Published in final edited form as:

Drug Alcohol Depend. 2010 July 1; 110(0): 55–61. doi:10.1016/j.drugalcdep.2010.02.004.

Gender differences in the relationship between white matter organization and adolescent substance use disorders

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Abstract

Few studies have focused on the neurobiological correlates of adolescent-onset substance use disorders (SUDs), particularly with respect to white matter development and organization. This study investigated microstructural white matter characteristics associated with SUDs during the adolescent developmental period. Twenty-four case adolescents (ages 14–18) entering treatment for SUDs and 12 sex- and age-matched control adolescents with no psychopathology were compared. Diffusion tensor imaging data were collected and analyzed using the whole brain, tract-based spatial statistics (TBSS) method. In order to comprehensively characterize diffusivity characteristics, we first studied fractional anisotropy (FA), and within regions that differed in FA, other indicators of microstructure, including the axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). A large cluster of significantly lower FA values was found in cases compared to controls in the superior longitudinal fasciculus (SLF). Within this cluster, AD and RD were also significantly different between the groups, while MD was not significantly different. For FA, a significant group by sex interaction was found; females with SUD exhibited lower FA than males with SUD, while control females exhibited higher FA than control males. These results indicated significantly lower white matter integrity in the superior longitudinal fasciculus region of association cortex, and assessed using multiple indicators of diffusion. These findings suggest that the disruption of normal white matter development due to substance exposure may be more severe in females than in males.

Keywords

Adolescents; Substance Use Disorders; Gender; Diffusion Tensor Imaging

1. Introduction

Despite the fact that substance use disorders (SUDs) often onset during adolescence, there has been limited investigation of the neurobiological correlates of this early substance exposure on adolescent brain development (Clark, Thatcher & Tapert, 2008). Several large studies have demonstrated that brain maturation, particularly white matter microstructure,

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proceeds dynamically during adolescence (Chambers, Taylor & Potenza, 2003; Giedd, 2004; Giorgio et al., 2008; Spear, 2000). Unlike grey matter volume, white matter volume, particularly in the prefrontal area, increases during adolescence (Durstion et al., 2001; Lenroot & Giedd, 2006). Given the continuing maturation of white matter microstructure during adolescence (Ashtari et al., 2007; Qiu et al., 2008), substance use during this critical period may have developmentally-specific effects on white matter development and organization.

A growing body of literature documents white matter microstructural disorganization associated with SUDs among adults (Agartz et al., 2003; Lim et al., 2002; Moeller et al., 2007; Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2000; Reneman et al., 2001; Schlaepfer et al., 2006). Findings extend across several types and combinations of substances used, as well as age range and population. However, results obtained in adults with SUDs may have limited generalizability to adolescents with SUDs or adults with a history of adolescent-onset SUDs. Premorbid brain characteristics may exist that are unique to adolescent-onset SUDs, and ongoing brain development may increase vulnerability to effects (Chambers et al., 2003; Clark, Thatcher and Tapert, 2008; Durstion et al., 2001). In addition, it is difficult to generalize studies of adults with SUDs to adolescents because the frequencies, amounts, duration and patterns of alcohol and other substance use tend to differ between adolescents and adults. Compared to adults with SUDs, adolescents with SUDs typically exhibit more episodic alcohol use (Schulenberg & Maggs, 2002). An episodic pattern of use during adolescence has been linked to alterations in brain structure in animal models (Crews et al., 2000) and in human adolescents (McQueeney et al., 2009). Symptom patterns of adolescents with alcohol use disorders differ as well. For example, adolescents are less likely to report alcohol withdrawal symptoms (Chung et al., 2002). For these reasons, the results of studies on adult-onset SUDs may differ from those on adolescent-onset SUDs.

Adults reporting adolescent-onset alcohol and other substance-related problems have formed the basis for a growing number of studies on white matter microstructure associated with SUDs. Studies have focused on marijuana use (Arnone et al., 2008; Ashtari et al., 2009), binge drinking (McQueeney et al., 2009), and both alcohol and marijuana use during adolescence (Bava et al., 2009). Arnone and colleagues studied 11 adult males (mean age 25) with a history of heavy marijuana use during adolescence and 11 matched controls with no history of drug use and found higher mean diffusivity (MD) in the prefrontal region of the corpus callosum in the marijuana-using group. No differences in fractional anisotropy (FA) were noted in this study. Ashtari and colleagues also studied males (mean age 18) with a history of heavy marijuana use during adolescence (n=14) and matched controls (n=14). Males with a history of marijuana use exhibited lower FA and higher mean diffusivity, as well as higher radial diffusivity (RD), in the fronto-temporal region of the arcuate fasciculus. These two studies are in contrast to an earlier report finding no differences in any of the diffusion parameters between a group of 10 adults who reported heavy marijuana use during adolescence and 10 demographically similar controls (DeLisi et al., 2006). These studies share the limitation of retrospective reporting of drug use during the adolescent development period, which limits the validity of the results as well as inferences that could be made about group differences in the population.

Three recent studies have focused on studying adolescents who are actively using alcohol and other substances. McQueeney and colleagues (2009) studied 14 adolescents (12 male) who engaged in recent binge drinking but did not have diagnosed alcohol use disorders and 14 age-, sex- and education-matched control adolescents. Subjects reported minimal use of other substances such as marijuana. DTI data were processed using tract-based spatial statistics (TBSS). Compared with controls, subjects with binge drinking exhibited lower FA

in 18 regions of the brain, including corpus callosum, superior longitudinal fasciculus (SLF), and others. Bava and colleagues (2009) recently reported a larger study involving adolescents with heavy marijuana- and alcohol-using adolescents (n=36) and non-using controls (n=36). DTI data were also processed using TBSS. Compared with controls, substance-using adolescents exhibited lower FA in 10 brain regions, including superior and inferior longitudinal fasciculus, and splenium, as well as others. Additionally, higher MD was noted in left inferior longitudinal fasciculus and right occipital-lingual cortex. De Bellis and colleagues (2008) reported contrasting results in a region of interest study focusing on the corpus callosum. In 32 adolescents with alcohol use disorders compared with 28 controls, no areas with lower FA were found within the seven regions of the corpus callosum studied. In sum, two adolescent studies noted significant differences in the SLF in adolescents with SUDs, a finding that differs from studies involving adults who retrospectively reported substance use during adolescence.

Gender has been recognized as an important variable affecting brain development (Durstun et al., 2001; Giedd, 2004). The male brain is approximately 10% larger than the female brain, although certain structures such as the caudate and hippocampus seem to be larger, and the amygdale smaller, in females (Durstun et al., 2001). In a large longitudinal study of adolescent brain development, Giedd found differences between males and females with respect to the rate at which white matter specifically increases in various cortical brain regions. Whereas males and females are found to have similar frontal white matter volume during childhood, volume in males seems to increase more rapidly than in females during adolescence, resulting in higher frontal white matter volumes in males by young adulthood (Giedd et al., 2004). During late adolescence, white matter has been found to decrease, and this effect was greater in females (Nagel et al., 2006). On the other hand, a developmental study of changes in white matter microstructure during adolescence utilizing DTI data, no significant gender effects or gender interactions were detected (Giorgio et al., 2008).

Despite increasing evidence that gender shapes and influence brain development, this variable has been inconsistently studied in the context of SUDs and brain structure and function. Many of the adolescent studies cited here either focused exclusively on males or did not report analyses involving gender, with a few notable exceptions. The De Bellis study of the corpus callosum (2008) reported a significant group by gender interaction in the expected direction. Compared to females with AUD, reference females had higher FA values in the posterior midbody of the corpus callosum. Additionally, two volumetric MRI study of adolescents with alcohol use disorders found a sex by group interaction for prefrontal cortex volume, where females with alcohol use disorders exhibited smaller prefrontal volumes than males with alcohol use disorders (Medina et al., 2008). Interestingly, the same group found a group by gender trend ($p < 0.09$) in the opposite direction with respect to marijuana use (Medina et al., 2009). After controlling for alcohol use, female marijuana users exhibited larger prefrontal volume relative to control females, and males exhibited smaller prefrontal volumes relative to control males. In contrast to these volumetric studies, Bava and colleagues (2009) tested for but did not detect a significant group by gender interaction within their DTI study. The role of gender clearly needs to be further explicated in future studies, but these preliminary volumetric results suggest that to the extent that brain volume may have functional implications, the adverse effects of alcohol and other substance use upon white matter microstructure could vary by gender and possibly by substance type.

The purpose of the current study was to investigate microstructural white matter characteristics in adolescents with SUDs compared with controls using a voxel-based, exploratory approach, and to consider gender as a possible moderating variable in the relationship. Diffusion tensor imaging (DTI) methodology was applied in a case-control

study of adolescents with SUDs entering treatment and demographically matched controls. Multiple indicators of diffusion including FA as well as axial, radial, and mean diffusivity, were investigated in order to comprehensively characterize white matter characteristics. Based on emerging results from adolescent studies, we predicted that adolescents with SUD would have lower FA in SLF (cf. McQueeney et al., 2009; Bava et al, 2009), as well as higher MD and RD in SLF, compared to demographically matched, healthy control adolescents. Decreased FA, and increased MD and RD in the same brain areas could indicate decreased or delayed myelination (Ashtari et al., 2009). We also predicted that gender would moderate the association between SUD and white matter integrity, such that females with SUD, compared to males with SUD, would have decreased white matter integrity.

2. Methods

2.1 Study Participants

The cases were 24 adolescents with a current DSM-IV SUD (12 female), ages 14-18, who were recruited from substance abuse treatment programs. Participants for the current study were drawn from an ongoing longitudinal naturalistic investigation of adolescents in substance abuse treatment. The ages 14-18 reflect the typical age of adolescents in such treatment. The controls were 12 age- and sex-matched adolescents (6 female) without a lifetime history of SUDs and other psychopathology recruited from the community. Control subjects were identified by random digit dialing and were screened for eligibility by trained staff at the University Center for Survey and Urban Research. Control subjects were excluded if they were found to have past or current alcohol or other substance use disorder, or any of the following psychiatric disorders (conduct disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, or major depressive disorder).

Mean ages of both groups were 16.7; groups were two-to-one age-matched within two months. Both groups were primarily Caucasian (88% SUD; 83% Control), and represented a broad range of socio-economic status. All subjects were right-handed. Exclusion criteria for both groups included inability to communicate in English, mental retardation or other significant developmental disorders, and a history of significant brain injury resulting in likely concussion. Adolescents in the treatment group were typically scanned within one month of entry into intensive outpatient treatment for SUDs. The average time between treatment entry and scan completion was 25 days (Range=2 to 60 days).

2.2 Study Procedures

This study was conducted with the approval of and in accordance with the University of Pittsburgh Institutional Review Board, which oversees all research studies involving human subjects. Written assent from the adolescent and consent from a biological or adoptive parent was obtained prior to any study procedures. Adolescents 18 years of age or older provided their own written informed consent.

2.2.1. MRI Acquisition Procedures—MRI scans were performed at the Brain Imaging Research Center (BIRC), located near the University of Pittsburgh campus. MRI images were acquired on a Siemens 3T Allegra Scanner (Siemens Medical Solutions, Erlangen, Germany). Diffusion images were acquired using standard fast echo-planar imaging. Scan parameters were: TR=6500ms; TE=88ms; FOV=205x205; b=1000s/mm². Forty-six contiguous 3mm slices with no gap in each of 12 directions in addition to b=0 was acquired. The entire sequence was collected twice in order to optimize signal to noise ratio. In addition to the DTI images, a series of magnetization-prepared rapid gradient echo (MPRAGE) images were acquired for region identification. Scan parameters were

TR=1400ms; TE=2.48ms; FOV=256x256; 176 1mm contiguous slices with two averages (matrix 256×256).

2.3 Clinical Measures

DSM-IV SUD diagnoses—An adapted version of the Structured Clinical Interview for DSM-IV SUDs (SCID; First et al., 1997; Martin et al., 1995) was used to determine lifetime and current (past 6-month) SUD diagnoses, and age of SUD onset. Adaptations to the SCID were made to accommodate developmental considerations in symptom assessment, and included providing examples of youth-relevant symptoms (e.g., school grades dropping due to substance use), and suggestions for follow-up probes to aid clinical significance determinations. The adapted SCID demonstrated moderate to high inter-rater reliability for diagnostic ratings, reports of SUD onset, and has good concurrent validity in adolescents (Martin et al., 2000).

Substance Use Frequency—The Time Line Follow-Back (TLFB; Sobell & Sobell, 1995) interview is a calendar-based method that was used to collect daily data on substance use in the 30 days prior to the scan. TLFB data provided summary variables on the number of days of substance use, and maximum drinks per day of alcohol use in the past 30 days. Substance use data collected using the TLFB method with adolescents have good reliability and validity (e.g., Waldron et al., 2001).

Co-occurring Psychopathology—Participants completed the adolescent version of the Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) to assess lifetime and current other DSM-IV Axis I psychopathology (e.g., conduct disorder, major depression) at baseline. The K-SADS demonstrated good inter-rater reliability (Clark et al., 1997).

2.3.1. MRI Image Processing and Analysis—Voxelwise statistical analysis of the diffusion tensor imaging (DTI) data were carried out using whole-brain TBSS (Tract-Based Spatial Statistics, Smith et al., 2006), part of the Functional Magnetic Resonance Imaging Software Library (FSL) library of imaging analysis tools (Smith et al., 2004). The primary diffusion parameter investigated was fractional anisotropy (FA) which describes the degree to which molecules within a given voxel are not isotropic. First, diffusion data were brain-extracted using the brain extraction tool (BET) within FSL (Smith, 2002), followed by motion and eddy current correction using false discovery rate (FDT, Behrens et al., 2003). Then FA images were created by fitting a tensor model to the raw diffusion data using DTIFIT. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson, 2007a; 2007b), which uses a b-spline representation of the registration warp field (Rueckert, 1999). Next, the mean FA image was created and thinned to produce a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Permutation-based nonparametric inference (Randomise) was used to test significance using Threshold-Free Cluster Enhancement (Smith, 2009). Significant clusters ($p < 0.05$) were fully corrected for multiple comparisons.

Supplemental indicators of white matter integrity included axial (AD: L1 eigenvalue) and radial (RD: mean of L2 and L3 eigenvalues) diffusivity, as well as mean diffusivity (MD; defined as the average degree of diffusion within a given voxel). The supplemental indicators of diffusion were processed similarly to FA data with the exception that FA images were used to drive the nonlinear registration and skeletonisation stages. Anatomical localization was done referencing an MRI atlas of human white matter (Mori et al., 2005).

2.3.2. Follow-up multivariate analysis—A follow-up ANOVA was conducted utilizing SPSS to assess whether gender moderated the relationship between SUD group and any clusters showing significant group differences in FA or any of the other diffusion indicators. Pearson's r correlation coefficients were obtained for demographic, substance use, and psychiatric comorbidity variables with any significant clusters. Additional exploratory analyses were conducted using SPSS to assess whether any of these variables added significant variance beyond group and gender. We did not make corrections for multiple comparisons given the preliminary nature of these follow-up analyses.

3. Results

3.1. Descriptive Information

Table 1 summarizes demographic and diagnostic information on the study groups. As noted the groups were matched on age and gender, and were similar in terms of race. Socioeconomic status (SES), as measured by the Hollingshead formula in the parents, was significantly lower in the cases relative to controls, which is to be expected in a typical sample of adolescents in substance abuse treatment relative to a representative sample of adolescents from the community, who are selected to be free from comorbidity. SES was considered as a covariate in subsequent analyses. The groups differed on most substance involvement variables as would be expected. Control adolescents were selected to be free of substance use and psychiatric diagnoses; therefore, no group analyses were run using these variables.

3.2. TBSS Results

The TBSS procedure detected a significant cluster with lower FA values in the SUD cases relative to controls (voxel $p < 0.05$ fully corrected for multiple comparisons; cluster FA values $t = -14.4$, $p < 0.001$). This cluster was composed of 20 voxels and was located (center of gravity = 37.3, -11.4, 27.9 mm) in the right superior longitudinal fasciculus (SLF). Within the cluster of lower FA in the right SLF region, compared with controls, L1 also was significantly lower in SUD cases ($t = -8.6$, $p < 0.001$). Additionally, compared with controls, RD was significantly higher in SUD cases ($t = 6.4$, $p < 0.001$). No significant MD differences were found between groups within this cluster. The TBSS procedure did not detect any significant clusters that were in the direction contrary to the hypotheses. Findings are summarized in Table 2 and Figures 1 and 2. Table 2 shows values for the multiple indicators of white matter integrity within the significant cluster. Figure 1 depicts the anatomical location of the significant cluster, and Figure 2 shows boxplots of the multiple indicators of diffusion within the significant cluster, including FA, AD, RD, and MD.

3.3. Gender Results

We conducted an ANOVA including group and gender main effects, and group $\times$ gender interaction, in order to investigate the role of gender in the DTI results. For FA, a significant group by sex interaction was found (Table 3: $F = 4.41$, $p = 0.04$). Within the SUD case group, females exhibited lower FA relative to males within the SLF cluster, resulting in a trend toward significance ($p = 0.05$), whereas within the control group, females exhibited slightly higher FA than males within this cluster ($p = 0.20$). The main effect for gender was not significant ($p = 0.60$). Figure 3 depicts the group by sex interaction.

3.4. Exploratory Results

Additional exploratory results are summarized in Table 4. Pearson's r correlation coefficients were obtained for age at scan and SES, substance use in the past 30 days, and psychiatric comorbidity with the significant cluster. Hollingshead SES, cigarette use, days of

abstinence prior to scan, and presence of disruptive behavior disorder or major depressive disorder were significantly correlated with the FA cluster in the SLF. However these variables also largely characterize the SUD group. In particular, the control group was selected to be free of psychiatric disorders, and the SUD group is characterized by lower SES, greater cigarette use, and less days of abstinence prior to the scan. None of these variables, including age at scan, SES, substance use or psychiatric comorbidity variables accounted for significant additional variance in the ANOVA model.

4.0 Discussion

This study investigated multiple indicators of white matter microstructure, comparing adolescents with SUDs entering treatment with age- and sex-matched healthy controls. Our use of a voxel-based approach provided the advantage of investigating essentially the entire brain simultaneously, whereas an ROI approach might underestimate the extent of changes occurring during neurodevelopment due to its sampling limitations (Snook, Plewes, & Beaulieu, 2007). Using TBSS, lower FA values were found in the right SLF in adolescents with SUDs, compared with controls. Within this SLF cluster, the L1 eigenvalue was lower and RD was higher in SUD cases relative to controls.

The SLF is part of a collection of long bundles of neurons known as association fibers connecting cortical areas of the brain, and is thought to connect frontal with parieto-temporal regions of the cortex (Makris et al., 2005). According to the segmentation of the SLF reported by Makris and colleagues, the significant cluster in this study corresponds to area SLF II within the fiber. The inferior parietal lobule of the SLF appears to have a functional role in spatial attention and spatial working memory, through bidirectional pathways between prefrontal and posterior parietal areas. The current results suggest decreased integrity of this pathway associated with adolescent SUDs, and that females with SUD might be more profoundly affected. These structural results are consistent with emerging findings of compromised aspects of executive functioning in adolescents with SUDs. Schweinsburg et al (2008) studied 15 marijuana-using teens and 17 demographically similar controls using a spatial working memory task. While the groups performed similarly on the task, teens who used marijuana demonstrated lower activation in right prefrontal cortical areas and relatively higher activation in right posterior parietal cortex. These findings could reflect disrupted SLF II white matter integrity. Additionally, Tapert et al (2007) found increased activation in right prefrontal and parietal areas during an inhibitory processing task in a similar sample of adolescents with marijuana use relative to controls.

While differences in multiple indicators of white matter integrity (FA, L1, and RD) were found, no differences in mean diffusivity (MD) were found in this study. Previous studies have primarily focused on FA, and some have also found MD differences (e.g., Bava et al., 2009). Given the literature on white matter integrity during the adolescent developmental period, one would expect linear increases in FA and corresponding decreases in MD. The discrepancy in results for FA and MD in this study could be a result of limited power due to the modest sample size. If the effect size for FA is larger in the population than that for MD, differences in FA could be detectable in this sample size whereas differences in MD would not be. Another explanation is that to the extent that FA and MD measure distinct aspects of white matter integrity, FA characteristics could be more susceptible to the effects of drug and alcohol use. The convergence of multiple compromised indicators of diffusion found here is consistent with decreased myelination, which could be associated with excessive substance use during the adolescent developmental period (Ashtari et al., 2009).

A group by gender interaction in FA was noted, where female SUD cases had lower FA in this cluster than male SUD cases, and female control cases had higher FA in this cluster than

male control cases. The current investigation advances previous research by highlighting gender as a potential moderating variable upon the relationship of alcohol and substance use and white matter organization. These results echo previous volumetric MRI study finding a similar group by gender interaction effect in prefrontal cortex volume (Medina et al., 2008, 2009). In contrast, Bava and colleagues (2009) tested for but did not detect a significant group by gender interaction in a similar sample of adolescents with both alcohol and marijuana use. The reasons for this discrepancy are not immediately apparent but could reflect and suggest that alcohol and drug use during the critical adolescent developmental period might have different, possibly more detrimental effects upon females compared with males.

The case (SUD) subjects reported here could be considered to comprise a ‘typical’ adolescent-onset SUD group, in that these individuals largely had multiple substance use and psychiatric comorbidity. While this improves the generalizability of the findings to similar clinical populations, it also obscures the possible etiology and mechanisms of the significant findings. The findings presented here could represent direct effects of substances on the developing brain or differences in the brain that predate the initiation of substance use and could represent a risk factor for problematic substance use that may be associated with co-occurring psychopathology. Studies of adolescents with risk characteristics for the development of SUDs utilizing DTI methodology have found differences similar to those in adolescents with SUDs. For example, adolescents with disruptive behavior disorders (n=36) were found to have reduced FA in frontal and left temporal regions, and specifically the arcuate fasciculus region of the SLF compared with matched controls (Li et al., 2005). Attention deficit hyperactivity disorder, considered by some to be a risk factor for the development of SUDs, has been associated with white matter differences in the SLF area as well (Silk et al., 2009). Volumetric studies have also reported differences by risk group that were correlated with externalizing symptoms (Benegal et al., 2006; Venkatasubramanian et al., 2007).

While none of the substance use or diagnostic variables explored accounted for the variance between groups in multivariate models in the current study, only large and well-controlled longitudinal studies will allow these possibilities to be disentangled. Specifically, future studies might consider including groups separated on substance use characteristics and childhood disruptive behavior disorders, which both seem to exert substantial effects upon brain development.

Study findings need to be considered in the context of certain limitations. As discussed above, the mechanism of these findings is unclear due to the high degree of comorbidity in our sample.

In addition to multiple substances and psychiatric comorbidity, the degree of parental drug use and associated problems could account for some of the variance in our results. Specifically with respect to the TBSS analysis approach, calculating FA values using voxels from the center of each subject’s tract (i.e., the skeleton map) minimizes inclusion of white matter boundary voxels. However, the potential for partial volume effects is still present, particularly in tracts that are adjacent to white matter boundaries. This issue is present in many types of voxel-based MRI analyses. On balance, the TBSS procedure holds great potential as a hypothesis-generating method with respect to neurobiological correlates of psychiatric disorders and other conditions. Although the sample sizes reported here are comparable to other published neuroimaging studies (e.g., McQueeney et al., 2009), they are still somewhat modest, particularly in light of the multiple comparisons involved in the TBSS procedure.

In sum, we found significant differences in white matter integrity in adolescents with SUD, in the hypothesized direction and in a region consistent with recent research with adolescent substance users. The identified region, the superior longitudinal fasciculus, is actively developing during adolescence and is thought to be involved in the emergence of higher level integration of environmental information and the development of executive functions (Spear, 2000). Future studies are needed to characterize causal factors in longitudinal designs, investigate gender differences in risk for decreased white matter integrity among adolescent substance users, and to examine the functional implications of reductions in white matter integrity associated with SUD for neuropsychological capabilities.

References

- Agartz I, Brag S, Franck J, Hammarberg A, Okugawa G, Svinhufvud K, Bergman H. MR volumetry during acute alcohol withdrawal and abstinence: a descriptive study. *Alcohol and Alcoholism*. 2003; 38(1):71–78. [PubMed: 12554612]
- Ashtari M, Cervellione KL, Hasan KM, Wu J, McIlree C, Kester H, Ardekani BA, Roofeh D, Szeszko PR, Kumra S. White matter development during late adolescence in healthy males: A cross-sectional diffusion tensor imaging study. *Neuroimage*. 2007; 35:501–510. [PubMed: 17258911]
- Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear optimization. FMRIB technical report TR07JA1. 2007a. from www.fmrib.ox.ac.uk/analysis/techrep
- Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear registration, aka Spatial normalization. FMRIB technical report TR07JA2. 2007b. from www.fmrib.ox.ac.uk/analysis/techrep
- Arnone D, Barrick TR, Chengappa S, Mackay CE, Clark CA, Abou-Saleh MT. Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *Neuroimage*. 2008; 41(3):1067–1074. [PubMed: 18424082]
- Ashtari M, Cervellione K, Cottone J, Ardekani BA, Kumra S. Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *J. Psychiatr. Res.* 2009; 43(3):189–204. [PubMed: 19111160]
- Bava S, Frank LR, McQueeney T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. *Psychiatry Res.: Neuroimaging*. 2009; 173:228–237.
- Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn. Reson. Med.* 2003; 50(5):1077–1088. [PubMed: 14587019]
- Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *Am. J. Psychiatry*. 2003; 160(6):1041–1052. [PubMed: 12777258]
- Chung T, Martin CS, Armstrong TD, Labouvie EW. Prevalence of DSM-IV alcohol diagnoses and symptoms in adolescent community and clinical samples. *J. Am. Acad. Child Adolesc. Psychiatry*. 2002; 41(5):546–554. [PubMed: 12014787]
- Clark DB, Pollock N, Bukstein OG, Mezzich AC, Bromberger JT, Donovan JE. Gender and comorbid psychopathology in adolescents with alcohol dependence. *J. Am. Acad. Child Adolesc. Psychiatry*. 1997; 36:1195–1203. [PubMed: 9291720]
- Clark DB, Thatcher DL, Tapert SF. Alcohol, psychological dysregulation, and adolescent brain development. *Alcohol Clin. Exp. Res.* 2008; 32(1):375–385. [PubMed: 18241320]
- Crews FT, Braun CJ, Hoplight B, Switzer RC 3rd, Knapp DJ. Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. *Alcohol Clin. Exp. Res.* 2000; 24(11):1712–1723. [PubMed: 11104119]
- De Bellis MD, Van Voorhees E, Hooper SR, Gibler N, Nelson L, Hege SG, Payne ME, MacFall J. Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. *Alcohol Clin Exp Res*. 2008; 32(1):395–413. [PubMed: 18241319]
- DeLisi LE, Bertisch HC, Szulc KU, Majcher M, Brown K, Bappal A, Ardekani BA. A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. *Harm Reduct. J.* 2006; 3:17–22. [PubMed: 16684342]

- Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H. Anatomical MRI of the developing human brain: what have we learned? *J. Am. Acad. Child Adolesc. Psychiatry.* 2001; 40(9):1012–1020. [PubMed: 11556624]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. Biometrics Research Department, New York State Psychiatric Institute; New York: 1997. Research Version, Non-Patient Edition (SCID-I/NP)
- Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Ann. N. Y. Acad. Sci.* 2004; 1021:77–85. [PubMed: 15251877]
- Giorgio A, Watkins KE, Douaud G, James AC, James S, De Stefano N, Matthews PM, Smith SM, Johansen-Berg H. Changes in white matter microstructure during adolescence. *Neuroimage.* 2008; 39(1):52–61. [PubMed: 17919933]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry.* 1997; 36(7):980–988. [PubMed: 9204677]
- Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neurosci. Biobehav. Rev.* 2006; 30(6):718–729. [PubMed: 16887188]
- Li TQ, Mathews VP, Wang Y, Dunn D, Kronenberger W. Adolescents with disruptive behavior disorder investigated using an optimized MR diffusion tensor imaging protocol. *Ann N Y Acad Sci.* 2005; 1064:184–92. [PubMed: 16394156]
- Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence, a controlled diffusion tensor imaging study. *Biol Psychiatry.* 2002; 51(11): 890–5. [PubMed: 12022962]
- Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr. Pandya DN. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb. Cortex.* 2005; 15(6):854–869. [PubMed: 15590909]
- Martin CS, Kaczynski NA, Maisto SA, Bukstein OM, Moss HB. Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *J. Stud. Alcohol.* 1995; 56(6):672–680. [PubMed: 8558899]
- Martin CS, Pollock NK, Bukstein OG, Lynch KG. Inter-rater reliability of the SCID alcohol and substance use disorders section among adolescents. *Drug Alcohol Depend.* 2000; 59(2):173–176. [PubMed: 10891630]
- McQueeney T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, Tapert S. Altered white matter integrity in adolescent binge drinkers. *Alcohol Clin. Exp. Res.* 2009; 33(7):1278–1285. [PubMed: 19389185]
- Medina KL, McQueeney T, Nagel BJ, Hanson KL, Schweinsburg AD, Tapert SF. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcohol Clin. Exp. Res.* 2008; 32(3):386–394. [PubMed: 18302722]
- Medina KL, McQueeney T, Nagel BJ, Hanson KL, Yang TT, Tapert SF. Prefrontal cortex morphometry in abstinent adolescent marijuana users, subtle gender effects. *Addict Biol.* 2009; 14(4):457–68. [PubMed: 19650817]
- Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM, Valdes I, Swann AC, Barratt ES, Narayana PA. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects, diffusion tensor imaging. *Neuropsychopharmacology.* 2005; 30(3):610–7. [PubMed: 15637640]
- Mori S, Wakana S, van Zijl PCM, Nagae-Poetscher LM. *MRI Atlas of Human White Matter.* Elsevier Science, Amsterdam, The Netherlands. 2005
- Nagel BJ, Medina KL, Yoshii J, Schweinsburg AD, Moadab I, Tapert SF. Age-related changes in prefrontal white matter volume across adolescence. *Neuroreport.* 2006; 17(13):1427–31. [PubMed: 16932152]
- Pfefferbaum A, Sullivan EV. Disruption of brain white matter microstructure by excessive intracellular and extracellular fluid in alcoholism, evidence from diffusion tensor imaging. *Neuropsychopharmacology.* 2005; 30(2):423–32. [PubMed: 15562292]

- Pfefferbaum A, Sullivan EV, Hedehus M, Adalsteinsson E, Lim KO, Moseley M. In vivo detection and functional correlates of white matter microstructural disruption in chronic alcoholism. *Alcohol Clin. Exp. Res.* 2000; 24(8):1214–1221. [PubMed: 10968660]
- Qiu D, Tan L, Zhou K, Khong P. Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: Voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. *Neuroimage.* 2008; 41(2):223–232. [PubMed: 18395471]
- Reneman L, Majoie CB, Habraken JB, den Heeten GJ. Effects of ecstasy (MDMA) on the brain in abstinent users, initial observations with diffusion and perfusion MR imaging. *Radiology.* 2001; 220(3):611–7. [PubMed: 11526257]
- Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ. Non-rigid registration using free-form deformations: Application to breast MR images. *IEEE Trans. Med. Imaging.* 1999; 18:712–721. [PubMed: 10534053]
- Schlaepfer TE, Lancaster E, Heidbreder R, Strain EC, Kosel M, Fisch HU, Pearlson GD. Decreased frontal white-matter volume in chronic substance abuse. *Int J Neuropsychopharmacol.* 2006; 9(2):147–53. [PubMed: 16004619]
- Schulenberg JE, Maggs JL. A developmental perspective on alcohol use and heavy drinking during adolescence and the transition to young adulthood. *J. Stud. Alcohol (Supplement).* 2002:54–70.
- Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Res.* 2008; 163(1):40–51. [PubMed: 18356027]
- Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunningham R. White-matter abnormalities in attention deficit hyperactivity disorder, a diffusion tensor imaging study. *Hum Brain Mapp.* 2009; 30(9):2757–65. [PubMed: 19107752]
- Smith SM. Fast robust automated brain extraction. *Hum. Brain Mapp.* 2002; 17(3):143–155. [PubMed: 12391568]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM. Tract-based spatial statistics, voxelwise analysis of multi-subject diffusion data. *Neuroimage.* 2006; 31(4):1487–505. others. [PubMed: 16624579]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, DeLuca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, DeStefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage.* 2004; 23(Supplement 1):S208–219. [PubMed: 15501092]
- Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* 2009; 44(1):83–98. [PubMed: 18501637]
- Snook L, Plewes C, Beaulieu C. Voxel based versus region of interest analysis in diffusion tensor imaging of neurodevelopment. *Neuroimage.* 2007; 34(1):243–252. [PubMed: 17070704]
- Sobell LC, Kwan E, Sobell MB. Reliability of a drug history questionnaire (DHQ). *Addict Behav.* 1995; 20(2):233–41. [PubMed: 7484317]
- Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* 2000; 24(4):417–463. [PubMed: 10817843]
- Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT, Frank LR. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology (Berl).* 2007; 194(2):173–83. [PubMed: 17558500]

Figure 1.
Significant FA Cluster in the Right Superior Longitudinal Fasciculus (SLF)

Figure 2.
Boxplots of Multiple DTI Indices in Right SLF Cluster

Figure 3.
SUD by Gender Interaction in Right SLF Cluster

Table 1
Demographic, Substance Use, and Diagnostic Information

	SUD Cases (n=24)		Controls (n=12)	
Demographic Characteristics				
Gender (n (%) Female)	12	50.00	6	50.00
Age at Scan (Mean (SD))	16.70	1.01	16.68	1.08
Race (n (%) Caucasian)	21	87.50	10	83.30
Hollingshead SES (Mean (SD)) **	42.25	12.72	48.83	10.32
Past 30 Day Substance Use (Mean (SD))				
Alcohol Use Days *	1.79	3.19	0.25	0.45
Maximum Drinks per Use Day *	3.17	4.97	0.42	0.79
Total Number of Drinks	10.38	23.97	0.42	0.79
Cannabis Use Days **	7.96	12.50	0.00	0.00
Cocaine Use Days	0.13	0.45	0.00	0.00
Cigarette Use Days **	21.42	13.67	0.42	0.79
Total Number of Cigarettes **	242.33	201.20	0.83	2.89
Days of Abstinence Prior to Scan **	12.17	13.07	26.00	8.89
SUD Diagnoses (n (%) positive) Lifetime or current? Ages of Onset (Mean (SD))				
Alcohol Dependence	8	33.30	-	-
Age of Onset	16.45	1.87		
Alcohol Abuse	14	58.30	-	-
Age of Onset	14.88	1.61		
Cannabis Dependence	9	37.50	-	-
Age of Onset	15.66	1.79		
Cannabis Abuse	22	91.70	-	-
Age of Onset	15.18	1.37		
Nicotine Dependence	10	41.70	-	-
Age of Onset	15.34	1.84		
Psychiatric Diagnoses (n (%) positive) Lifetime or current? Ages of Onset (Mean (SD))				
Conduct Disorder	10	41.7	-	-
Age of Onset	13.50	1.58		
Attention Deficit Hyperactivity Disorder	11	45.8	-	-
Age of Onset	9.95	4.96		
Oppositional Defiant Disorder	2	8.3	-	-
Age of Onset	13.00	1.41		
Major Depressive Disorder	9	37.5	-	-
Age of Onset	13.99	3.22		

Notes:

The Control subjects were recruited to be free of SUD and other psychiatric diagnoses.

*
indicates $p < 0.05$

**
indicates $p < 0.01$

Table 2

Diffusion Indices of Significant Cluster FA

	SUD Group (n=24)		Reference Group (n=12)	
Right SLF (M(SD))				
Fractional Anisotropy (FA) **	0.45	0.04	0.60	0.02
Axial Diffusivity (L1) **	1.02	0.08	1.22	0.06
Radial Diffusivity (RD) **	0.50	0.05	0.43	0.02
Mean Diffusivity (MD)	0.67	0.67	0.69	0.02

Note: SLF=Superior Longitudinal Fasciculus; SUD=Substance Use Disorder

**
=p<0.001

Table 3

ANOVA Table of Significant Cluster FA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	0.195	3	.065	57.988	.000
Intercept	8.814	1	8.814	7862.570	.000
GROUP	.188	1	.188	167.858	.000
SEX	.000	1	.000	.281	.600
GROUP * SEX	.005	1	.005	4.405	.044
Error	.036	32	.001		
Total	9.204	36			
Corrected Total	.231	35			

Table 4

Exploratory Analysis of Demographic, Substance Use and Diagnostic Variables with Significant Cluster

Demographic	Correlation with FA	Model Covariate (F)
Age at Scan	– 0.09	1.37
Hollingshead SES	0.40 *	1.64
Past 30 Day Substance Use (Mean (SD))	Correlation with FA	Model Covariate (F)
Alcohol Use Days	– 0.24	0.83
Maximum Drinks per Use Day	– 0.32	0.25
Total Number of Drinks	– 0.25	0.02
Cannabis Use Days	– 0.31	0.94
Cocaine use Days	– 0.24	0.62
Cigarette Use Days	– 0.59 **	0.89
Total Number of Cigarettes	–0.52 **	0.12
Days of Abstinence Prior to Scan	–0.51 **	0.01
Psychiatric Lifetime Diagnoses	T-test with FA	Model Covariate (F)
Disruptive Behavior Disorders (CD, ADHD, or ODD)	– 4.06 **	0.03
Major Depressive Disorders	– 4.69 **	1.77