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Substance-use initiation moderates the effect of stress on white-matter microstructure in adolescents

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Abstract

Background—While childhood stress may contribute risk to substance-use initiation and differences in brain white-matter development, understanding of the potential impact of substance-use initiation on the relationship between experienced stress and white-matter microstructure remains limited.

Objectives—This study examined whether substance-use initiation moderated the effect of perceived stress on white-matter differences using measures of primary white-matter fiber anisotropy.

Methods—Forty adolescents (age $14.75 \pm .87$ years) were assessed on the Perceived Stress Scale, and 50% were determined to have presence of substance-use initiation. White-matter microstructure was examined using primary-fiber orientations anisotropy, which may reflect white-matter integrity, modeled separately from other fiber orientations in the same voxels.

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Analyses were conducted on regions of interest previously associated with childhood stress and substance use.

Results—Lower perceived stress and presence of substance-use initiation were related to greater right cingulum primary-fiber measures. Substance-use-initiation status moderated the association between perceived stress and right cingulum primary-fiber measures, such that higher perceived stress was associated with lower right cingulum primary-fiber anisotropy in adolescents without substance-use initiation, but not in those with substance-use initiation.

Conclusions and Scientific Significance—Findings in primary-fiber anisotropy suggest differences in right cingulum white-matter integrity is associated with substance-use initiation in higher-stress adolescents. This reflects a possible pre-existing risk factor, an impact of early substance use, or a combination thereof. Examination of potential markers associated with substance-use initiation in white-matter microstructure among stress-exposed youth warrant additional investigation as such biomarkers may inform efforts relating to tailored interventions.

Keywords

Primary fibers; Diffusion Tensor Imaging; Stress; Substance-Use Initiation; White matter

INTRODUCTION

Childhood experiences of psychological stress, including maltreatment and trauma, have been associated with differences in brain structure and function in regions implicated in adult psychopathology.¹ Hyper-activation of the stress systems, which include the adrenomedullary system, and the hypothalamic-pituitary-adrenocortical (HPA) system, responsible for producing cortisol, potentially leads to neurotoxic effects.² In the developing brain, elevated levels of stress chemicals may lead to abnormal brain development through loss of neurons and dendritic spines,³ and interruptions in myelination.⁴ Prolonged stress may have lasting effects on the brain including reduced cell proliferation⁵ and lower spine densities in neurons of the prefrontal cortex.⁶ While acute stress is associated with changes in neuronal physiology, signaling, and gene expression,⁷ early exposure to stress may potentiate later cortisol responses to acute stress.⁸

Diffusion-weighted MRI (dMRI), with the application of tensor models termed diffusion tensor imaging (DTI), has been employed to assess white-matter characteristics across development. Fractional anisotropy (FA), a metric of overall directionally dependent water diffusion, increases throughout childhood and adolescence in white-matter regions critical to self-regulation and reward motivation including the cingulum, corpus callosum, and superior longitudinal fasciculus (SLF).⁹ Early stress has been linked to white-matter differences, suggesting alterations in several areas containing association and commissural fiber tracts. Specifically, decreased FA was found in the corpus callosum among children and adolescents exposed to maltreatment.^{10,11} Adults who experienced childhood maltreatment demonstrated decreased FA in the cingulum and SLF.¹² Results of a meta-analysis of dMRI findings among healthy and traumatic-stress-exposed adults showed that lower FA values in cingulum and SLF clusters in traumatic-stress-exposed individuals converged across multiple studies.¹²

Early substance-use initiation (SI), which strongly relates to the risk of subsequent substance-use disorders, may also be particularly harmful to white-matter microstructural integrity.¹³ The presence of substance use has been associated with microstructural differences in multiple white-matter pathways similarly observed in individuals with early stress, including association and commissural tracts that connect multiple cortical areas within and between cerebral hemispheres.^{12,14} Adolescents who initiated substance use showed reduced FA in multiple white-matter clusters throughout the brain, including the corpus callosum and SLF, which facilitates executive functions and attention.¹⁵ Youth who initiated drinking, compared to those who remained non-initiated, showed attenuated increases in white-matter volume in a 3.5-year follow-up.¹⁶ These findings suggest that differences in these intrahemispheric and callosal white-matter tracts may be indicative of SI.

Most research to date on the contributions of SI and perceived stress to white-matter differences has focused on their individual effects. Recent data suggest that stress and SI may interact on brain white-matter microstructure. One of the few initial studies on the relationship between substance involvement and stress on white-matter microstructure, which are limited to clinical samples, found differences in cingulum FA between patients with alcohol-use disorder (AUD) and those with comorbid post-traumatic stress disorder (PTSD) and AUD, suggesting a more severe deleterious effect of AUD on white-matter among PTSD patients.¹⁷ Additionally, substances with abuse liability may heighten stress responses including stress hormone release.⁸ In light of evidence for the neurotoxic effects of high stress, these studies suggest that SI may moderate the relationship between stress and differences in white-matter microstructure. However, as this relationship has not been directly examined, research is necessary to delineate a potentially moderating role of SI in the relationship between perceived psychological stress and white-matter microstructure in non-clinical adolescents to better understand the relationships between neurophysiological factors and SI in stress-exposed adolescents. Given the stress often experienced relative to minority status and social disadvantage, the current study investigated predominantly racial/ethnic minority youth of low socio-economic status.

Together, evidence suggest differences occur in measures of white-matter FA among individuals with high stress and SI. However, the percentage of multiple fiber orientations contributing to a single voxel is estimated to be 63–90% of the brain's white-matter-containing voxels, as most white-matter tracks transverse regions with different fiber orientations along their paths.¹⁸ While clusters of single fiber voxels may be found, mainly in the largest bundles (e.g., parts of the corpus callosum), large clusters of voxels containing two or more fiber orientations are also present throughout the brain, including the SLF and corpus callosum.¹⁸ Hence, the current study focuses on the white-matter primary-fiber (PF) population anisotropy, estimated apart from possible other differently oriented white-matter fibers in the same voxel using the crossing fiber model.¹⁹

As the tensor model assumes a Gaussian diffusion profile that does not specifically account for complex tissue microstructure, changes in tensor-based scalar measures, including overall anisotropy of FA, may not always be related to micro-architecture in a straightforward manner.²⁰ The crossing-fiber model estimates the anisotropy of white-matter fiber

populations with distinct orientations (e.g., PF), which allows less ambiguous interpretations in regions with complex micro-architecture than traditional tensor-based measures.^{19,20} The advantages include the ability to infer the integrity of dominant direction PF bundles among differently oriented fibers. This approach was recently used to examine white-matter microstructure differences in adults with addictions and will provide a more specific examination of white-matter differences.^{20,21}

The aim of the current study was to determine the moderating effect of SI on the relationship between perceived stress and white-matter PF microstructure. To that end, this study examined white-matter fiber anisotropy in regions of interest (ROIs) defined *a priori* in a comprehensive review and meta-analysis of multiple studies to be associated with early experiences of adversity and stress.¹² The strength of this approach is in enabling complex modeling and analysis of independent ROIs that is not biased by “double-dipping”²² and is focused on regions associated with stress exposure as identified across multiple studies. Furthermore, to better resolve microstructural properties in the ROIs, this study also explored tract-based-spatial-statistic measures that allow modeling and analysis of anisotropy in PF orientation, separate from putative differently oriented fibers, in each voxel.¹⁸ We hypothesized that SI would moderate a negative association between perceived stress and PF anisotropy, indicating a SI-dependent difference in the relationship between stress and PF measures.

METHODS

Participants

Forty adolescents (65% boys) between 14 and 18 years of age (mean=14.75, SD=.87) completed dMRI and had sufficient imaging data as part of a larger, ongoing longitudinal study of youths²³ who were recruited in a metropolitan area in the state of Connecticut at birth and followed every 6 months thereafter. The sample was predominantly African American (80%), with a minority of Caucasian (7.5%) and other (12.5%) participants. IQ (mean=93.46, SD=13.9, range=65–134) was determined using the Kaufman Assessment Battery for Children composite score (KABC). Twenty-six (65%) of the adolescents were prenatally exposed to cocaine, as determined by urine screen at prenatal visits or delivery and maternal-reported use during pregnancy. Prenatal cocaine exposure was controlled for as a factor of non-interest in all analyses. Though the current hypothesis has yet to be addressed, previous studies have found no differences in primary white-matter anisotropy between prenatally cocaine-exposed and non-exposed adolescents within brain regions that overlapped within this study.²⁴

Procedures were approved by the Yale Human Investigation Committee and written informed consent was received from the parent (with participant assent) or participant. Exclusion criteria included any contraindication to scanning such as non-removable metal in the body and significant discomfort with MRI due to body size or claustrophobia, significant medical or mental illness, significant head trauma, use of psychotropic medications, and medications that might influence autonomic responses. No participants met criteria for any Axis-I disorder assessed with the National Institute of Mental Health Diagnostic Interview Schedule for Children (NIMH DISC-IV).

Psychological Stress

Psychological stress was assessed on a Likert scale using the 10-item Perceived Stress Scale (PSS; mean=10.43, SD=4.2),²⁵ a validated and widely used self-reported instrument measuring subjective experiences of stress that is appropriate for use in adolescents.²⁶ PSS scores were selected from the same time point across all participants. Higher levels of psychological stress measured by the PSS has been associated with higher cortisol levels, poorer health practices, and greater substance use.²⁵

Substance-Use Initiation

As previously described,²⁷ adolescent SI was determined by self-reports on the Youth Risk Behavior Survey²⁸ and toxicology results from laboratory-analyzed urine samples obtained at study visits. Samples were analyzed for the presence of amphetamines, cocaine, cotinine (for nicotine/tobacco use), ethyl glucuronide (for alcohol use), opiates, phencyclidine, and tetrahydrocannabinol (for cannabis use). Substance use was coded as a dichotomous variable (yes/no). Adolescents who indicated initiating or had recreational use of a substance, or showed a positive urine drug screen by the time of their dMRI scan, were classified as having SI, and others were considered as not having SI. Previous indices using dichotomous indicators of SI across ten drug categories have shown to be reliable and prognostic of health and psychiatric disturbances, as well as level of substance-use behavior and substance-use-disorder severity²⁹. Twenty adolescents (50%) were classified as having SI. The most commonly used substances reported among these adolescents were alcohol (80%), marijuana (65%), and tobacco (60%), and 55% reported use of more than one substance. PSS scores did not differ between adolescents with SI (mean=10.5, SD=4.74) and those without SI (mean=10.35, SD=3.59) ($t(38)=-.11$, $p=.91$).

Image Acquisition, Pre-processing, and Diffusion Estimates

As described previously²⁴, forty contiguous slices parallel to the AC-PC line were acquired using two 3T Siemens Trio scanners with the following parameters: TR=7400ms; TE=115; B values=0, 1000s/mm²; bandwidth=1396 Hz/px; directions=32 [+0]; matrix=128×128; FOV=256×256mm²; slice thickness=3.0mm; averages=2. Due to an equipment upgrade, nine participants were scanned on one Siemens 3T Trio system, and remaining subjects were scanned on another Siemens 3T Trio system. All analyses controlled for scanner.

As previously,³⁰ diffusion magnetic resonance imaging (dMRI) data were analyzed with tract-based spatial statistics (TBSS) in FSL.^{20,31} DMRI acquisitions (two per participant) were affine-registered to correct for gradient coil eddy currents and head movement.³¹ After averaging the acquisitions and performing brain extraction, the diffusion tensor was fitted on corrected data and FA was calculated. FA images were aligned to a common space (FMRIB58_FA) using nonlinear registration (FNIRT) and affine-transformed to MNI152 space. Standard-space FA images were concatenated, averaged and thinned to create the mean FA skeleton common across all participants.³¹

Diffusion estimates of anisotropy for the PF orientation per voxel were calculated using the Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques for Crossing Fibers (BEDPOSTX) in FSL.^{19,20} This employs Markov Chain Monte Carlo

sampling to build empirical distributions of diffusion parameters, then estimates the mean PF orientations and the portion of the total anisotropic volume accounted for by the PF orientation, among other putative fibers populations, denoted as primary partial volume estimates.^{19,20} Estimates for each voxel were incorporated in TBSS analyses using `tbss_x`.²⁰ Individual participant aligned anisotropy data were projected onto the mean skeleton for analyses.

ROI Analysis of Diffusion Estimates

The bilateral genu, body, and splenium of the corpus callosum, cingulum, and left and right SLF were selected *a priori* as ROIs implicated in stress and substance use^{12,14} to assess their moderating effect on primary white-matter fiber microstructure. The ROIs were defined using the JHU ICBM-DTI-81 white-matter labels atlas in FSL³² and applied directly to single-subject diffusivity maps to generate mean ROI values for PF measures. Hence, for each ROI, this produced diffusion estimates for the primary/majority white-matter fiber population that contributed to the anisotropic volume within each voxel.

Statistical Analyses

Statistical analyses were conducted using SPSS 24. Pearson and bi-serial correlations were used to determine the relationships between perceived stress, SI, and PF measures in *a priori*-defined anatomical ROIs. Significant correlations were indicated by $p < .01$ to reduce Type I errors from multiple ROIs in correlation analyses. Because moderation presumes an independent-dependent variable relationship,³³ moderation analyses focused on ROIs having correlations with perceived stress. Moderation analyses were conducted in PROCESS for SPSS,³⁴ which is effective in handling limited sample sizes through the use of bootstrapping.³⁵ Perceived stress scores, PF, and SI status were included respectively as the independent, dependent, and moderator variables. The statistical procedure also calculates the conditional effects of perceived stress on PF in the groups with and without SI. A significant moderating effect was indicated when the perceived stress and SI interaction and the variance in PF accounted for by the model reached statistical significance ($p < .05$). Moderation analyses, with 5000 bootstrap resamples, were conducted and 95% confidence intervals were calculated. All analyses controlled for demographic variables of age, gender, IQ, prenatal exposure and MRI scanner as factors of non-interest.

RESULTS

Sample Demographics

Demographic information is displayed in Table 1. The distributions of gender, race/ethnicity, and prenatal cocaine exposure were comparable between adolescents with and without SI (all $p > .1$). Age and IQ were also equivalent between groups (all $p > .1$). These variables were also not correlated with perceived stress (all $p > .1$). Inasmuch as the demographic variables were not associated with the independent and moderator variables, they may possibly impact adolescent white-matter. Hence, these demographic variables were statistically controlled in white-matter analyses to more precisely elucidate the effects of perceived stress and SI.

Intercorrelation Between Perceived Stress, Substance-Use Initiation, and Primary Fiber Anisotropy

The results of correlation analyses are shown in Table 2. Regional white-matter PF anisotropy was significantly correlated between each ROI ($p < .01$), except between right cingulum and corpus callosum body (Pearson $r = .29$, $p = .04$), as well as between left cingulum and bilateral genu (Pearson $r = .33$, $p = .02$) and splenium (Pearson $r = .21$, $p = .1$) of the corpus callosum. Both perceived stress (Pearson $r = -.38$, $p = .01$) and SI (Pearson $r = .44$, $p = .003$) were correlated with right cingulum PF. While the independent variable, perceived stress, was also related to left SLF PF (Pearson $r = .31$, $p = .03$), it did not reach the $p < .01$ threshold. As no other ROIs except the right cingulum (Figure 1a) was significantly associated with perceived stress, which precludes the independent-dependent variable relationship for moderation,³³ subsequent analyses focused on measures of right cingulum PF anisotropy.

Substance-Use Initiation Moderates Perceived Stress and Primary White-Matter Fiber Anisotropy

In the overall moderation model, perceived stress, SI, and their interaction accounted for significant variance in the right cingulum PF anisotropy ($R^2 = .56$, $p < .001$). A significant perceived-stress-by-SI interaction effect on anisotropy in the right cingulum was found ($b = .01$, $p = .03$, 95%CI = .001, .01). The interaction accounted for a significant proportion of variance in the right cingulum anisotropy beyond the individual variables ($R^2 = .05$, $f(1,31) = 4.97$, $p = .03$). Simple slopes analysis of the conditional effects in the moderation relationship showed that perceived stress was significantly associated with right cingulum anisotropy in adolescents with no SI ($b = -.01$, $p = .04$, 95%CI = $-.01$, $-.001$), but not in those with SI ($b = .001$, $p = .60$, 95%CI = $-.003$, $.005$), as shown in Figure 1b.

Additionally, gender-related differences and other factors may impact adolescent white-matter findings in relationship to SI. However, within the model, gender ($b = .01$, $p = .31$, 95%CI = $-.01$, $.04$), age ($b = .02$, $p = .11$, 95%CI = $-.004$, $.03$), and prenatal cocaine exposure ($b = .01$, $p = .48$, 95%CI = $-.02$, $.05$) were not associated with right cingulum PF anisotropy. Together with no associations found between demographic variables and perceived stress or SI (Table 1), these results further suggest the moderating relationship was not impacted by these factors in the current study.

DISCUSSION

This is the first study to investigate the moderating effect of SI on the relationship between psychological stress and primary brain white-matter fiber anisotropy derived from tract-based-spatial-statistics incorporating local-orientation modeling.^{19,20} While crossing fibers may not necessarily confound traditional anisotropy measures (e.g., FA) in all areas of the brain, this modeling isolates the contribution of the primary white-matter fibers from differently oriented fiber populations in the same voxel, allowing for more comprehensive and precise analyses. Given the adverse effects of experienced stress on white-matter development, this study focused on *a priori*-defined ROIs that were previously associated with early stress exposure (i.e., maltreatment) and PTSD across multiple studies.¹² While

the current analyses utilized measures of perceived stress, the results that lower stress was related to greater right cingulum PF anisotropy resonate with those using these distinct yet theoretically linked stress-related measures. Within the right cingulum, a significant moderation effect of SI was found such that greater perceived stress was related to lower right cingulum PF anisotropy among adolescents without SI. However, greater perceived stress was not related to lower right cingulum anisotropy in those with SI.

The unexpected finding of a positive correlation between SI and greater right cingulum PF is contrary to studies that observed substance-use associations with reduced FA in multiple white-matter tracts.³⁶ While most studies examined the effects of one substance, the heterogeneity of substances used by our study participants as well as their adolescent developmental status may partly contribute to the mixed findings, particularly given associations between tobacco-smoking and increased FA in adolescents.³⁷ In a recent systematic review, Gogliettino and colleagues³⁷ highlighted evidence that adolescent and young adult smokers had elevated FA in white-matter regions including the cingulum, corpus callosum and SLF. As 60% of the current study participants with SI reported tobacco use, this feature may have contributed to the observed positive relationship between SI and higher right cingulum anisotropy. In a previously studied clinical sample, adolescents diagnosed with AUDs demonstrated higher white-matter FA compared to sociodemographically similar healthy controls.³⁸ The authors suggested that elevated FA values may indicate a pre-morbid vulnerability, in that accelerated myelination may not be optimal and might enhance risk of substance-use disorders in adolescents.³⁸ Our findings of elevated anisotropy in the right cingulum appear in line with this hypothesis, though in regards to the risk of SI. However, as recently reviewed by Silveri and colleagues,³⁹³⁸³⁷³⁷³⁷ complex changes in white-matter may vary by region, severity, and different substances in a manner beyond the scope of the current study. Hence, other types of SI warrant future consideration, and additional longitudinal research incorporating white-matter measures before and after SI should be conducted to examine further these relationships.

Perceived-stress-related reduction in right cingulum PF was found in adolescents without SI, but not in those with SI. Previous studies on stress and substance involvement interactions on white-matter measures were largely limited to clinical populations, making comparisons with the current findings difficult. However, parallels may still be drawn with the current results in premorbid adolescents. One previous study similarly showed no FA differences between alcohol-dependent adults with and without PTSD in the bilateral cingulum.⁴⁰ The findings suggested that anisotropic indicators of white-matter microstructure related to AUD vulnerabilities and traumatic stress may 'average out'. Our findings of diminished cingulum PF in higher-stress adolescents without SI to 'average out' stress effects in the current study is consistent with this interpretation of the lack of cingulum FA differences between alcohol-dependent adults with and without PTSD in the previous study.⁴⁰

Furthermore, greater FA in multiple white-matter tracts were recently reported in individuals with co-occurring panic disorder and AUDs compared to those with only panic disorder.⁴¹ Building on these data, our findings suggest the impact of SI on the relationship between stress and white-matter microstructure may not be immediately apparent on dMRI-based measures. Substance use may alter multiple physiological factors linked to differences in

white-matter measures. As reviewed by Gogliettino and colleagues,³⁷³⁶³⁵ nicotine has been demonstrated to enhance nerve growth factor expression, neurogenesis, and myelination. Additionally, cannabinoids may reduce damaging inflammatory activity, oxidative stress, and excitotoxic neuronal cell death.⁴² Future studies may more accurately examine the neuropsychological and behavioral correlates of stress by accounting for adolescent substance use. Furthermore, precise investigations of white-matter connectivity may help elucidate the relationship between dMRI measures, brain functioning, and behavior among adolescents with differing substance-use behaviors and stress levels.

Several study limitations should be considered. Classification of SI included a range of drugs with abuse potential, and was limited to initiation and intermittent recreational use of drugs. Given the limited sample, the interpretation of findings could not be related to any one specific substance and propensity score matching of subjects, which allows more stringent stress and SI comparisons, was precluded. Whereas the current study examined a single model to reduce Type 1 errors, further examination of other models regarding the extent of substance-use involvement on the perceived stress and white-matter microstructure relationship should be conducted. Given the diversity of substance-use patterns, analyses were not sufficiently powered to explore within-group effects related to initiation of use of different substances and patterns thereof (e.g., mono- and poly-substance use) or the timing, quantities, and durations of use. However, SI was specific to use prior to scanning, and no adolescents exhibited substance-use problems. Several demographic covariates, including gender and prenatal cocaine exposure, were included in analyses to control for their potential effects, and results showed they had no significant impact on the moderation relationship. This is in line with previous studies in this population showing the effects of trauma on functional brain activation while controlling for these variables.⁴³ It is important for future studies to examine the effects of these covariates within larger samples. Additionally, ROI analyses were specific to primary white-matter pathways identified in *a-priori*-defined regions that were shown to demonstrate stress- and substance-use-related differences in previous studies. Additional regions not in our hypotheses may relate to stress and SI. Finally, our sample was disadvantaged and largely of racial/ethnic minority status. The extent to which the findings may generalize to other groups warrants investigation.

CONCLUSIONS

Despite these limitations, the current study is among the first to directly examine the moderating effects of SI on the relationship between perceived psychological stress and adolescent white-matter microstructure. It also expands on the previous literature by employing measures of the PF orientation and anisotropy, modeled separately from other contributing fiber orientations in the same voxels, which allows clearer examination of white-matter differences. Lower perceived stress and the presence of SI correlated with greater right cingulum PF anisotropy. SI significantly moderated the relationship between perceived stress and adolescent right cingulum anisotropy. Whereas greater perceived stress was associated with lower right cingulum anisotropy in adolescents with no SI, perceived-stress-related reduction in right cingulum anisotropy was not found in those with SI. As early SI increases the risk of subsequent substance-use disorders, the differences in stress-related reduction of PF anisotropy measures between SI groups may be a potential marker in

white-matter microstructure that distinguishes between adversity-exposed adolescents who may be at differential risk for substance abuse and dependence.

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Figure 1.

A. Right cingulum (blue) defined by JHU ICBM-DTI-81 white-matter atlas in FSL overlaid on mean FA skeleton (green) calculated from subjects, slice ($x=7$, $y=-11$, $z=36$); B. Perceived stress is associated with right cingulum primary white-matter fiber anisotropy as a function of substance-use initiation. Significant overall model, interaction term, and simple slopes indicate that substance-use initiation is a significant moderator, such that greater perceived stress is related to lower cingulum primary fiber anisotropy among non-substance-use-initiated adolescents.

Table 1

Demographic Information by Study Variables of Interest

	Substance Initiation Differences			Perceived Stress Correlation		
	Non-Initiated (SD)	Initiated (SD)	<i>t</i> / χ^2	<i>p</i>	<i>r</i>	<i>p</i>
Age (Years)	14.65 (.75)	14.85 (1.0)	-.72	.47	-.25	.11
Sex (Male/Female)	12/8	14/6	.44	.51	-.20	.20
Ethnicity (AA/C/O)	14/2/4	18/1/1	2.63	.27	.03	.86
Prenatal Cocaine Exposure (Y/N)	11/9	15/5	1.76	.19	-.24	.13
KABC mental processing (IQ)	92.97 (14.85)	93.94 (11.16)	-.23	.82	.08	.64

Table 2

Intercorrelations of Study Variables and Primary White-Matter Fibers

	1	2	3	4	5	6	7	8
1. Perceived Stress								
2. Substance Initiation	-.03							
3. Right Cingulum	-.38**	.44**						
4. Left Cingulum	-.15	.27*	.60***					
5. Corpus Genu	-.09	.10	.38**	.33*				
6. Corpus Body	-.22	.05	.29*	.48***	.68***			
7. Corpus Splenium	-.21	-.04	.40**	.21	.71***	.50***		
8. Right Superior Longitudinal Fasciculus	-.18	.32*	.59***	.48***	.59***	.67***	.62***	
9. Left Superior Longitudinal Fasciculus	-.31*	.23	.62***	.54***	.51***	.62***	.52***	.87***

*
p .05,

**
p .01,

p .001;

Correlations were considered significant at the level of p .01.