depressive symptoms (Medina et al., 2007b) and poor complex attention (Medina et al., 2007a) in adolescent MJ users, future studies are needed to assess the role of the vermis on affective processing and attention in adolescent MJ users.

Within the controls, we found significant linear and quadratic relationships between age and total cerebellar hemisphere volumes in this cross-sectional sample. Younger teens had larger cerebellar volumes than older teens, suggesting a late peak (approximately 17.5 years old) in cerebellar volumes with pruning in the latter teen years. However, our sample included more older than younger teens. This finding is consistent with prior research suggesting slight increases in cerebellar volume until the later teen years followed by pruning in late adolescence/early adulthood (Castellanos et al., 2002; Hill et al., 2007; Mackie et al., 2007). Consistent with Giedd and colleagues (1996), we did not find a relationship between age and vermal volumes, which may be because the cerebellum appears particularly vulnerable to environmental impact (Wallace et al., 2006); therefore, individual differences in vermis volume during the adolescent stage may be more due to lifestyle (i.e., smoking MJ or using other drugs such as alcohol) than innate programmatic neurodevelopment. It is notable that findings were primarily driven by the boys in this cross-sectional sample and need to be replicated in larger, longitudinal studies including both males and females.

Given the possibility of ongoing pruning in the cerebellum during late adolescence, one possible interpretation of increased inferior posterior vermal volumes in the MJ users is that chronic MJ exposure interrupts healthy gray matter pruning process. This would be consistent with our other structural findings indicating that increased MJ use is associated with larger left hippocampal volumes, greater left vs. right hippocampal asymmetry (Medina et al., 2007c), and increased PFC volumes in females (Medina et al., in press). Although the mechanism underlying healthy gray matter pruning is unknown, endogenous endocannabinoids have a role in regulating synaptic activity and neuronal plasticity (e.g., affecting brain derived neurotrophic factor, TrkB signaling, Wnt ligands, and glutamate release) (see Harkany et al., 2008a; 2008b). Further, recent findings suggest astrocytes mediate neuronal release of the C1q protein, which in turn tags neurons with weak synaptic connections (Stevens et al., 2007) and chronic cannabinoid exposure is associated with astrocytic dysfunction (Bindukumar et al., 2008). Therefore, chronic exposure to MJ may disrupt the endogenous cannabinoid system (Casu et al., 2005; Dar, 2000; DeSanty & Dar, 2001), interrupting its role in synaptic pruning and leading to poorer executive functioning in adolescent MJ users (Medina et al., 2007a). Other possible mechanisms include alterations of other neurotransmitter systems (Childers & Breivogel,

1998; Ghozland et al., 2002; Harkany et al., 2008 Iverson, 2003; Pazos et al., 2005; Pistis et al., 2004; Lau & Schloss, 2008; Suárez et al., 2008), changed cerebral blood flow in the cerebellum (Block et al., 2000; Herning et al., 2005; Mathew et al., 1998; O'Leary et al., 2003; O'Leary et al., 2007; Sneider et al., 2008; Volkow et al., 1996) or vasoconstriction (Herning et al., 2001), which may lead to morphological alterations.

In this sample of adolescents, significant relationships were observed between cerebellar vermis volumes and executive functioning, which is consistent with diffusion tensor imaging and functional connectivity/fMRI studies demonstrating connectivity between the cerebellum and the PFC (Allen et al., 2005; Leh et al., 2007; Rubia et al., 2007; Luna et al., 2001; Neufang et al., 2008). Although psychomotor differences were seen in a larger sample of adolescent MJ users (Medina et al., 2007), a lack of relationship between psychomotor processing speed and cerebellar volumes may indicate that psychomotor speed in these adolescents is mediated primarily by the basal ganglia (Egerton et al., 2005; Iverson 2003; Rodriguez de Fonseca et al., 1998), a brain region that has greater CB_1 receptor binding compared to the cerebellum in humans (Burns et al., 2007). Inconsistent with prior adult research (Solowij et al., 2002), we did not observe time estimation differences in this sample of adolescent MJ users. This may be due to differences in methodology; Solowij and colleagues utilized a time estimation method where participants had to estimate how long it took to complete a task. In contrast, we had the adolescents estimate when 60 seconds have passed. Therefore, differences in time estimation may not be seen on this relatively easy time estimation procedure.

Consistent with prior adult (e.g., Sullivan & Pfefferbaum, 2009) and prenatal alcohol exposure (O'Hare et al., 2005) findings, increased alcohol use was associated with smaller vermis volumes. However, this is in contrast to DeBellis and colleagues (2005), who did not find vermis volume differences in adolescents with and without alcohol use disorders. This may be due to differences in defining the vermal ROIs; DeBellis et al. (2005) combined all lobes of the vermis while the current study differentiated three distinct regions and only found differences in the inferior posterior vermis. It is notable that MJ and alcohol effects were in the opposite directions, which we also found in the hippocampus (Medina et al., 2007) and PFC (Medina et al., in press) in adolescent MJ users. Further, nicotine use in combination with alcohol use has been associated with vermal metabolite levels (Durazzo et al., 2004). Therefore, future research is needed to examine the effects of *combined use* of alcohol, nicotine, and MJ use on the cerebellum. For example, animal research has shown that a CB_1 agonist (WIN-55212) decrease GABA release in cerebellar purkinje neurons and Win-5512 administration blocked ethanol-induced GABA release (Kelm et al., 2008). In contrast, the cannabinoid antagonist AM-251 did not reduce ethanol-induced GABA release (Kelm et al., 2007).

Limitations of this study are important to consider. It is difficult to disentangle possible preexisting differences from specific drug effects (Aytaclar et al., 1999; Nigg et al., 2004; Ridenour et al., in press). The current sample had strong internal reliability as it excluded individuals with Axis I comorbid disorders such as conduct disorder and attention-deficit hyperactivity disorder, and groups were well-matched on family history of SUD, education, parental income status, and reading ability. Still, subclinical attentional and mood symptoms may predate substance use. Further, as previously mentioned, the current sample was relatively small and primarily male. Finally, due to unreliable parcellation of white matter and CSF from gray matter with these T1 MRI images, we were not able to confirm that vermis volume differences were primarily driven by the gray matter; additional research segmenting gray from white matter is needed to examine the effects of MJ use on gray matter pruning and white matter integrity. The latter could be examined further with diffusion tensor imaging.

In conclusion, after one month of abstinence, MJ users demonstrated significantly larger inferior posterior vermis volumes compared to controls. Given that larger vermis volumes were associated with poorer executive functioning, this is preliminary evidence of a pathological process affecting vermis morphometry in MJ users. Longitudinal research is needed to explore both normal cerebellar development during adolescence and the influence of chronic early MJ use on adolescent neurodevelopment.

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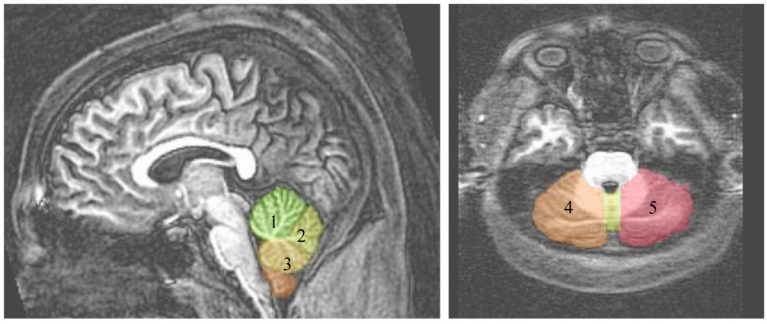

Figure 1.
Midsagittal and axial sections of three vermis (1=anterior vermis, 2=superior posterior vermis, 3=inferior posterior vermis) and two cerebellar hemisphere (4=right hemisphere, 5=left hemisphere) boundary delineations.

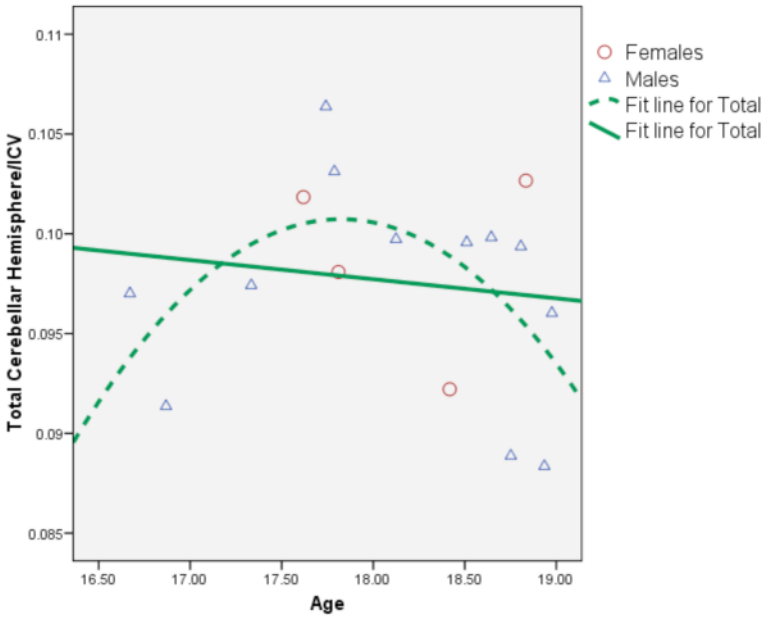

Figure 2.
Scatterplot demonstrating significant linear (p<.03) and quadratic (p<.02) relationships between age and cerebellar hemisphere volumes in the healthy controls (n=16).

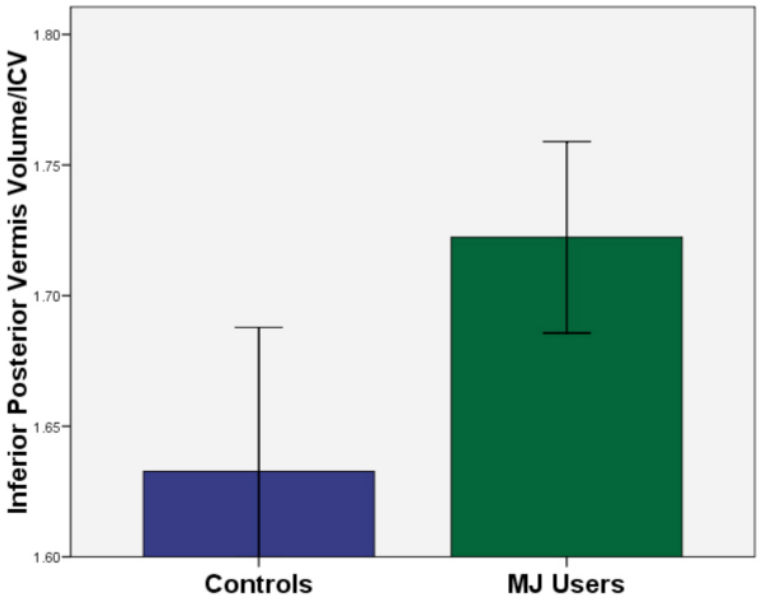

Figure 3.
Mean (+/− 1 SE) inferior posterior vermis volume/ICV by group (MJ group status significantly predicted inferior posterior vermis volume/ICV after controlling for gender, alcohol and other drug use; N=32, p<.009).

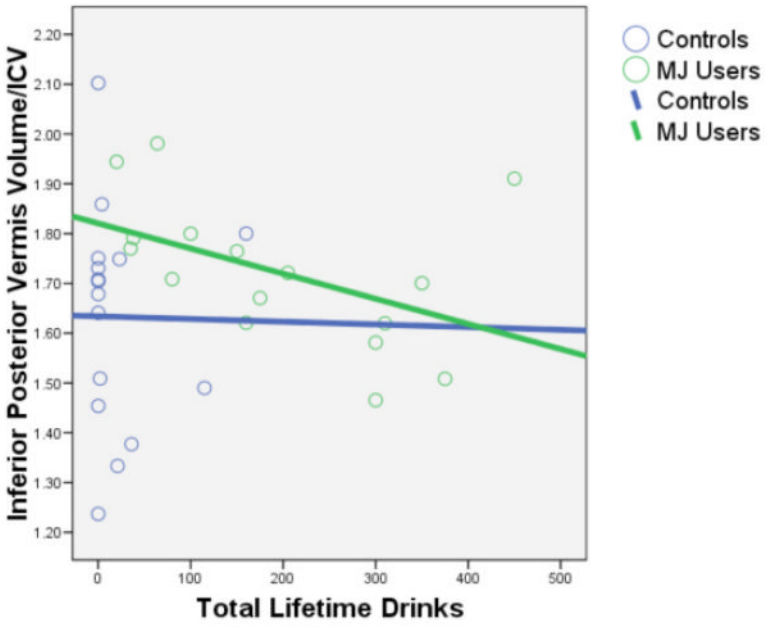

Figure 4.

Bivariate scatterplot between the inferior posterior vermis volume/ICV and total lifetime alcohol drinks by group. Lifetime alcohol use significantly predicted inferior posterior vermis volume/ICV after controlling for MJ use, other drug use, and gender (N=32, p<.04).

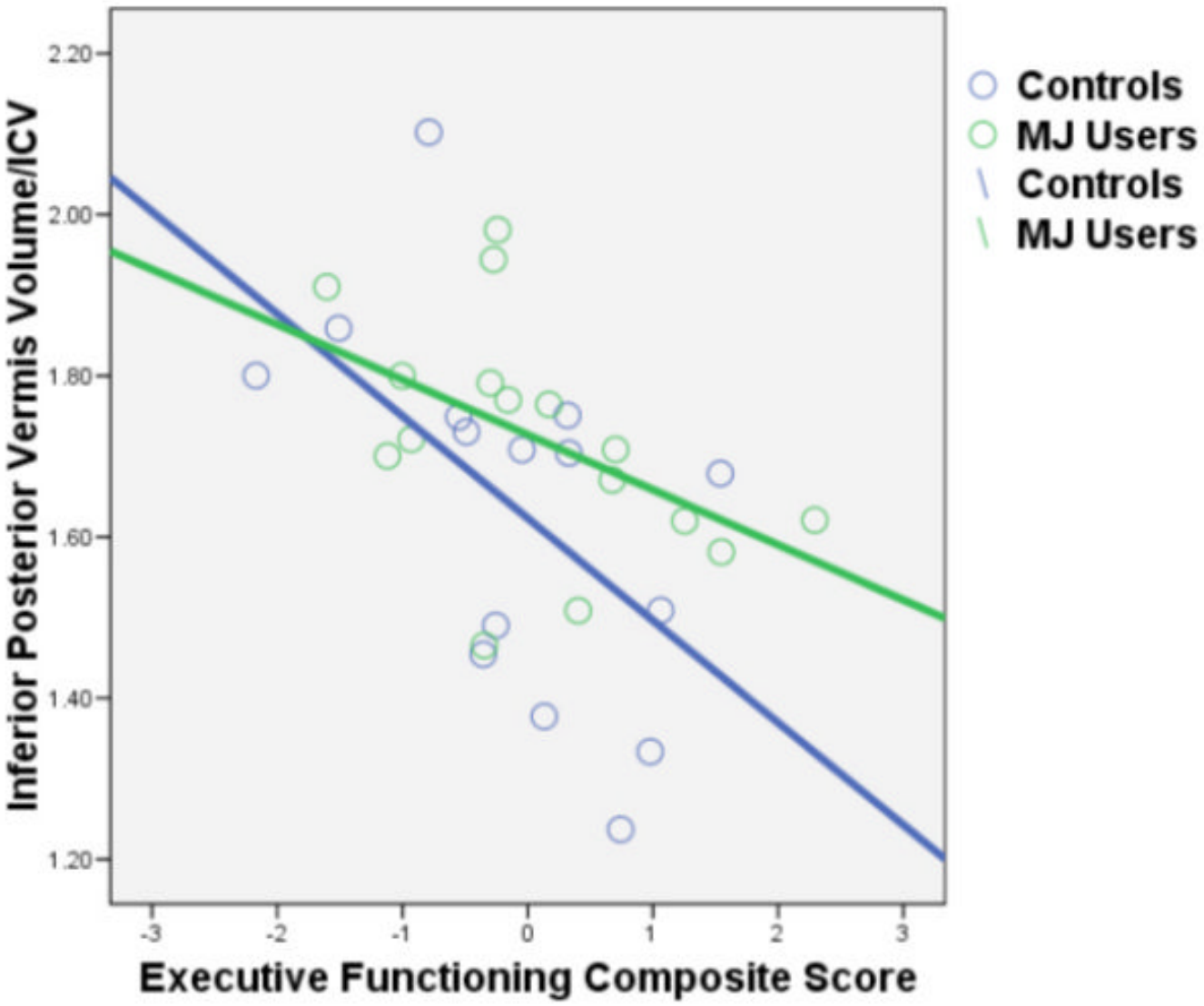

Figure 5.
Bivariate scatterplot between the inferior posterior vermis volume/ICV and executive functioning composite score by group. Executive functioning predicted inferior posterior vermis volume after controlling for MJ group status, gender, alcohol and other drug use (*N*=32, *p*<.001).

Table 1
Demographic, substance use, and cerebellar volume variables by group

	MJ Users (*n*=16) % or M±SD	Controls (*n*=16) % or M±SD
Gender (male)	75%	63%
Ethnicity (Caucasian) *	75%	63%
Age	18±0.7	18±0.9
Reading standard score (WRAT-3)	107±6	106±9
Lifetime alcohol use (episodes) *	195±137	23±47
Lifetime marijuana use (episodes) *	476±269	1±1
Lifetime other drug use (episodes)*	7±9	0±0
Intracranial volume (cc^3)	1492.88 ± 108.39	1476.22±137.50
Right cerebellar hemisphere (cc^3)	48.7±3	46.86±2.83
Left cerebellar hemisphere (cc^3)	48.9±3	47.27±2.97
Anterior vermis (cc^3)	2.34±0.25	2.50±0.37
Posterior superior vermis (cc^3)	1.37±0.27	1.37±0.33
Posterior inferior vermis (cc^3)	1.72±0.15	1.63±0.22

* $p<.05$.