Title

Depressive symptoms in adolescents: associations with white matter volume and marijuana use

Journal

Journal of Child Psychology and Psychiatry, 48(6)

ISSN

0021-9630

Authors

Medina, Krista Lisdahl
Nagel, Bonnie J
Park, Ann
et al.

Publication Date

2007-06-01

Peer reviewed

Depressive Symptoms in Adolescents:

Associations with White Matter Volume and Marijuana Use

Krista Lisdahl Medina, Ph.D. [2,3], Bonnie J. Nagel, Ph.D. [2,3], Ann Park, B.A.[3],

Tim McQueeny, B.A.[3], & Susan F. Tapert, Ph.D. [1,2,3]

[1] Veterans Affairs San Diego Healthcare System

[2] Department of Psychiatry, University of California, San Diego

[3] Veterans Medical Research Foundation, San Diego, CA

Correspondence: Susan F. Tapert, Ph.D., 3350 La Jolla Village Drive (151B), San Diego, CA 92161, Phone: (858) 552-8585 x2599. Fax: (858) 642-6474. stapert@ucsd.edu.

ABSTRACT

Background. Depressed mood has been associated with decreased white matter and reduced hippocampal volumes. However, the relationship between brain structure and mood may be unique among adolescents who use marijuana heavily. The goal of this study was to examine the relationship between white matter and hippocampal volumes and depressive symptoms among adolescent marijuana users and controls.

Methods. Data were collected from marijuana users (n=16) and demographically similar controls (n=16) aged 16-18. Extensive exclusionary criteria included psychiatric and neurologic disorders, including major depression. Substance use, mood, and anatomical measures were collected after 28 days of monitored abstinence.

Results. Marijuana (MJ) users demonstrated more depressive symptoms than controls (p<.05). MJ use (β= .42, p<.005) and smaller white matter volume (β= -.34, p<.03) each predicted higher levels of depressive symptoms on the *Hamilton Depression Rating Scale*. MJ use interacted with white matter volume (β= -.55, p<.03) in predicting depression scores on the *Beck Depression Inventory*: among MJ users, but not controls, white matter volume was negatively associated with depressive symptoms.

Conclusions. Marijuana use and white matter volume were additive and interactive in predicting depressive symptoms among adolescents. Subtle neurodevelopmental white matter abnormalities may disrupt the connections between areas involved in mood regulation.

Keywords: Adolescence; Depression; Cannabis; Neuroimaging; MRI; White Matter; Hippocampus

INTRODUCTION

Depressive disorders have been associated with morphological brain abnormalities, although the majority of studies have been conducted in adults. Reduced hippocampal volumes have been found among depressed adults (Campbell et al., 2004; Frodl et al., 2002; Videbech and Ravnkilde, 2004), although this may be associated with age of onset (Lloyd et al., 2004) and one found no hippocampal differences (Hastings et al., 2004). White matter abnormalities (e.g., hyperintensities) have also been associated with increased depressive symptoms and suicidality in adult populations (Erlich et al., 2005; Firbank et al., 2005; Heiden et al., 2005; Taylor et al., 2004).

Due to adolescent neuromaturation, which includes pruning of gray matter and proliferation of white matter, these adult results cannot be generalized to depressed adolescents (Benes, 1998; Sowell et al., 1999). Three studies including depressed children and adolescents found no significant differences in hippocampal volumes (DeBellis et al., 2002), although one did report larger amygdala-hippocampus ratios (MacMillan et al., 2003) and another reported reduced amygdale volumes (Rosso et al., 2005). White matter hyperintensities have also been found among depressed children and adolescents (Lyoo et al., 2002). Further, one study found that depressed adolescents had smaller overall and frontal white matter volumes compared to healthy controls (Steingard et al., 2002).

To make matters more complicated, marijuana use is highly prevalent among adolescents; nearly half (46%) of high school seniors have tried it during their lifetime (Johnson et al., 2004). Further, marijuana use appears moderately associated with an increased risk of depressive symptoms in both adults and adolescents (see Degenhardt et al., 2003). While some longitudinal studies found no or weak links between marijuana use and depression (Fergusson et al., 1997; Kandel, 1984), recent studies have shown that heavy marijuana use during adolescence

is associated with later risk for depressive symptoms (Arseneault et al., 2002; Bovasso, 2001; Brook et al., 2002; Green and Ritter, 2000; Fergusson et al., 2002; Patton et al., 2002).

There are several possible explanations for the link between major depressive disorders and chronic marijuana use. The endogenous cannabinoid system is widely distributed throughout the central nervous system, including the prefrontal and hippocampal regions (Iversen, 2003), as well as white matter areas (Romero et al., 1997; Romero et al., 2002). Although animal studies have suggested cellular effects, especially in hippocampal regions (Childers and Breivogel, 1998; Pistis et al., 2004; Stiglick and Kalant, 1985), and despite developmental changes to the endogenous cannabinoid system during adolescence (Romero et al., 1997; Belue et al., 1995), no studies to date have examined structural brain changes associated with marijuana use among human adolescents (Verdejo-Garcia et al., 2004). Adult animal models suggest that damage to the cannabinoid system, specifically to the CB1 receptors, results in depressive-like symptoms in mice (Martin et al., 2002). Adult human studies utilizing magnetic resonance imaging have yielded conflicting results, with two studies finding gray and white matter abnormalities among young adult marijuana polydrug users (Aasly et al., 1993; Matochik et al., 2005) and one study found no differences (Block et al., 2000). Wilson and colleagues (2000), found that adult participants who had used marijuana before age 17 had smaller gray matter and larger white matter volumes compared to later-onset users.

In sum, because marijuana may disrupt adolescent neurodevelopment (Wilson et al., 2000), including the developing endogenous cannibinoid system (Romero et al., 1997; Belue et al., 1995), previous findings among depressed adolescents without comorbid substance use cannot necessarily be generalized to the rather sizeable population of marijuana users (e.g., Tapert & Brown, 1999; Tapert et al., 2002). Therefore, the goals of the present study were to examine: 1) the relationship between white matter and hippocampal volumes and depressive

symptoms and 2) whether marijuana use moderates the relationship between brain structure and depressive symptoms in a sample of thirty-two adolescents.

METHOD

Participants

Adolescents were recruited from high schools, universities, and through ads. All youth were between 16 to 18 years old, fluent in English, and had a parent/guardian available to consent and provide history. Other comprehensive *exclusionary* criteria included: psychotropic medication use; history of DSM-IV Axis I disorder (other than substance use); LOC >2 minutes; serious medical illness; learning disability/mental retardation; significant maternal drinking or drug use during pregnancy; complicated birth (<33 weeks); parental history of bipolar I or psychotic disorders; left handedness; vision or hearing problem; and MRI contraindications. Finally, any youth with data suggestive of substance use in the 28 days prior to the session were excluded from analyses.

All participants and, if under age 18, their parent/guardian, underwent written informed consent and, for minors, assent in accordance with the UCSD IRB. Of those eligible, data were collected from sixteen marijuana using ("MJ-users") and sixteen drug-free adolescents ("controls"). MJ-users took marijuana at least 60 times in their lifetime, did not meet criteria for Heavy Drinker status (Cahalan et al., 1969), and did not use substances other than marijuana, alcohol, or nicotine > 25 times in their lifetime. Controls never met criteria for Heavy Drinker, had < 5 experiences with marijuana, and never used any other drug besides nicotine.

Measures

Youth History. The Structured Clinical Interview (SCI) was used to measure psychosocial functioning. The computerized NIMH Diagnostic Interview Schedule for Children was also

administered (C-DISC-4.0; Shaffer et al., 2000), which reliably diagnoses major psychiatric disorders in adolescents. Parallel modules of the Computerized Diagnostic Interview Schedule (Robins et al., 1996) were used for any 18-year-olds who lived independently (Thompson et al., 1996).

Youth Drug Use. Youth were administered the Customary Drinking and Drug use Record (CDDR) to assess frequency of lifetime and past 3-month use, and DSM-IV abuse and dependence criteria (Brown et al., 1998; Stewart and Brown, 1995). To more closely examine frequency of drug use during the past 60 days, the Time-Line Followback (TLFB) was utilized (Sobell et al., 1979; Sobell and Sobell, 1992). The following drug categories were assessed by both instruments: marijuana, alcohol, nicotine, stimulants (cocaine, amphetamine, methamphetamine, MDMA), opiates (heroin, morphine, opium), hallucinogens (PCP, mushrooms, LSD, ketamine), sedatives (GHB, barbiturates, benzodiazepines), and prescription/ OTC medications.

Parent Interview. To corroborate the youth's information, parents were administered the parent version of the SCI and the parent version of the C-DISC-4.0. In addition, the parents/guardians were given the TLFB to corroborate youth reports of alcohol and drug use for the past 60 days.

Depressive Symptoms. The *Beck Depression Inventory* (*BDI;* (Beck et al., 1988) and *Hamilton Depression Rating Scale* (*HAM-D;* Hamilton, 1986) assessed current mood. The BDI is a 21-item self-report questionnaire that measures depressive symptoms over the previous two weeks; the BDI has been used previously with adolescents (Bennet et al., 1997). The HAM-D, which has also been used with adolescents (e.g., Nixon et al., 2001), is a 26-item semi-structured interview that assesses depressive symptoms during the previous 7 days.

Procedures

Trained laboratory assistants administered the youth screening interviews to assess the aforementioned inclusion and exclusion criteria. Parents or guardians of youth were then contacted. Parents and youth were informed that they would not receive information regarding each other's responses or test results. If still eligible, potential youth and parent/guardians were administered a detailed interview assessing demographic and psychosocial functioning, Axis I psychiatric disorders, and drug use history. To improve open disclosure, different lab assistants interviewed the parent and youth. If eligible, they were scheduled to begin the monitored abstinence protocol.

The youth were monitored with supervised urine and breath samples every 3-4 days for 28 days. If all toxicology tests were negative, the youth was scheduled for psychological evaluation and imaging. These sessions included a brief questionnaire and interview (including the depressive measures), neuropsychological evaluation, hair sample toxicology to confirm the urine toxicology results, and magnetic resonance imaging (MRI). Of eligible MJ-using youth who initiated monitored abstinence, 29% had data suggesting substance use during the 28-day period. Youth who did not maintain abstinence were discontinued and compensated for their time. Upon completion of the study, youth and parents/guardians received financial compensation.

Imaging

Imaging data were acquired on a 1.5 Tesla General Electric Signa LX 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 x 0.9375 x 1.328 mm, 128 continuous slices, acquisition time = 8:36) (Wong, 2000).

Data Processing and Analysis

Removal of non-brain materials from each T1-weighted 3D anatomical dataset used a combination of a hybrid watershed and deformable surface semi-automated skull-stripping program (Segonne et al., 2004) and manual editing. All manual editing was performed in AFNI (Cox, 1996) by trained assistants blind to participant characteristics who attained high levels of inter- and intra-rater reliability (intraclass correlation coefficients >.90) prior to data collection. Next, fully skull-stripped T1 anatomical images were processed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's automated segmentation tool (FAST) (Zhang et al., 2001). Utilizing a hidden Markov random field model and an associated expectation-maximization algorithm, this automated program was used to segment the white matter of the brain from other tissue types (see Figure 1).

Insert Figure 1 About Here

Hippocampal regions of interest were manually traced on contiguous 1.3 mm slices in the coronal plane through the structure (see Nagel et al., 2005) by trained assistants blind to participant characteristics (ICC >.90). Briefly, the stereotactic boundaries were as follows: anterior: coronal slice through the fullest portion of the mammillary bodies; superior/lateral: temporal horn and alveus; inferior: white matter of the parahippocampal gyrus; medial: ambient cistern; posterior: columns of the fornix. All volumes were analyzed as a ratio to overall intracranial volume (ICV) to control for individual variability in brain size (Giedd et al., 1996).

The primary analysis included three series of multiple regressions that tested whether white matter or hippocampal (right and left) volume was significantly associated with depressive symptoms after controlling for marijuana use group status, gender, alcohol use, and interactions between group and white matter/hippocampal volume. Specifically, three regressions testing the

relationship between each independent variable of interest [overall white matter volume/ICV, left hippocampal volume/ICV, or right hippocampal volume/ICV] and each dependent variable (BDI and HAM-D) were run, totaling six regressions. BDI and HAM-D scores were log-transformed to adhere to linear regression assumptions. Independent variables were entered first as a block (standard entry): white matter or hippocampal volume, group, lifetime alcohol use, and gender. Interactions between brain volume and group were then entered as a second block.

RESULTS

Group Comparisons

Demographics. ANOVAs and chi-squares tested whether the MJ-users and controls differed demographically. The MJ-users and controls (n=16/group) did not differ significantly in age [average=18.0 years, range 16.0-18.9; $F(1,31)=.12$, $p=.74$]; WRAT-3 (Wilkinson, 1993) Reading standard score [MJ-users 106.7 mean±6.4 SD, range 98-119; controls 106.0±8.6, range 85-116; $F(1,31)=.14$, $p=.71$], or gender composition [MJ-users 4 females, 12 males; controls 5 females, 11 males; $x^2(1)=.16$, $p=.69$]. However, groups differed in ethnic identification [$x^2(4)=10.18$, $p=.04$]: MJ-users were 75% Caucasian, 13% multiple ethnicities, 6% Pacific Islander, and 6% "other," while controls were 63% Caucasian and 37% Asian-American (see Table 1).

White Matter/Hippocampal Volume. The MJ-users and controls did not significantly differ in their intracranial volume (ICV) [$F(1,31)=.15$, $p=.71$], white matter volume/ICV [$F(1,31)=.60$, $p=.44$], left hippocampal volume/ICV [$F(1,31)=2.0$, $p=.16$], or right hippocampal volume/ICV [$F(1,31)=.26$, $p=.61$]. (See Table 1 for raw values.)

Drug Use. All participants were abstinent from all drugs for a minimum of 28 days (light to moderate alcohol use may have occurred because breathalyzer tests were given only every 3-4 days; participants who self-reported binge drinking were excluded). The average length of

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 length of abstinence from all other drugs for the MJ-users was 107 days (±33, range=30-300 days). MJ-users reported more lifetime episodes of MJ use than controls [MJ-users 475.6±268.5, range 60-1000; controls 0.6±1.4, range 0-5; $F(1,31)=50.0$, $p=.0001$]. On average, the MJ-users had used marijuana for 3.4 years (±1.7, range= 0.8-6.7). MJ-users also had more lifetime episodes of alcohol consumption than controls [MJ-users 194.5±136.8, range 20-420; controls 22.6±46.9, range 0-160; $F(1,31)=22.6$, $p=.0001$]. No control had used any drug besides alcohol or marijuana, but MJ-users had used other drugs an average of 6.9 times [±8.6, range 0-25; $F(1,31)=10.42$, $p=.003$] (see Table 1).

Depressive Symptoms. In general, MJ-users reported marginally higher scores on the BDI [MJ-users 4.6±7.0, range 0-20; controls 1.3±2.0, range 0-6; $F(1,31)=3.4$, $p=.08$] and significantly greater scores on the HAM-D [MJ-users 4.0 ±5.9, range 0-21; controls 1.0±2.0, range 0-8; $F(1,31)=4.2$, $p=.05$]. Compared to published norms (Beck et al., 1996; Bennet et al., 1997), 0% of controls and 19% of MJ-users were clinically elevated (>13) on the BDI. On the HAM-D, 6% of controls and 13% of MJ-users evidenced mild symptoms (scores 7-17) and 6% of MJ-users reported moderate (>18) depressive symptoms (Nixon et al., 2001).

Insert Table 1 About Here

Bivariate Relationships

Table 1 shows correlations between the demographic variables, brain volumes, and depressive measures for each group. Effect sizes (Cohen, 1988) reflecting the magnitude of the difference between correlation coefficients (with equal sample sizes) revealed that the correlations between white matter volume and BDI scores ($q=.89$, large effect size) and HAM-D

scores (q=.22, small effect size) were stronger among the MJ-users compared to controls. All other effect sizes were not significant (q<.10).

Multivariate Relationships

As stated earlier, a series of regressions (predictors: gender, group, alcohol use, white matter or left/right hippocampal volume, and group-by-brain volume interaction term) was run to predict depressive symptoms on the BDI and HAM-D.

Predictor: White Matter Volume. When predicting BDI scores, there was a significant interaction between group membership and white matter volume (*beta* = -.59, p = .03) indicated that, among MJ-users only, smaller white matter volume was associated with higher depressive scores. For the HAM-D, *s*maller white matter volume was significantly associated with higher levels of depressive symptoms among all the adolescents (*beta* = -.34, p = .03; see Figures 2 and 3). MJ-users (*beta* = .42, = < .04), and all female adolescents (*beta* = -.42, p = .01) reported higher scores on the HAM-D.

Predictor: Hippocampal Volume. No hippocampal (left or right) variables predicted depressive symptoms on the BDI or HAM-D. When hippocampal volumes were predictors instead of white matter volume, similar relationships were found between group status and gender and HAM-D scores in that MJ-users (p = .03) and female adolescents (p = .002) reported higher scores.

Insert Figures 2 and 3 About Here

DISCUSSION

The primary findings revealed that marijuana use and white matter volume were additive and interactive in predicting depressive symptoms among adolescents. It is notable that the relationship between white matter volume and depressive symptoms was observed in a sample of

adolescents who did not meet past or current criteria for a depressive disorder. Therefore, the findings are not confounded by the influences of mood disorder duration or psychiatric medications. Consistent with previous research, we also found that marijuana users had significantly higher scores on a depression rating scale (HAM-D) compared to the controls.

The relationship between reduced white matter volume and increased depressive symptoms in this sample may be driven primarily by disruption in the frontal-limbic-basal ganglia circuitry (e.g., Levy and Dubois, 2005; Rogers et al., 1998; Tekin and Cummings, 2002). Indeed, differences in prefrontal white matter volume and integrity have been shown in pediatric (Nolan et al., 2002), adolescent (Steingard et al., 2002), adult, and elderly (Ballmaier et al., 2004; Heiden et al., 2005; Taylor et al., 2004) depressed patients compared to non-depressed controls. Among depressed adolescents, it has been hypothesized that reduced prefrontal lobe white matter volume is due to abnormal myelination during neuromaturation (Steingard et al., 2002). However, it remains difficult to determine whether abnormal neurodevelopment caused depression, or if depression interrupts developmental myelination.

Notably, we found that the relationship between smaller white matter volume and increased depressive symptoms was most prominent among the marijuana users. Due to the cross-sectional nature of this study, the directional and temporal relationship of white matter volume, marijuana use, and depressive symptoms cannot be ascertained. One possible explanation for these findings is that the MJ users demonstrated increased variance in depressive symptoms compared to controls, especially on the BDI; therefore, statistical relationships were more likely to be observed in this group compared to controls. However, we did detect a small difference in the correlations between the HAM-D and white matter volume between the groups. Therefore, based on these findings and previous research demonstrating higher rates of depressive symptoms among marijuana users (Degenhardt et al., 2003; Rey et al., 2004), we

believe that the current results support the hypothesis that chronic marijuana use may cause or worsen depressive symptoms. In turn, morphological abnormalities may be observed earlier in the mood disorder process among marijuana users.

The endogenous cannabinoid receptors are found in brain regions associated with mood regulation, such as limbic and frontal areas, as well as white matter (Eggan and Lewis, 2006; Romero et al., 1997; Soares and Mann, 1997). Therefore, it is possible that chronic marijuana use may alter white matter tracts in these areas (Matochik et al., 2005), directly causing depressive symptoms. However, we did not find white matter volume differences between the groups, although differences in white matter microstructure may exist. Still, we believe it is unlikely that marijuana use is directly or solely responsible for the subtle white matter abnormalities associated with depressive symptoms in this sample. A possible alternative is that chronic marijuana use worsens existing depressive symptoms by disrupting the neuronal functioning of the frontal and limbic brain circuits (Loeber and Yurgelun-Todd, 1999; Lungqvist, et al., 2001; Martin et al., 2002). Due to compromised neuronal functioning in these areas, adolescent marijuana users may be less able to compensate for additional neuropathological processes associated with depressive symptoms. Finally, this observed interaction between marijuana use and white matter could be due to other moderating factors, such as shared genetic or environmental vulnerability for both disorders (e.g., Fu et al., 2002).

We did not find relationships between hippocampal volume and depressive symptoms in this sample of adolescents. It is possible that hippocampal volume reductions occur later in the depressive disorder course (MacQueen et al., 2003; Sheline et al., 1999). However, the current findings are consistent with studies focused on depressed pediatric patients (DeBellis et al., 1999; MacMillan et al., 2003; Rosso et al., 2005) and medication free young adults (average age 30) (Hastings et al., 2004). Therefore, the relationship between hippocampal volume and

depressive symptoms may occur primarily in the elderly (Lloyd et al., 2004), particularly those with comorbid cerebrovascular disease (Iosifescu et al., 2005; Thomas et al., 2002).

Some limitations of this study warrant consideration. Although comparable to previous neuroimaging studies, the sample size is relatively small, which may influence generalizability and power. Further, the control group had limited variability of depressive symptoms, which may have influenced the group-white matter interaction results. Samples with substantially different patterns of substance use may yield different results. Further, the marijuana users had greater histories of alcohol and other drug use, although these variables were not related to depressive symptoms or white matter in this sample. Still, statistical control is not equivalent to matching, so it is possible that the combination of alcohol and marijuana use contributed to these findings.

In summary, the present study found significant negative relationships between white matter volume and depressive symptoms in adolescents, especially among marijuana users. These structural findings may be primarily due to frontal-limbic-basal ganglia circuitry disruption. Therefore, further research investigating white matter integrity in specific regions of interest (e.g., dorsolateral prefrontal cortex, cingulum) combining morphological analysis with diffusion tensor imaging in adolescent marijuana users is warranted. Further, longitudinal studies are needed to examine the developmental course of brain structure in conjunction with depressive symptoms among substance-using and non-using adolescents.

ACKNOWLEDGEMENTS

We would like to thank the research associates in the LOCI, UCSD, as well as the adolescent participants and their families. Funding was provided by grants from the National Institute on Drug Abuse (PI: Tapert, R21 DA15228 and R01 DA021182; PI: Medina, F32 DA020206).

REFERENCES

Aasly, J., Storsaeter, O., Nilsen, G., Smevik, O. & Rinck, P. (1993). Minor structural brain changes in young drug abusers. *Acta Neurologica Scandinavica, 87,* 210-214.

Altshuler, L., Post, R., & Fedio, P. (1991). Assessment of affective variables in clinical trials. In Mohr, I.E. & Brouwers, P. (Eds.) *Handbook of Clinical Trials: The neurobehavioral approach.* Berwyn, PA: Swets & Zeitlinger.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal, 325,* 1212-1213.

Ballmaier, M., Toga, A.W., Blanton, R.E., Sowell, E.R., Lavretsky, H., Peterson, J., Pham, D., & Kumar, A. (2004). Anterior cingulated, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: An MRI-based parcellation of the prefrontal cortex. *American Journal of Psychiatry, 161,* 99-108.

Beck, A.T., Steer, R.A., & Garbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8(1),* 77-100.

Belue, R.C., Howlett, A.C., Westlake, T.M., Hutchings, D.E. (1995). The ontogeny of cannabinoid receptors in the brain of postnatal and aging rats. *Neurotoxicol Teratol, 17(1),* 25-30.

Benes, F.M. (1998). Brain Development, VII. Human brain growth spans decades. *American Journal of Psychiatry, 155(11),* 1489.

Bennet, D.S., Ambrosini, P.J., Bianchi, M., Barnett, D., Metz, C., & Rabinovich, H. (1997). Relationship of Beck Depression Inventory factors to depression among adolescents. *Journal of Affective Disorders, 45,* 127-134.

Block, R.I., O'Leary, D.S., Ehrhardt, J.C., Augustinack, J.C., Ghoneim, M.M., Arndt, S., & Hall, J.A. (2000). Effects of frequent marijuana use on brain tissue volume and composition. *NeuroReport,11(3),* 491-496.

Bovasso, G. (2001). Cannabis abuse as risk factor for depressive symptoms. *American Journal of Psychiatry, 158,* 2033-2037.

Brook, D., Brook, J., Zhang, C., Cohen, P. & Whiteman, M. (2002). Drug use and the risk of marjor depressive disorder, alcohol dependence, and substance use disorders. *Archives of General Psychiatry, 59,* 1093-1044.

Brown, S.A., Myers, M.G., Lippke, L., Tapert, S.F., Stewart, D.G., & Vik, P.W. (1998). Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): a measure of adolescent alcohol and drug involvement. *Journal of Studies on Alcohol* **59**, 427–438.

Cahalan D., Cisin I.H., & Crossley H.M. (1969). A*merican drinking practices: A national study of drinking behavior and attitudes.* New Brunswick, NJ: Rutgers Center of Alcohol Studies.

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G.M. (2004). Lower hippocampal volume in patients suffering from depression: A meta-analysis. *American Journal of Psychiatry, 161,* 598-607.

Chen, C.Y., Wagner, F.A., Anthony, J.C. (2002). Marijuana use and the risk of Major Depressive Episode: Epidemiological evidence from the United States National Comorbidity Survey. *Society of Psychiatry and Psychiatric Epidemiology, 37,* 199-206.

Childers, S.R., & Breivogel, C.S. (1998). Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence, 51* 173-187.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences, 2nd Edition.* Lawrence Erlbaum Associates: Hillsdale, New Jersey.

Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29,* 162-173.

DeBellis, M.D., Keshavan, M.S., Shifflett, H., Satish, I., Beers, S.R., Hall, J., & Moritz, G. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. *Biological Psychiatry, 52(11),* 1066-1078.

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction, 98,* 1493-1504.

Eggan, S.M. & Lewis, D.A. (2006). Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: A regional and laminar analysis. *Cerebral Cortex* (Epub ahead of print).

Erlich, S., Breeze, J.L., Hesdorffer, D.C., Noam, G.G., Hong, X., Alban, R.L., Davis, S.E., & Renshaw, P.F. (2005). White matter hyperintensities and their association with suicidality in depressed young adults. *Journal of Affective Disorders, 86, 281-287.*

Fergusson, D.M. & Horwood, L.J. (1997). Early onset cannabis use and psychosocial adjustment in young adulthood. *Addiction, 92,* 279-296.

Fergusson, D.M., Horwood, L.J. & Swain-Campbell, M. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,* 1123-1135.

Firbank, M.J., O'Brien, J.T., Pakraski, S., Pantoni, L., Simoni, M., Erkinjuntti, T., Wallin, A., Wahlund, L., van Straaten, I., & Inzitari, D. (2005). White matter hyperintensities and depression- Preliminary results from the LADIS study. *International Journal of Geriatric Psychiatry, 20,* 674-679.

Frodl, T., Meisenzahl, E.V., Zetzsche, T., Born, C., Groll, C., Jäger, M., Leinsinger, G., Bottlender, R., Hahn, K., Möller, H.J. (2002). Hippocampal changes in patients with first episode of major depression. *American Journal of Psychiatry, 150,* 1112-1118.

Fu, Q., Heath, A.C., Bucholz, K.K., Nelson, E., Goldberg, J., Lyons, M.J., True, W.R., Jacob, T., Tsuang, M.T., & Eisen, S.A. (2002). Shared genetic risk of major depression, alcohol dependence, and marijuana dependence. *Archives of General Psychiatry, 50,* 1125-1132.

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D. & Rapoport, J.L. (1996). Quantitative magnetic resonance imaging of human brain development: ages 4–18, *Cerebral Cortex, 6,* 551–560.

Green, B.E. & Ritter, C. (2000). Marijuana use and depression. *Journal of Health and Social Behavior, 41,* 40-49.

Hamilton, M. (1986). The Hamilton Rating Scale for Depression. In N. Sartorius & T.A. Ban (Eds.), *Assessment of Depression* (pp. 143-152). New York: Springer-Verlag.

Hastings, R.S., Parsey, R.V., Oquendo, M.A., Arango, V., & Mann, J.J. (2004). Volumetric analysis of the prefrontal cortex, amygdale, and hippocampus in Major Depression. *Neuropsychopharmacology, 29,* 952-959.

Heiden, A., Kettenbach, J., Fischer, P. Schein, B., Ba-Ssalamah, A., Frey, R., Naderi, M.M., Gulesserian, T., Schmid, D., Trattnig, S., Imhof, H., & Kasper, S. (2005). White matter hyperintensities and chronicity of depression. *Journal of Psychiatric Research, 30,* 285-293.

Iosifescu, D.V., Papakostas, G.I., Lyoo, I.K., Lee, H.K., Renshaw, P.F., Alpert, J.E., Nierenberg, A., & Fava, M. (2005). Brain MRI white matter hyperintensities and one-carbon cycle

metabolism in non-geriatric outpatients with major depressive disorder (Part I). *Psychiatry Research: Neuroimaging, 140,* 291-299.

Iverson, L. (2003). Invited review: Cannabis and the brain. *Brain, 126,* 1252-1270.

Johnston, L.D., O'Malley, P.M., Backman, J.G., & Schulenberg, J.E. (2004). *Monitoring the future national results of adolescent drug use: Overview of key findings, 2003 (NIH publication No. 04-5506).* Bethesda, MD: National Institute on Drug Abuse.

Kandel, D.B. (1984). Marijuana users in young adulthood. *Archives of General Psychiatry, 41,* 200-209.

Levy, R., & Dubois, B. (2005). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex, (Oct. 5),* 1-13.

Lloyd, A.J., Ferrier, I.N., Barber, R., Gholkar, A., Young, A.H., & O'Brien, J.T. (2004). Hippocampal volume change in depression: Late- and early-onset illness compared. *British Journal of Psychiatry, 184,* 488-495.

Loeber, R.T., & Yurgelun-Todd, D.A. (1999). Human neuroimaging of acute and chronic marijuana use: Implications for frontocerebellar dysfunction. *Human Psychopharmacology, 14,* 291-304.

Lundqvist, T., Jönsson, S., & Warkentin, S. (2001). Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicology and Teratology, 23,* 437-443.

Lyoo, I.K., Lee, H.K., Jung, J.H., Noam, G.G., & Renshaw, P.F. (2002). White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Comprehensive Psychiatry, 43(5), 361-368.*

MacMillan, S., Szeszko, P., Moore, G.J., Madden, R., Lorch, E., Ivey, J., Banerjee, P., & Rosenberg, D.R. (2003). Increased amygdale: hippocampal volume ratios associated

with severity of anxiety in pediatric major depression. *Journal of Child and Adolescent Psychopharmacology, 13(1),* 65-73.

MacQueen, G.M., Campbell, S., McEwen, B.S., Macdonald, K. Amano, S., Joffe, R.T., Nahmias, C. Young, L.T (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceeds of the National Academy of Science (100),* 1387-392.

Martin, M., Ledent, C., Parmentier, M., Maldonado, R., & Valverde (2002). Involvement of CB1 cannabinoid receptors in emotional behavior. *Psychopharmacology, 159,* 379-387.

Matochik, J.A., Eldreth, D.A., Cadet, J.L., & Bolla, K.I. (2005). Altered brain tissue composition in heavy marijuana users. *Drug and Alcohol Dependence, 77,* 23-30.

McNamara, K. (1992). Depression assessment and intervention: Current status and future directions. In Brown, S. & Lent, R., *Handbook of Counseling Psychology*, (pp. 691-718).

Nagel, B.J., Schweinsburg, A.D., Phan, V., & Tapert, S.F. (2005). Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Research: Neuroimaging, 139(3),* 181-190.

Nixon, J.K., Milin, R., Simeon, J.G., Cloutier, P., & Spenst, W. (2001). Sertraline effects in adolescent Major Depression and Dysthymia: A six-month open trial. *Journal of Child and Adolescent Psychopharmacology, 11(2),* 131-142.

Nolan, C.L., Moore, G.J., Madden, R., Farchione, T., Bartoi, M., Lorch, E., Stewart, C.M., & Rosenberg, D.R. (2002). Prefrontal cortical volume in childhood-onset major depression. *Archives of General Psychiatry, 59,* 173-179.

Patton, G.C., Coffey, C., Carlin, M.B., Degenhardt, L. Lynskey, M., & Hall, W. (2002). Cannabis use and mental health in young people: Cohort study. *British Medical Journal, 325,* 1195-1198.

Pistis, M., Pera, S., Pillolla, G., Melis, M., Muntoni, A.L., Gessa, G.L. (2004). Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. *Biological Psychiatry, 56,* 86-94.

Robins L, Cottler L, Bucholz K, & Compton W (1996). *The Diagnostic Interview Schedule, Version 4.0. (DIS 4.0).*

Rogers, M.A., Bradshaw, J.L., Pantelis, C., & Phillips, J.G. (1998). Frotostriatal deficits in unipolar major depression. *Brain Research Bulletin, 47(4),* 297-310.

Romero, J., Garcia-Palomero, E., Berrendero, F., Garcia-Gil, L., Hernandez, M.L., et al. (1997). Atypical location of cannabinoid receptors in white matter areas during rat brain development. *Synapse, 27,* 317-323.

Romero, J., Hillard, C.J., Calero, M., Rabano, A. (2002). Fatty acid amide hydrolase localization in the human central nervous system: an immunohistochemical study. *Molecular Brain Research, 100,* 85-93.

Rosso, I.M., Cintron, C.M., Steingard, R.J., Renshaw, P.F., Young, A.D., & Yurgelun-Todd (2005). Amygdala and hippocampus volumes in pediatric major depression. *Biological Psychiatry, 57,* 21-26.

Segonne, F., Dale, A.M., Busa, E., Glessner, M., Salat, D., Hahn, H.K. & Fischl, B. (2004).A hybrid approach to the skull stripping problem in MRI, *NeuroImage*, 22, 1060-75.

Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., Schwab-Stone, M.E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliablility of some common diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry. 39(1),* 28-38

Sheline, Y.I., Sanghavi, M., Mintun, M.A., & Gado, M.H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience, 19,* 5034-5043.

Soares, J.C. & Mann, J.J. (1997). The anatomy of mood disorders- Review of structural neuroimaging studies. *Biological Psychiatry, 41,* 86-106.

Sobell L.C., Maisto S.A., Sobell M.B., & Cooper A.M. (1979). Reliability of alcohol abusers' self-reports of drinking behavior. *Behaviour Research & Therapy, 17,* 157-160.

Sobell L.C. & Sobell M.B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: Raye Z. Litten JPA, ed. *Measuring alcohol consumption: Psychosocial and biochemical methods*.: Humana Press, Inc, Totowa, NJ, US.

Sowell, E.R., Thompson, P.M., Holmes, C.J., Batth, R., Jernigan, T.L., & Toga, A.W. (1999). Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *NeuroImage, 9(6), 587-597.*

Steingard, R.J., Renshaw, P.F., Hennen, J., Lenox, M., Cintron, C.B., Young, A.D., Connor, D.F., Au, T.H., & Yurgelun-Todd, D.A. (2002). Smaller frontal lobe white matter volumes in depressed adolescents. *Biological Psychology, 52,* 413-417.

Stewart, D.G. & Brown, S.A. (1995). Withdrawal and dependency symptoms among adolescent alcohol and drug abusers. *Addiction, 90,* 627–635.

Stiglick & Kalant, (1985). Behavioral effects of prolonged administration of delta 9-Tetrahydrocannabinol in the rat. *Psychopharmacology, 80,* 325-330.

Tapert, S. F., & Brown, S. A. (1999). Neuropsychological correlates of adolescent substance abuse: Four year outcomes. *J Int Neuropsychol Soc, 5*(6), 481-493.

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. *J Int Neuropsychol Soc, 8*(7), 873-883.

Taylor, W.D., MacFall, J.R., Payne, M.E., McQuoid, D.R., Provenzale, J.M., Steffens, D.C., & Krishnan, K.R.R. (2004). Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. *American Journal of Psychiatry, 161,* 1293-1296.

Tekin, S., & Cummings, J.L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. *Journal of Psychosomatic Research, 53,* 647-654.

Thompson, C. (1989). Affective disorders. In C. Thompson (Ed.), *The instruments of psychiatric research (pp. 87-126).* New York: Wiley.

Thompson, L.L., Riggs, P.D., Mikulich, S.K., & Crowley, T.J. (1996). Contribution of ADHD symptoms to substance problems and delinquency in conduct-disordered adolescents. *Journal of Abnormal Child Psychology, 24,* 325-347.

Thomas, A.J., O'Brien, J.T., Davis, S., Ballard, C., Barber, R., Kalaria, R.N., & Perry, R.H. (2002). Ischemic basis for deep white matter hyperintensities in major depresision. *Archives of General Psychiatry, 59,* 785-792.

Videbech, P. & Ravnkilde, B. (2004). Hippocampal volume and depression: A meta-analysis of MRI studies. *American Journal of Psychiatry, 161,* 1957-1966.

Wilkinson, G. (1993). *Wide Range Achievement Test, 3rd Edition (WRAT-3) Manual.* Wilmington, DE: Wide Range, Inc.

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R.E., Provenzale, J. (2000). Brain morphological changes and early marijuana use: A magnetic resonance and positron emission tomography study. *Journal of Addictive Diseases, 19(1),* 1-22.

Wong, E. C., Luh, W.M., Buxton, R.B., & Frank, R.L. (2000). Single slab high resolution 3D whole brain imaging using spiral FSE. *Proceedings of the International Society of Magnetic Resonance Medicine, 8*, 683.

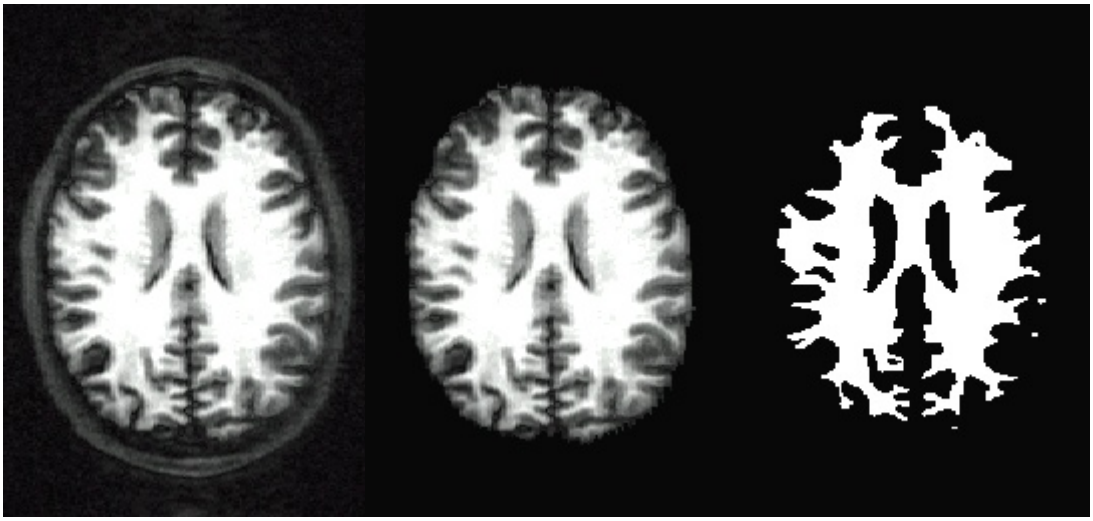
Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging, 20*(1), 45-57.

Table 1: Demographic, brain volume characteristics, and simple bivariate relationships with depression

	Marijuana Users (*n*=16)			Controls (*n*=16)		
	% or M±SD	*r* with BDI	*r* with HAM-D	% or M±SD	*r* with BDI	*r* with HAM-D
Gender (male)	75%	-.80***	-.64**	69%	.29	-.41
Ethnicity (Caucasian) *	75%	.22	-.05	63%	-.29	.00
Age	18±0.7	-.23	.10	18±0.9	.01	.31
Lifetime alcohol use (episodes) ***	195±137	.26	.13	23±47	.06	-.06
Lifetime marijuana use (episodes) ***	476±269	.06	-.13	1±1	n/a	n/a
Global white matter volume/ICV (cc^3)	.2998±.0139	-.60**	-.56*	.2963±.0116	.19	-.42
Raw white matter volume (cc^3)	448.56±48.6	n/a	n/a	437.89±48.5	n/a	n/a
Left hippocampus volume/ICV (cc^3)	.0026±.0003	.10	-.09	.0025±.0002	.15	.03
Raw left hippocampal volume (cc^3)	4.05±.45	n/a	n/a	3.89±.40	n/a	n/a
Right hippocampus volume/ICV (cc^3)	.0024±.0003	.02	-.15	.0023±.0002	.03	-.13
Raw right hippocampal volume (cc^3)	3.72±.46	n/a	n/a	3.67±.39	n/a	n/a

ICV=Intracranial Volume. Analyses utilizing brain volumes were corrected for total intracranial volume. *p<.05 **p<.01 ***p<.001

Figure 1: Example (axial orientation) of an anatomical image in the skull, after skull stripping, and after white matter segmentation.



Original T1 Anatomical | **Skull-Stripped Anatomical** | **Segmented White Matter**

Figure 2: Simple bivariate relationships between white matter volume and BDI by group.

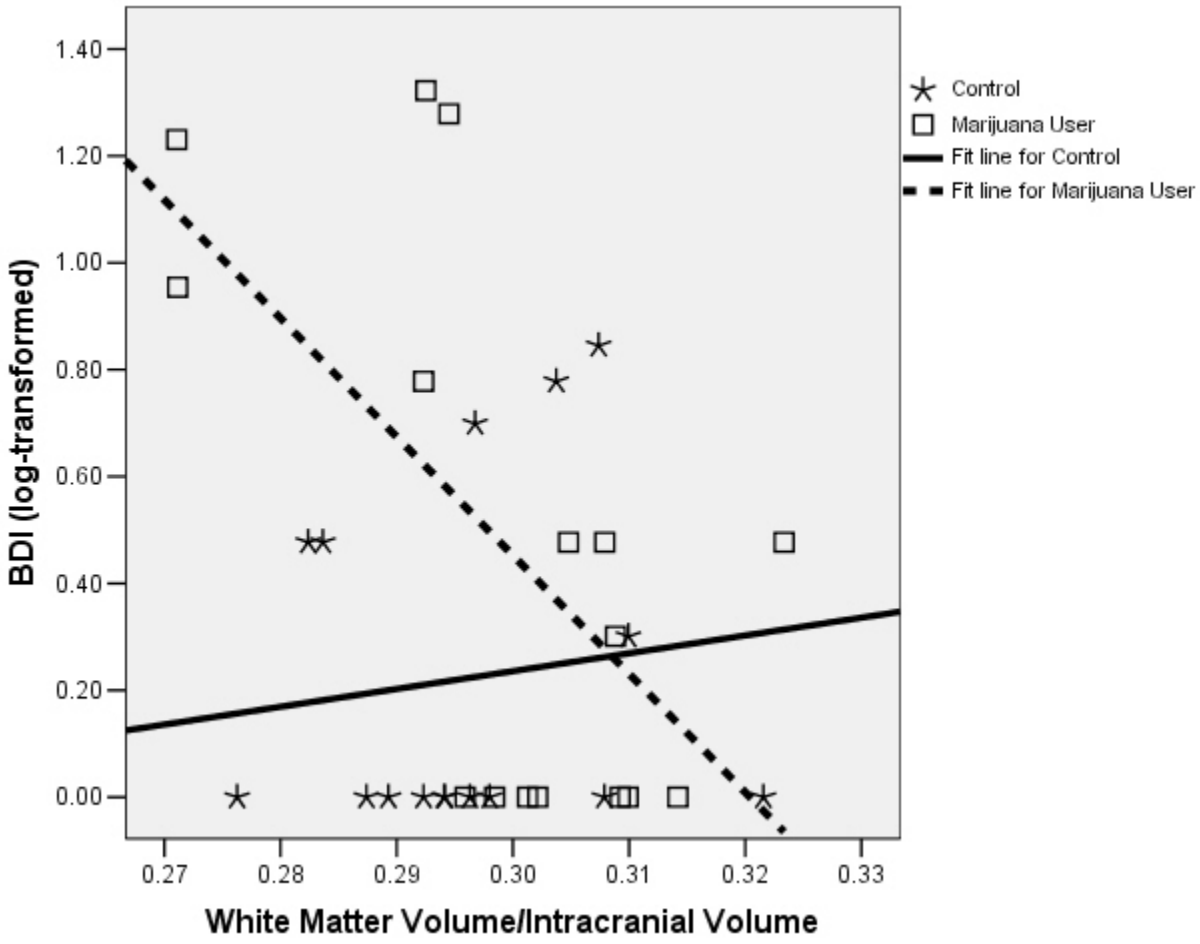


Figure 3: Simple bivariate relationships between white matter volume and HAM-D by group.