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White matter integrity as a link in the association between motivation to abstain and treatment outcome in adolescent substance users

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Abstract

Readiness to change constitutes an important treatment target. This study examined white matter (WM) integrity as a possible link in the pathway between motivation to abstain and treatment outcome. Adolescents (age 14–18, N=32) were recruited from intensive outpatient (IOP) substance use treatment, and reported on motivation to abstain from alcohol and marijuana shortly after treatment admission (i.e., at baseline). Diffusion tensor imaging data were collected approximately seven weeks after starting IOP, and were used to quantify WM integrity (indexed by fractional anisotropy, FA) using a region of interest (ROI) approach. Treatment outcomes were assessed 6-months after baseline. Indirect effects analyses tested FA in prefrontal, orbitofrontal, and temporal ROIs as a linking variable in the pathway from motivation to abstain, to alcohol and marijuana outcomes. Bivariate correlations indicated that greater motivation to abstain from alcohol was associated with lower FA in prefrontal, orbitofrontal and temporal ROIs; and that lower FA in these 3 ROIs was associated with greater 6-month alcohol problem severity. The indirect effect of FA was significant for the prefrontal ROI in the pathway from motivation to outcome for alcohol. FA values were not associated with motivation to abstain from marijuana, or marijuana-related outcomes. Results suggest that lower WM integrity, particularly in the prefrontal brain region, may help to explain greater alcohol problem severity at 6-months, despite higher motivation to abstain from alcohol. Interventions that aim to enhance white matter integrity warrant attention to improve adolescent treatment outcomes.

Keywords

white matter; adolescent substance use; readiness to change; treatment outcome

Increasing readiness to change substance use behavior is an important treatment goal (Miller & Rollnick, 2002), particularly since readiness to change has been shown to predict treatment outcomes in adolescents (e.g., Maisto et al., in press). Although readiness to change predicts outcomes, as the time between the assessment of readiness to change and outcomes increases, the association tends to weaken (King, Chung, & Maisto, 2009), in part, because readiness to change is fluid, varying over time and in relation to specific contexts

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(e.g., active treatment). Intervening variables (e.g., ability to apply relapse prevention skills) in the pathway between readiness to change and treatment outcome also may affect the association. An understudied area involves the role of neurobiological factors, such as white matter (WM) integrity, as a possible link in the pathway from readiness to change to treatment outcome.

WM integrity, or the coherence and organization of WM tracts in the brain, facilitates efficient communication among brain regions, and is associated with optimal cognitive performance (e.g., Schmithorst, Wilke, Dardzinski, & Holland, 2005). Diffusion tensor imaging (DTI) is a non-invasive method used to infer the microstructure (e.g., fiber density, coherence, organization) of WM axons in the brain. Based on diffusion of water in brain tissues, fractional anisotropy (FA) provides an estimate of the directional coherence of WM tracts in the brain, such that higher FA indicates greater WM integrity.

Youth with substance use disorder (SUD), compared to controls, generally show lower FA in regions of the fronto-parietal network (e.g., superior longitudinal fasciculus [SLF], which connects prefrontal and parietal cortices), fronto-temporal network (Ashtari et al., 2009), and corpus callosum (review: Squeglia, Jacobus, & Tapert, 2009). In prior analyses of the sample used here, SUD youth had lower FA in SLF compared to controls (Thatcher, Pajtek, Chung, Terwilliger, & Clark, 2010), and lower FA in the prefrontal cortex was associated with greater psychological dysregulation (Clark, Chung, Thatcher, Pajtek, & Long, in press). Among adolescent substance users, WM deficits have been associated with poorer cognitive performance (e.g., attention, working memory) (e.g., Bava, Jacobus, Mahmood, Yang, & Tapert, 2010). More generally, lower FA in regions of the fronto-parietal network and corpus callosum may be associated with inefficiencies in executive control functions (e.g., initiation and maintenance of a task set; Dosenbach et al., 2007), whereas lower FA in regions of the fronto-temporal network may be associated with impairment in memory and language processing (e.g., Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011). WM deficits may compromise an adolescent's ability to reduce substance involvement.

WM deficits might adversely impact treatment outcome by affecting an individual's ability to engage in and benefit from treatment. For example, in a sample of 16 cocaine dependent adults, who were scanned prior to outpatient treatment, WM integrity (i.e., higher FA in corpus callosum, frontal, parietal, and temporal lobes) at treatment onset was associated with longer cocaine abstinence during 8-weeks of treatment (Xu et al., 2010). Another study, of 70 adult outpatients with alcohol dependence (scanned near the end of 14–30 days of treatment), found that greater abnormalities in frontal WM as indicated by surrogate markers of neuronal integrity (*N*-acetylaspartate) were associated with return to alcohol use at 6–12 month follow-up (Durazzo, Gazdzinski, Yeh, & Meyerhoff, 2008). Similarly, among 45 treatment-seeking inpatients with alcohol use disorder, lower frontal white matter integrity (the DTI scan occurred during inpatient treatment after at least 2 weeks of abstinence) was observed among those who resumed heavy drinking in the 6-months following alcohol treatment compared to those who remained abstinent or drank minimally (Sorg et al., 2011). Little is known regarding the role of WM integrity in predicting adolescent treatment outcomes, or the extent to which treatment-related processes may be linked to outcomes through WM integrity.

This study tested the indirect effect of WM integrity in the pathway from treatment-related processes (i.e., treatment attendance, motivation to abstain) to substance problem severity at 6-month follow-up in adolescents (see Figure 1). We hypothesized that greater treatment attendance would be positively associated with FA (e.g., follow-through on recommended treatment would be associated with greater FA), and that greater FA would be associated

with better outcome. An alternative pathway tested FA as an intervening or “linking” variable in the path between a treatment-related process (i.e., motivation to abstain) and 6-month alcohol and marijuana outcomes. In this pathway, the treatment-related process variable (motivation to abstain measured prior to DTI) would be associated with FA (without proposing that such treatment-related processes cause changes in FA), and FA, in turn, would predict treatment outcome. Specifically, we hypothesized that greater motivation to abstain, in the context of a treatment episode, would be associated with greater WM integrity (i.e., higher FA). The rationale for this prediction is that in the specific context of active treatment, it might be the case that greater motivation to abstain would be associated with greater WM integrity, because WM integrity might be associated with better ability to absorb and effectively apply treatment content (cf., Blume, Davis, & Schmalzing, 1999). Higher FA, in turn, was predicted to be associated with lower problem severity at 6-month follow-up. That is, the translation of motivation to abstain into successful reduction in or abstinence from alcohol use might be associated, in part, with WM integrity, such that greater WM integrity would be associated with better treatment outcome.

Method

Participants

Adolescents (n=38; ages 14–18) were recruited from community-based intensive outpatient (IOP) treatment for substance use. Imaging data from 6 participants were excluded due to excess motion (n=3), faulty cortical segmentation (n=2) or a problem with resampling of DTI data (n=1), as detailed below. Thus, the analysis sample included 32 adolescents (see Table 1 for descriptive statistics). Treatment involved three 3-hour group sessions per week for 6–8 weeks, with content (e.g., relapse prevention, 12-step facilitation) that supported a goal of abstinence from alcohol and illicit drugs.

The sample was 59.4% male; 90.6% European American, 6.3% African American and 3.1% other ethnicity. Participants were, on average, middle-class in socio-economic status (Hollingshead, 1975). Only 1 participant was left-handed. The mean full scale IQ score was in the average range (Wechsler Abbreviated Scale of Intelligence; Psychological Corporation, 1999). All reported lifetime use of alcohol and marijuana, but marijuana was more commonly used than alcohol in this treatment sample. On average, participants reported more frequent cannabis use (average of 5.6 days, $SD=2.6$), relative to alcohol use (average of 3.2 days, $SD=1.7$) in the 6-months prior to baseline. Most participants (90.6%) had a current (past 6-months) DSM-IV cannabis use disorder, and almost half (46.9%) had a current DSM-IV alcohol use disorder. The average age of SUD (excluding nicotine) onset was 14.8 years old ($SD=1.5$; range 11 to 18). The most common types of current psychopathology at baseline were conduct disorder (34.4%) and Attention Deficit Hyperactivity Disorder (ADHD; 37.5%).

Procedure

Youth admitted to IOP were approached to participate in a longitudinal study on treatment outcome through 2-year follow-up, which included monthly follow-ups during the first follow-up year (King et al., 2009; Maisto et al., in press; Chung, Maisto, et al., 2011). The baseline assessment, which was completed shortly after IOP admission, collected comprehensive substance use and psychiatric data, and urine drug screens were used to facilitate valid self-report of substance use; the same domains were assessed 6-months after baseline in a repeated measures design. Monthly follow-up assessments collected data on treatment attendance and substance use.

After completing baseline (see Figure 1 for timeline of procedures), youth were invited to participate in a neuroimaging protocol (Thatcher et al., 2010; Chung, Geier, et al., 2011; Clark et al., in press). Exclusion criteria for the imaging protocol included standard restrictions (e.g., unremovable metal in the body), and a history of brain injury or concussion. Eligible adolescents who agreed to participate in the imaging study provided informed consent or assent (with parental consent) prior to the imaging protocol, which was approved by the university's Institutional Review Board. Youth included in these analyses did not report any substance use (except tobacco) <24 hours prior to imaging. Youth were scanned, on average, roughly 7 weeks after starting IOP (mean days=51.4, SD=26.4). On scan day, youth reported on substance use in the past 30 days. Most 87.5% (n=28) youth completed 6-month follow-up. Those who did versus did not complete 6-month follow-up did not differ on demographic characteristics, baseline alcohol or marijuana use, or FA variables.

Measures of substance involvement and psychopathology

An adapted Structured Clinical Interview for DSM-IV SUDs (SCID: First, Spitzer, Gibbon, & Williams, 2002) was used to determine SUD diagnoses at baseline (lifetime, and past 6-months) and 6-month follow-up (past 6-month time frame). The adapted SCID has acceptable reliability and validity (Chung, Martin, San Pedro, Shriberg, & Cornelius, 2004). The Kiddie-Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997), which has acceptable reliability and validity, was used at baseline to determine current (past 6-months) DSM-IV psychopathology.

The Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989; White & Labouvie, 2000) and Rutgers Marijuana Problem Index (RMPI; White, Labouvie, & Papadaratsakis, 2005), which each include 18 items rated on a 0–4 scale (0= 0 times, 1= 1–2 times, 2= 3–5 times, 3= 6–10 times, 4= >10 times), assessed alcohol and marijuana problem severity at baseline (past year time frame) and at 6-month follow-up (past 6-month time frame) (at 6-months: RAPI alpha= .91; RMPI alpha= .91).¹

At baseline, age at regular (i.e., onset of using at least once per month for at least six months) alcohol and marijuana use was determined using the Lifetime Drug Use History, which has good reliability and validity (Skinner, 1982). Frequency of substance use (past 6-months) was assessed at baseline and at 6-month follow-up with a standard series of items (separately for alcohol, marijuana, and tobacco) rated on a 9-point scale: 0=never tried, 1=no use in past 6 months, 2=less than once per month, 3=once per month, 4=2–3 times per month, 5=once per week, 6=2–3 times per week, 7=4–6 times per week, 8=daily.

The Time Line Follow Back method (TLFB; Sobell & Sobell, 1995), which has satisfactory reliability and validity (Donohue, Hill, Azrin, Cross, & Strada, 2007), was used to assess daily substance use in the 30 days prior to imaging, and was completed prior to the scan as part of the neuroimaging protocol. The TLFB also was completed at baseline and over 6-month follow-up as part of the larger study to determine the number of IOP treatment days attended since the start of IOP treatment to the day of the scan.

At baseline, motivation to abstain from alcohol and marijuana in the next 30 days was assessed with 1-item (asked separately for alcohol and for marijuana) that asked youth to rate “How motivated are you to abstain (not use at all) from [alcohol or marijuana] in the next 30 days?” on a 10-point scale (1=not at all through 10=very motivated). The item has good predictive validity in treated youth (King et al., 2009).

¹Baseline RAPI and RMPI were not significantly correlated with FA values, $p>.05$. Lifetime alcohol and marijuana symptom count (from the baseline SCID) were not significantly correlated with FA in the 5 ROIs ($p>.07$).

Image Acquisition and Processing

MRI images were acquired on a Siemens 3T Allegra Scanner. T1 weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired for morphometric analyses (scan parameters: TR=1400ms; TE=2.48ms; FOV=256×256; 176 1mm slices × 2; matrix 256 × 256). In addition, diffusion images were acquired using standard fast echo-planar imaging (TR=6500ms; TE=88ms; FOV=205×205; b=1000s/mm²; 46 3mm slices × 12 directions in addition to b=0), with images collected twice to optimize the signal to noise ratio.

In brief, image processing involved the creation of white matter regions of interest (ROIs) using Freesurfer (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002, Fischl et al., 2004), analysis of DTI data to create FA maps for each participant, followed by resampling of FA into the structural space of each subject, and extraction of mean FA values for Freesurfer-defined ROIs (Clark et al., in press). The ROI approach used here, compared to whole-brain voxel-based approaches (e.g., Tract-Based Spatial Statistics), permits tests of hypotheses involving specific brain regions with greater sensitivity (Niogi, Mukherjee, & McCandliss, 2007).

Cortical reconstruction processing and volumetric segmentation were conducted according to standard procedures using Freesurfer, a processing stream controlled by the recon-all shell script. Processing in Freesurfer included motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation and volumetry of the subcortical white matter and deep gray matter structures, intensity normalization, tessellation of the gray matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally locate the gray/white and gray/cerebrospinal fluid borders. Procedures then included registration to standard space using individual cortical folding patterns to match cortical geometry across subjects, and parcellation of the cerebral cortex into units based on gyral and sulcal structure. Next, white matter parcellation was performed, such that white matter volumes were calculated for each cortical parcellation. Freesurfer measurements and white/gray matter parcellation have been validated against histological and manual measurements (Han et al., 2006; Kuperberg et al., 2003; Rosas et al., 2002). ROIs created by Freesurfer white matter parcellation also were visually inspected to ensure anatomical accuracy. After performing Freesurfer segmentation, two participants were excluded due to inaccurate Freesurfer segmentation, as determined by visual inspection of each participant's data.

Because DTI data are highly susceptible to motion, we visually assessed motion artifacts (i.e., striping), and examined motion parameters graphically, as generated by FSL's eddy correct program (fmrib.ox.ac.uk/fsl). Three participants were excluded due to excess motion. DTI images were processed using Freesurfer's dt_recon processing stream. DTI data were motion and distortion corrected using FSL's eddy correct. DTI General Linear Model (GLM) Fit (fmrib.ox.ac.uk/fsl/fdt/) was used to fit a tensor to the corrected diffusion data at each voxel, resulting in the creation of FA maps for each participant. FA images were resampled into each participant's structural space using Freesurfer's mri_vol2vol. At this point, one subject was excluded due to failure to properly resample DTI data into structural space. FA resampling into each individual's structural space was followed by extraction of mean FA values (range: 0–1, higher values indicate greater WM integrity) within Freesurfer-defined ROIs (e.g., left frontal pole, right frontal pole; Figure 2) using Freesurfer's mri_segstats.

The 5 larger ROIs examined in this study were constructed by defining non-overlapping areas (e.g., prefrontal, orbitofrontal) that are thought to be functionally relevant for psychological regulation and treatment outcome (Clark et al., in press). The larger ROIs

were created by combining Freesurfer-defined bilateral white matter regions (see Table 2, Figure 3). Mean FA for the larger ROIs was computed by summing the volume-weighted average FA values of the Freesurfer-defined component regions (e.g. frontal pole), and dividing by total volume of the summary ROI (e.g., prefrontal region).

The prefrontal ROI (a region associated with, e.g., executive functioning processes such as response inhibition, planning; Clark et al., in press) included: frontal pole, frontal superior, frontal caudalmiddle, frontal rostralmiddle, parsopercularis, and parstriangularis. Orbitofrontal ROI (a region associated with, e.g., regulation of behavior associated with reward and punishment; Bechara, Damasio, Damasio, & Anderson, 1994) included: frontal lateral orbital, frontal medial orbital, and parsorbitalis. Parietal ROI (a region associated with, e.g., selective attention; Behrmann, Geng, & Shomstein, 2004) included parietal inferior and parietal superior subregions. Temporal ROI (a region associated with, e.g., memory-related processes) included temporal inferior, temporal middle, temporal pole, temporal superior, and temporal transverse regions. Corpus callosum (a region associated with, e.g., inter-hemispheric communication) included left and right subregions. We examined these five ROIs because prior research suggested that high FA in these areas predicted better treatment outcomes in adult substance users (Xu et al., 2010; Sorg et al., 2011).

Data analysis

Bivariate correlations were examined to determine the utility of testing the hypothesized indirect effect models. Based on correlation results (Table 3), indirect effects analyses focused on the association between the treatment-related variable of motivation to abstain from alcohol and WM integrity in 3 ROIs (prefrontal, orbitofrontal, temporal), because treatment attendance was not correlated with FA values (see Table 3). Indirect effect analyses also focused only on 6-month alcohol problem severity, because FA values were not correlated with 6-month marijuana involvement.

Tests for indirect effects (product of coefficients: *ab* in Figure 1) used a bootstrapping procedure (5,000 resamples) available as an SPSS macro (Preacher & Hayes, 2004). A significant indirect effect was indicated when the 95% bias-corrected and accelerated (BCa) confidence interval around the unstandardized coefficient did not include zero (Preacher & Hayes, 2004). Bootstrapping is a preferred method for testing indirect effects in small samples (Preacher & Hayes, 2004). The analysis sample meets the minimum sample size to test for indirect effects (Preacher & Hayes, 2004). Analyses of indirect FA effects controlled for gender (cf. Thatcher et al., 2010), age (due to WM maturation through adolescence; Giorgio et al., 2008), number of treatment days attended since IOP admission to scan (since it was not viable as an independent variable), number of drinking days in the 30 days prior to scan², and current conduct disorder diagnosis at baseline (because conduct disorder may be associated with WM integrity [Li, Mathews, Wang, Dunn, & Kronenberger, 2005], and conduct disorder was associated with younger onset of regular use of alcohol and marijuana, $r = -.61$ and $-.37$, $p < .05$, respectively). ADHD was not correlated with FA in the 5 ROIs ($p > .12$), and therefore was not included as a covariate. The above analyses evaluated statistical significance at $p < .05$; supplementary analyses were run to examine the effects of using the more stringent $p = .01$ criterion to minimize false positive results.

²Number of alcohol and marijuana abstinent days prior to the scan, when included as an additional covariate, was not a significant predictor of outcome, and did not change the pattern of results; thus, the simpler models are presented. Inclusion of IQ score as a covariate also did not change the pattern of results, so the simpler models are presented.

Results

Bivariate correlations

Prefrontal, orbitofrontal, and temporal FA values were negatively correlated with motivation to abstain from alcohol at baseline, and with 6-month RAPI score³ (Table 3). That is, contrary to prediction, greater motivation to abstain was associated with less WM integrity, but consistent with prediction, less FA was associated with greater alcohol problem severity at 6-months. This pattern of correlations suggests a potential role for these three ROIs, as intervening or linking variables, in the pathway between motivation to abstain from alcohol and 6-month RAPI score. Motivation to abstain from alcohol (independent variable in mediation model) was not correlated with 6-month RAPI score (dependent variable in mediation model) ($r=.12$).⁴ However, a significant association between independent and dependent variables is not needed to test for indirect effects (e.g., MacKinnon, 2008; Hayes, 2009).

Treatment attendance prior to imaging (mean= 18.2 ± 8.7 sessions, corresponding to roughly 6 weeks of treatment) was not significantly associated with FA values, contrary to prediction. However, because longer time in treatment tends to be associated with better outcomes (review: Chung & Maisto, 2006), treatment attendance was included as a covariate (not an independent variable) in the FA indirect effect analyses. Number of alcohol use days in the 30 days prior to the scan was not associated with FA values, but also was included as a covariate in the indirect effect analyses. FA values were not significantly associated, at 6-month follow-up, with frequency of alcohol or marijuana use, or RMPI score. However, lower FA in all five ROIs was associated with greater 6-month alcohol severity (RAPI score: Table 3).

Tests of indirect effects

Significant indirect effects linking baseline motivation to abstain from alcohol, FA values, and 6-month alcohol problem severity were detected for the three ROIs tested: prefrontal, orbitofrontal, and temporal (see Table 4 for parameter estimates). Adjusting for covariates, baseline motivation to abstain from alcohol showed a significant indirect effect on 6-month alcohol problem severity through prefrontal FA, point estimate= .555 (BCa 95% CI: .072, 1.597). Likewise, indirect effects involving orbitofrontal FA, point estimate= .485 (BCa 95% CI: .005, 1.995)⁵, and temporal FA point estimate= .721 (BCa 95% CI: .055, 2.222) in the pathway between motivation to abstain and 6-month alcohol severity were significant. In each model, motivation to abstain was negatively associated with FA, and FA was negatively associated with 6-month alcohol severity.

Accounting for multiple tests of statistical significance

We hypothesized correlations between 5 ROIs and 7 variables (i.e., alcohol motivation, marijuana motivation, treatment days attended, alcohol abstinent days, marijuana abstinent days, 6-month RAPI score, and 6-month RMPI score), for a total of 35 tests. If we use $p=.01$ to minimize false positive results, then bivariate correlations (Table 3) between baseline alcohol motivation to abstain and prefrontal ($-.49$, $p=.006$), orbitofrontal ($-.48$, $p=.007$), and temporal ($-.46$, $p=.01$) ROIs would be considered significant. Among these 3 ROIs, only prefrontal and temporal (not orbitofrontal) ROIs would be considered significantly

³6-month RAPI items correlating most highly with WM ROIs represented dyscontrolled drinking, e.g., alcohol-related fights, friends or relatives avoided you when you were drinking, tried to your control drinking

⁴In the larger treatment sample from which participants were drawn, greater baseline motivation to abstain was associated, as would be expected, with lower 6-month RAPI score ($n=148$, $r=-.16$, $p=.05$; unpublished data), although the magnitude of the correlation is relatively low, suggesting the possible effect of intervening variables.

associated with 6-month RAPI score ($-.49, p=.01$; $-.47, p=.01$; respectively). Using $p=.01$ to determine statistical significance would suggest focusing on testing mediation (i.e., following up on bivariate correlation results) for prefrontal and temporal (but not orbitofrontal) ROIs.

In the mediation analyses reported above, we used $p<.05$ to test indirect effects. If $p=.01$ is used to determine the significance of the indirect effect (with inclusion of all 5 covariates), none of the 3 indirect effects is statistically significant at $p<.01$. However, in testing a mediation model ($p<.01$) for each of the 3 ROIs (prefrontal, orbitofrontal, temporal) in which no covariates were included, the indirect effect for the prefrontal ROI was statistically significant (point estimate = .80, BCa 99% CI: .117, 2.231). Indirect effects for orbitofrontal (point estimate = .77, BCa 99% CI: $-.110, 2.858$) and temporal (point estimate = .73, BCa 99% CI: $-.085, 2.439$) ROIs were not significant at $p<.01$. In sum, using the more stringent $p=.01$ to determine statistical significance, mediation results were most robust for the indirect effect involving the prefrontal ROI.

Discussion

Investigation of intervening variables and indirect effects can reveal important linking mechanisms (Hayes, 2009) relevant to understanding treatment processes and outcomes among adolescent substance users. Bivariate correlations ($p=.01$) indicated, contrary to prediction, that greater motivation to abstain from alcohol was associated with lower FA in three brain regions (i.e., prefrontal, orbitofrontal, temporal), but, as hypothesized, that lower FA in certain regions (prefrontal, temporal, corpus callosum) predicted greater alcohol problem severity at 6-months. Given that this study is among the first to examine WM integrity as a linking variable between motivation to abstain and treatment outcome, and we were testing specific hypotheses, we used $p<.05$ to determine the selection of ROIs (i.e., prefrontal, orbitofrontal, temporal) for follow-up as possible linking variables based on bivariate correlations. Indirect effects were observed for each of these ROIs in the context of relevant covariates ($p<.05$). If a correction is applied to control for multiple comparisons (i.e., $p<.01$), only the prefrontal ROI showed a significant indirect effect, in a model with no covariates included.

Bivariate correlations indicating that greater motivation to abstain from alcohol was associated with lower FA (prefrontal, orbitofrontal, temporal ROIs) were contrary to prediction, and with research that has demonstrated that deficits in white matter, particularly

⁵Table 4 shows that for the indirect effect model in which orbitofrontal FA is the intervening variable being tested, for the B path, $p=.06$ when current conduct disorder is included as a covariate. When conduct disorder is not included as a covariate (but retaining the other covariates), the B path is statistically significant ($p<.05$). Further, the simple correlation between orbitofrontal FA and outcome is statistically significant ($p<.05$), and the overall indirect effect in the model with conduct disorder included as a covariate is estimated to be statistically significant (i.e., zero is not contained within the 95% confidence interval for the indirect effect point estimate).

Regarding possible association of age at onset of regular alcohol and marijuana use with the 5 ROIs, only age of regular alcohol onset and prefrontal FA showed a significant correlation (Table 3: $r=.50, p<.01$; youth with later onset of regular drinking tended to have higher prefrontal FA). Although including age of regular alcohol onset in the mediation analysis would increase the number of covariates to 6 (with an analysis sample of 26), the mediation model continued to indicate that prefrontal FA mediated the association between baseline motivation to abstain and 6-month RAPI score (point estimate: .47, 95% CI: .08–1.89); likewise for orbitofrontal FA (point estimate: .42, 95% CI: .03–6.65), and temporal FA (point estimate: .66, 95% CI: .07–3.00).

To address the possibility that other drug use may be associated with white matter integrity, we created a variable that summed the number of SCID abuse and dependence symptoms (i.e., 11 abuse and dependence symptoms per substance, excluding alcohol and cannabis, but including: sedative, stimulant, opiate, cocaine, hallucinogen/PCP) that were met in the 6-months prior to baseline. The actual range for this variable was 0–21 symptoms, mean = 2.9, SD = 5.1. Other drug symptom count was not correlated with any of the 5 ROIs ($p>.23$). Including other drug symptom count as a covariate (6 total covariates in each mediation model), the mediation model continued to indicate that prefrontal FA mediated the association between baseline motivation to abstain and 6-month RAPI score (point estimate: .56, 95% CI: .06–2.14); likewise for orbitofrontal FA (point estimate: .41, 95% CI: .02–3.84), and temporal FA (point estimate: .77, 95% CI: .13–2.63). Including marijuana symptom count as a covariate in the alcohol mediation analyses also did not change the results.

for prefrontal regions, are associated with decreased executive cognitive functioning (e.g., Clark et al., in press), which includes metacognitive abilities such as insight into the possible adverse consequences of risky behaviors. The unexpected findings, however, are consistent with a study in which lower (rather than higher) executive cognitive functioning (ECF) was associated with greater motivation to change in young adult drinkers who were concerned about their alcohol use (Blume & Marlatt, 2009). Blume and Marlatt (2009) interpreted their findings as suggesting that drinkers with lower ECF might have some awareness of their difficulties in behavioral regulation, which could contribute to greater motivation to change and marshalling of resources to support behavior change. Similarly, in this adolescent treatment sample, those with lower FA, particularly in the prefrontal ROI, which is associated with executive cognitive functioning, might have had some awareness of potential problems related to continuing alcohol use, and greater motivation to abstain from alcohol. In addition, the similar pattern of bivariate correlations for orbitofrontal and temporal ROIs might reflect a possible connection between WM integrity in regions associated with processing of reward and punishment, and memory functions (e.g., for past alcohol-related problems), respectively, in relation to level of motivation to abstain from alcohol during treatment, a context in which a goal to abstain from drinking is encouraged. However, given the unexpected direction of the correlations, replication of these results is warranted.

The finding that lower FA in certain brain areas predicted 6-month alcohol problem severity is consistent with adult treatment studies, in which WM integrity predicted later cocaine or alcohol use (Xu et al., 2010, Sorg et al., 2011). Of note, greater FA in all five of this study's ROIs was associated with lower 6-month alcohol problem severity ($p < .05$), with the largest associations observed for prefrontal, orbitofrontal, temporal, and corpus callosum ROIs ($p < .01$). These results suggest that, similar to the adult studies, greater WM integrity in multiple brain regions is associated with better treatment outcome in adolescents. In contrast to the studies of treated adults, however, FA did not predict level of alcohol/marijuana "use" in this sample of treated adolescents. Results suggest that a more severe indicator of substance involvement (i.e., substance-related problems) was needed here, and might reflect developmental differences between treated adolescents and adults in, for example, motivation to "abstain" from specific substances.

The specificity of the FA association to alcohol problem severity in this adolescent treatment sample suggests the possibility that substance-specific differences, for example, in the duration of use (e.g., age of onset of regular use), or the types of problems experienced as a consequence of using a particular substance (e.g., physical fights more likely to occur as a result of alcohol, than marijuana use) could partially explain the alcohol-specific associations observed. Sample-specific characteristics, such as the higher prevalence of marijuana, compared to alcohol, use disorder at baseline in this treatment sample also might have influenced the results obtained. For example, motivation to abstain from alcohol during treatment may have been most relevant to a certain subgroup of youth within this sample, since marijuana was used, on average, more frequently relative to alcohol prior to treatment.

Mediation analyses, using a more lenient criterion to determine statistical significance ($p < .05$) in the context of covariates, suggested indirect effects of prefrontal, orbitofrontal, and temporal ROIs as links in the association between motivation to abstain from alcohol during treatment and alcohol problem severity at 6-month follow-up. These three regions are consistent with brain areas for which SUD youth had lower FA compared to controls (Squeglia et al., 2009). WM integrity in each of these ROIs might be associated with the translation of "motivation to abstain" into the initiation and maintenance of abstinence from alcohol in a sample of treated youth. After controlling for multiple comparisons (with the caveat that this control might result in "missed" or "overlooked" findings), however, the

indirect effect only for the prefrontal ROI was statistically significant ($p < .01$, with no covariates). WM integrity in the prefrontal ROI, which is associated with executive cognitive functioning (Clark et al., in press) and behaviors such as effective cognitive control and response inhibition (Chung et al., 2011), appears to provide a link between “motivation to abstain from alcohol” during treatment and alcohol problem severity at 6-month follow-up. Given that WM integrity might improve or be restored with abstinence from alcohol (e.g., Gazdzinski, Durazzo, Mon, Yeh, & Meyerhoff, 2010), and WM continues to develop into young adulthood (e.g., Bashat et al., 2005), abstinence from alcohol remains an important treatment goal.

Other treatment-related variables, such as number of treatment sessions attended and length of abstinence from alcohol and marijuana prior to the scan, were not associated with FA values. The duration of abstinence (e.g., recommended 6–8 weeks of outpatient treatment) that might be related to IOP treatment in this study might not have been long enough to observe effects of abstinence in relation to FA. In addition, treatment “dose” as represented by number of sessions attended might not adequately reflect treatment effects, relative to constructs (e.g., readiness to change) that may better capture the extent to which treatment content has been absorbed and applied by an adolescent.

WM deficits may be associated with both co-occurring psychopathology (i.e., conduct disorder) and substance involvement. In this sample, conduct disorder was correlated with lower prefrontal and orbitofrontal FA, similar to a study that found lower FA in frontal (and temporal) regions in youth with disruptive behavior disorders (Li et al., 2005). Research has indicated that lower FA in the ROIs investigated may signify a premorbid condition that may serve as a risk factor for the development of a substance use disorder (e.g., review: Tessner & Hill, 2010). Thus, study findings need to be interpreted in the context that WM deficits, particularly those associated with disruptive behavior, may have existed prior to substance use, resulted from substance use, or been exacerbated by substance use. Research is needed to determine the role of WM integrity in the development of and desistance from externalizing behaviors and substance use.

Study limitations warrant comment. Sample size was relatively small, and may have provided limited power to detect certain effects. Although this study’s voxel-based approach is no more susceptible to measurement error (e.g., crossing fiber and partial volume effects) in generating estimates of FA relative to other methods (e.g., Tract based spatial statistics), study findings warrant replication. A relatively large number of analyses was conducted; the Type I error rate (i.e., false positive results) for the study is a limitation that urges replication of study findings given the number of statistical tests conducted with limited sample size. A control group was not included in these analyses, although prior work with this treatment sample reported lower FA in specific regions (e.g., prefrontal and parietal ROIs) relative to healthy controls (Clark et al., in press). It is important to note that other factors, which were not assessed in the study, such as prenatal substance exposure, lifetime total alcohol use, and neurological illness or insult, might have impacted WM integrity and warrant investigation as possible confounding factors. More specific measures of treatment process (e.g., improvement in coping responses) appear to be needed to increase understanding of the associations between treatment attendance, WM integrity, and treatment outcomes. Ideally, pre- and post-treatment scans would be used to detect possible effects of an index episode of treatment on WM integrity and cognitive functioning.

There is a need to better specify and test possible treatment-related mechanisms that may impact brain structure and functioning, and that might result in improved treatment outcomes. For example, extended abstinence during or as a result of treatment may influence WM integrity, and training in certain skills (e.g., meditation) might enhance WM integrity

(e.g., Tang et al., 2010). Results in this adolescent treatment sample suggest substance-specific effects associated with FA (particularly in the prefrontal region) in relation to treatment outcomes, and that, lower FA may explain greater alcohol problem severity at 6-months, despite relatively high motivation to abstain from alcohol. WM integrity could provide an important link, and potential target for intervention, in the pathway between motivation and outcome in treated adolescents.

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STUDY TIMELINE

Figure 1.

Model of the indirect effect of white matter integrity in the association between baseline motivation to abstain from alcohol and 6-month alcohol problem severity

Notes:

C' = direct effect of independent variable (motivation to abstain) on the dependent variable (alcohol problems at 6-months) after controlling for the intervening variable (white matter integrity).

Covariates: gender, age, number of treatment days attended since the start of intensive outpatient treatment to scan day, number of alcohol use days in the 30 days prior to scan, and current conduct disorder diagnosis at baseline

Figure 2.
Freesurfer-defined subregions of interest overlaid on a representative participant's brain

Figure 3.

“Composite” regions of interest used in analyses, overlaid on a representative participant’s brain

Note: The gray region between the prefrontal and parietal regions of interest was not included in the analyses conducted here; this gray region includes the post-central area (primary and secondary somatosensory cortex) and pre-central area (motor cortex of the frontal lobe).

Table 1

Baseline sample descriptive statistics

Demographics	n	%
Gender: Female	13	40.6
Male	19	59.4
Ethnicity		
European American	29	90.6
African American	2	6.3
Multi-racial	1	3.1
	<u>Mean (SD)</u>	
Age	16.7 (1.1)	
Socio-economic status	2.6 (1.2)	
WASI IQ score	98.4 (12.6)	
Frequency of substance use (past 6 months)		
Alcohol use	3.2 (1.7)	
Cannabis use	5.6 (2.6)	
Tobacco use	6.1 (3.0)	
	<u>n</u>	<u>%</u>
Current DSM-IV alcohol use disorder	15	46.9
Alcohol Abuse	11	34.4
Alcohol Dependence	4	12.5
Current DSM-IV cannabis use disorder	29	90.6
Cannabis Abuse	20	62.5
Cannabis Dependence	9	28.1
Current DSM-IV nicotine dependence diagnosis	10	31.3
Current DSM-IV "other drug" diagnosis ^I	14	43.8
Current DSM-IV psychopathology	<u>n</u>	<u>%</u>
Major depression	5	15.6
Conduct disorder	11	34.4
Attention deficit hyperactivity disorder	12	37.5
Oppositional defiant disorder	3	9.4

Notes: N=32. SD= standard deviation. Current=past 6 months. WASI= Wechsler Abbreviated Scale of Intelligence. Frequency of substance use: 0=never tried, 1=no use in past 6 months, 2=less than once per month, 3=once per month, 4=2–3 times per month, 5=once per week, 6=2–3 times per week, 7=4–6 times per week, 8=daily. "Other drug" refers to substances other than alcohol, cannabis or nicotine.

^I Among those with a current "other drug" diagnosis at baseline (n=14), the most common were related to opiates (n=10; 6=abuse, 4=dependence) and cocaine (n=6; 4=abuse, 2=dependence).

Table 2

Descriptive statistics for white matter, treatment, and alcohol and marijuana involvement

	<u>Mean</u>	<u>SD</u>
Fractional anisotropy (N=32)		
Prefrontal	0.348	0.023
Orbitofrontal	0.329	0.028
Parietal	0.363	0.034
Temporal	0.312	0.024
Corpus callosum	0.494	0.034
Age at regular alcohol use	14.8	1.5
Age at regular marijuana use	14.1	1.9
BL motivation to abstain from alc in the next 30 days	6.3	3.6
BL motivation to abstain from mj in the next 30 days	7.5	3.4
Number of treatment days attended prior to the scan	18.2	8.7
Number of days abstinent from alcohol prior to scan	81.0	154.3
Number of days abstinent from marijuana prior to scan	55.4	67.1
Days of alcohol use in the 30 days prior to scan	1.6	2.8
Days of marijuana use in the 30 days prior to scan	5.8	10.8
Alcohol frequency at 6-mo (n=26)	3.0	1.9
Marijuana frequency at 6-mo (n=26)	2.9	2.5
6-mo RAPI score (n=27)	7.2	9.2
6-mo RMPI score (n=26)	9.8	11.8
Total drinks at 6-months (n=31)	34.4	71.3

Notes: N=32 unless noted otherwise. SD=standard deviation, BL=baseline, alc=alcohol, mj=marijuana, 6-mo= 6-month follow-up, RAPI= Rutgers Alcohol Problem Index, RMPI=Rutgers Marijuana Problems Index, Total drinks at 6-months= Total number of drinks consumed in the 30 days prior to 6-month follow-up (some adolescents who missed 6-months provided this TLFB-based data at a later follow-up). Substance use frequency response categories are listed in a note to Table 2.

Table 3

Correlations among white matter fractional anisotropy, treatment, and substance use

	Prefrontal	Orbitofrontal	Parietal	Temporal	Corpus callosum
Current conduct disorder (yes/no)	-.39 *	-.37 *	-.22	-.33	-.16
Full scale IQ score	.09	.12	.24	.29	-.17
Age at regular alcohol use	.50 **	.36	.08	.23	.04
Age at regular marijuana use	.22	.21	.24	.25	.09
BL Alcohol Motivation to Abstain	-.49 **	-.48 **	-.11	-.46 *	-.15
BL Marijuana Motivation to Abstain	.03	-.27	.20	.17	-.12
Treatment days attended	.21	.02	-.08	.13	.06
Alcohol abstinent days pre-scan	-.13	-.06	-.15	-.01	-.12
Marijuana abstinent days pre-scan	.12	-.06	.09	.04	-.10
Alcohol use days prior to scan	.14	.13	.09	.19	-.03
Marijuana use days prior to scan	.12	.32	.00	.00	.40 *
Alcohol frequency at 6-months	-.12	.00	-.20	-.17	.01
Marijuana frequency at 6-months	-.01	.18	.03	-.06	.35
6-month RAPI score	-.49 **	-.45 *	-.42 *	-.47 *	-.58 **
6-month RMPI score	-.23	-.17	-.04	-.01	-.30
Total number of drinks at 6-mo	-.13	-.23	-.37 *	-.36 *	-.22

Notes: Ns range from 26–32 due to missing data for certain items.

* p<.05,

** p .01.

Current=past 6 months. BL Alc/MJ Motiv=Baseline motivation to abstain from alcohol/marijuana in the next 30 days. Treatment days= number of treatment days attended from the start of intensive outpatient treatment to scan day. Alcohol/Marijuana use days prior to scan=number of days of use in the 30 days prior to imaging. 6-mo: 6-month follow-up. RAPI/RMPI=Rutgers Alcohol/Marijuana Problems index at 6-months. Total drinks 6-mo= total number of drinks in the past 30 days at 6-month follow-up.

Table 4

Parameter estimates for models testing indirect effects of white matter fractional anisotropy on the association between motivation to abstain and alcohol problem severity

	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
A path	0.00	0.00	-2.38	.03
B path	-194.68	75.59	-2.57	.02
C path	0.36	0.46	0.77	.45
C' path	-0.21	0.46	-0.46	.65
Controls	-2.53	2.97	-0.85	.40
Age	-0.79	1.27	-0.62	.54
Days alcohol use	1.24	0.49	2.54	.02
Treatment days	0.16	0.18	0.89	.38
Conduct disorder	6.65	3.32	2.00	.06
Model summary: $R^2=0.65$, $F(7, 18)=4.75$, $p=.004$				
A path	0.00	0.00	-2.50	.02
B path	-110.92	56.35	-1.97	.06
C path	0.36	0.46	0.77	.45
C' path	-0.13	0.50	-0.26	.80
Controls	-2.93	3.14	-0.93	.36
Age	-0.78	1.35	-0.57	.57
Days alcohol use	1.22	0.52	2.36	.03
Treatment days	0.01	0.19	0.06	.95
Conduct Disorder	6.72	3.56	1.89	.07
Model summary: $R^2=0.60$, $F(7, 18)=3.93$, $p=.01$				
A path	0.00	0.00	-2.68	.01
B path	-210.99	67.29	-3.13	.006
C path	0.36	0.46	0.77	.45
C' path	-0.38	0.45	-0.84	.41
Controls	-1.27	2.89	-0.44	.66
Age	-0.91	1.20	-0.76	.45
Days alcohol use	1.28	0.46	2.80	.01

	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Treatment days	0.19	0.17	1.08	.29
Conduct disorder	8.08	3.06	2.64	.02
Model summary: $R^2=0.69$, $F(7, 18)=5.71$, $p<.001$				

Notes: $n=26$ (in addition to the 4 participants not followed at 6-months, 2 participants who reported no alcohol use in the past 6 months at baseline left the “motivation to abstain from alcohol” item blank, which was coded as “missing” data), B = unstandardized coefficient, SE =standard error. “Mediator”=intervening variable being tested. OF =orbitofrontal. Days alcohol use=Number of drinking days in the 30 days prior to scan. Treatment days=Number of treatment days attended from the start of intensive outpatient treatment to the scan. Conduct disorder (0=no, 1=yes)=current conduct disorder diagnosis at baseline A path (see Figure): independent variable (baseline motivation to abstain from alcohol) to intervening variable (fractional anisotropy). B path: direct effect of intervening variable (fractional anisotropy) on dependent variable (6-month Rutgers alcohol problems inventory score). C path: Total effect of independent variable (baseline motivation to abstain from alcohol) on dependent variable (6-month Rutgers alcohol problems inventory score). C' path: Direct effect of independent variable (baseline motivation to abstain from alcohol) on dependent variable (6-month Rutgers alcohol problems inventory score), after controlling for the intervening variable (white matter integrity). Controls: partial effect of control variables on dependent variable.