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Neurocognitive Correlates of White Matter Quality in Adolescent Substance Users

Sunita Bava[2,3], **Joanna Jacobus**[1,2], **Omar Mahmood**[2], **Tony T. Yang**[2], and **Susan F. Tapert**[1,2,*]

[1]VA San Diego Healthcare System

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

[3]University of California, San Diego – Department of Radiology

Abstract

Background—Progressive myelination during adolescence implicates an increased vulnerability to neurotoxic substances and enduring neurocognitive consequences. This study examined the cognitive manifestations of altered white matter microstructure in chronic marijuana and alcohol-using (MJ+ALC) adolescents.

Methods—Thirty-six MJ+ALC adolescents (ages 16-19) and 36 demographically similar controls were evaluated with diffusion tensor imaging (Bava et al., 2009) and neurocognitive tests. Regions of group difference in fractional anisotropy (FA) and mean diffusivity (MD) were analyzed in relation to cognitive performance.

Results—In users, lower FA in temporal areas related to poorer performance on attention, working memory, and speeded processing tasks. Among regions where users had higher FA than controls, occipital FA was positively associated with working memory and complex visuomotor sequencing, whereas FA in anterior regions was negatively associated with verbal memory performance.

Conclusions—Findings suggest differential influences of white matter development on cognition in MJ+ALC using adolescents than in non-using peers. Neuroadaptation may reflect additive and subtractive responses to substance use that are complicated by competing maturational processes.

Keywords

Marijuana; Alcohol; DTI; Adolescence; White matter; Neuropsychology; Cognition

Introduction

Adolescent substance use continues to be a prevalent concern, stimulating widespread initiatives aimed at better understanding the developmental consequences of early and chronic exposure. Marijuana and alcohol are often used in tandem, and are consistently the most frequently used substances among teens (Schweinsburg, Brown, & Tapert, 2008) (SAMSHA, 2007). Harmful effects of marijuana and alcohol span physiological, social, and psychological

* Address correspondence to: S. F. Tapert, Ph.D., VA San Diego Healthcare System, 3350 La Jolla Village Drive 116B, San Diego, CA 92161, USA, Telephone: 858-552-8585 x2599, Fax: (858) 642-6474, stapert@ucsd.edu.

functioning (Macleod et al., 2004; Tucker, Ellickson, Collins, & Klein, 2006a, 2006b). Given the extent of neuromaturation occurring during this time, the neurobiological and neurocognitive vulnerabilities associated with combined marijuana and alcohol use are of great interest.

The principal active component of marijuana, delta9-tetrahydrocannabinol (delta9-THC), produces complex alterations in cognition and behavior (Fant, Heishman, Bunker, & Pickworth, 1998; Johns, 2001; Solowij et al., 2002). Brain regions with high densities of cannabinoid receptors include the frontal cortex, hippocampus, basal ganglia, cerebellum, amygdala, and striatum (Eggan & Lewis, 2006; Freedland, Whitlow, Miller, & Porrino, 2002; Pontieri, Conti, Zocchi, Fieschi, & Orzi, 1999; Quickfall & Crockford, 2006). Human studies provide evidence for increased metabolism (Block et al., 2002; Mathew et al., 2002), decreased gray matter density (Matochik, Eldreth, Cadet, & Bolla, 2005) and atypical activation within these regions (Eldreth, Matochik, Cadet, & Bolla, 2004; Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004). Similarly, chronic alcohol exposure is associated with cortical and white matter (WM) volume loss in the hippocampus, cingulate, corpus callosum, cerebellum, and frontal brain regions (De Bellis et al., 2000; De Bellis et al., 2005; Harris et al., 2008; Medina et al., 2008; Nagel, Schweinsburg, Phan, & Tapert, 2005; Pfefferbaum, Adalsteinsson, & Sullivan, 2006a).

Indication that chronic marijuana and alcohol use may detrimentally influence the developing brain comes from neuroimaging studies showing a more distributed functional network and recruitment of alternate neural pathways (Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007; Schweinsburg, Nagel et al., 2008; Schweinsburg et al., 2005; Tapert et al., 2001; Tapert et al., 2004; Tapert et al., 2007); weaknesses in neurocognitive functioning especially attention, visuospatial functioning, and learning and retrieval of verbal and nonverbal information (Brown, Tapert, Granholm, & Delis, 2000; Medina et al., 2007; Tapert & Brown, 1999, 2000; Tapert, Granholm, Leedy, & Brown, 2002); morphological changes (Medina et al., 2008; Nagel et al., 2005); and anisotropic differences in WM (De Bellis et al., 2008; McQueeny et al., 2009). Vulnerability to marijuana use has been suggested in WM pathways within and connecting superior medial, and inferior frontal areas (Arnone et al., 2008; Bonekamp et al., 2007; Gruber & Yurgelun-Todd, 2005; Kanayama et al., 2004), temporal and parietal lobes (Ashtari, Cervellione, Cottone, Ardekani, & Kumra, 2009; Ashtari et al., 2007; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003) and areas of the cerebellum including the tonsil (Ashtari et al., 2007; Chang, Yakupov, Cloak, & Ernst, 2006; Schweinsburg et al., 2006).

Heavy alcohol use during adolescence is similarly associated with smaller prefrontal WM volumes (De Bellis et al., 2005; Medina et al., 2008). Increased anisotropy in the genu and isthmus of the corpus callosum in alcohol-using teens lends further support to atypical developmental trajectories (De Bellis et al., 2008). Correlates of these changes are seen in attenuated frontal response during spatial working memory (Tapert et al., 2001; Tapert et al., 2004) and deficits on neuropsychological measures of attention, memory retrieval, and visuospatial functioning (Brown et al., 2000; Tapert & Brown, 1999, 2000; Tapert et al., 2002).

Given the frequency of comorbid marijuana and alcohol use and their potential interaction, the extent of underlying circuitry disruptions and neurocognitive consequences needs further elucidation. Using diffusion tensor imaging (DTI), we previously characterized the relationship between marijuana and alcohol use and WM integrity among adolescent users and age-matched controls (Bava et al., 2009). Decreased fractional anisotropy (FA) was found most prominently in frontal-parietal circuitry comprising fibers of the inferior frontal region, splenium of the corpus callosum, postcentral gyrus, and left superior longitudinal fasciculus (SLF). Although mean diffusivity (MD) was similar between groups in regions of FA discrepancy, MD in WM

adjacent the lingual gyrus was higher in users but lower in the inferior longitudinal fasciculus (ILF) as compared to controls. These findings suggest the presence of selective aberrancies in cerebral WM in adolescent marijuana and alcohol use, and are the basis for neurobehavioral correlation in the current study.

Based on findings of reduced neurocognitive functioning in marijuana and alcohol using adolescents (Brown et al., 2000; Medina et al., 2007; Tapert & Brown, 1999, 2000; Tapert et al., 2002), we predicted that regions of decreased anisotropic diffusion would be associated with poorer performance on neuropsychological measures. Considering that increased FA in users may be associated with compensatory mechanisms, we hypothesized that FA in these brain areas would be associated with improved performance. In marijuana and alcohol using adolescents, scores on verbal learning and memory were expected to correlate positively with temporal FA, speeded processing and visuomotor sequencing with bilateral crus cerebri FA, and complex sequencing with FA in frontal regions and frontal association tracts such as the SLF.

Methods

Participants

Participants were 72 adolescents ranging in age from 16 through 19 years. Thirty-six adolescents were heavy marijuana and alcohol (MJ+ALC) users, and 36 were demographically similar controls with very limited substance use histories (see Table 1). Adolescents were recruited from San Diego area schools from 2005 to 2007. Inclusionary criteria required participants and their parents or legal guardians to provide consent and comprehensive medical history. Adolescents and their parents were screened with separate, private interviews to ascertain eligibility. Exclusionary criteria for both users and controls were: DSM-IV Axis I disorder; nicotine dependence (e.g., Fagerstrom Test for Nicotine Dependence (FTND; (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) score ≥ 3), use of psychoactive medications; chronic medical illness, history of neurological disorder, head trauma with loss of consciousness >2 minutes, learning disability or mental retardation, complicated/premature birth (<33 weeks gestation); evidence of maternal drinking (>7 drinks in a week or >4 drinks in a day) or illicit drug use during pregnancy; parental history of bipolar I or psychotic disorder; left handedness; non-fluency in English; MRI contraindications; and clinically abnormal brain anatomy. Having surpassed these exclusionary criteria, participants were classified as: (1) Controls with limited substance use history (i.e., <5 lifetime occurrences of marijuana use, <50 lifetime drinks, <2 lifetime episodes of other drug use); or (2) MJ+ALC users with history of lifetime marijuana use between 180 to 1800 times and lifetime drinks between 50 and 700. The most recent marijuana use occurred 24 hours prior to imaging and last heavy alcohol use (4 or 5 alcoholic beverages in one sitting for females and males, respectively) was 3 days prior (see Table 1), verified by breathalyzer and urine toxicology. MJ+ALC users were excluded if they met criteria for a DSM-IV Axis I disorder other than a marijuana or alcohol use disorder. Informed assent and consent were obtained from participants and legal guardians in accordance with UCSD Human Research Protections Program procedures.

Measures

Substance use—The Customary Drinking and Drug use Record (Brown et al., 1998) collected from all teens detailed information on quantity and frequency of lifetime and past 3-month alcohol, marijuana and other drug use (including misuse of prescription and over-the-counter medications), as well as abuse/dependence, withdrawal, and negative consequences. The Timeline Followback (Sobell & Sobell, 1992) assessed youth and parent report of teens' chronicity and intensity of substance use for each of the 28 days preceding the scan session (see Tapert et al., 2007).

Neuropsychological functioning—Based on findings of neurocognitive decrements in adolescent substance users (Tapert & Brown, 1999; Tapert et al., 2002), including users with primary marijuana and alcohol use (Brown et al., 2000; Medina et al., 2007; Tapert & Brown, 2000), we examined indices from measures that previously differentiated users from controls: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol total scaled score, Digit Span backward score and Digit Span total scaled score (Wechsler, 1997b); Paced Auditory Serial Addition Test (PASAT) 2-second and 3-second trial total scores (Gronwall, 1974); Delis-Kaplan Executive Function System (D-KEFS) TMT Number Sequencing, Letter Sequencing, and Switching scaled scores and TMT total errors (Delis, Kaplan, & Kramer, 2001); California Verbal Learning Test-II (CVLT-II) List A Trial 1 standard score (Delis, Kramer, Kaplan, & Ober, 2000); and Wechsler Memory Scale-Third Edition (WMS-III) Logical Memory first, immediate and delayed recall scaled scores and recognition total score (Wechsler, 1997a). Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary (Wechsler, 1999) and Wide Range Achievement Test – 3 (WRAT-3) Reading (Wilkinson, 1993) provided estimates of premorbid intellectual functioning.

Mood and psychopathological syndromes—The Beck Depression Inventory (Beck, 1978) and Spielberger State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) assessed mood prior to scanning. The Child Behavior Checklist (Achenbach & Rescorla, 2001) was completed by parents to assay internalizing and externalizing psychopathological symptoms.

Image acquisition and DTI quantification

Image acquisition, pre-processing and calculation of DTI indices are provided in detail in (Bava et al., 2009). Briefly, participants were imaged in a 3T General Electric Excite MR system with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). Diffusion-weighted images were generated with a single-shot dual spin echo excitation and collected along 15 non-collinear directions in addition to a reference image with no diffusion weighting (b=0). The following sequence parameters were applied and averaged over four volumes: TE/TR=93/12,000 ms, FOV=240 mm, matrix =128×128, 36 contiguous slices, 3 mm slice thickness, b-value=2000 s/mm^2. Two field maps were collected (TE/TR=3.8/1,000 ms) to correct for signal loss and geometric distortion due to B0 field inhomogeneities (Andersson & Skare, 2002; Jezzard & Balaban, 1995).

Data were corrected for motion, eddy current, and field distortions using FMRIB Software Library (FSL; Oxford, United Kingdom; (Smith et al., 2004)). Corrected images were subjected to tensor decomposition to derive scalar diffusion indices, FA and MD (Le Bihan et al., 2001). Computations were performed in native coordinate space using Analysis of Functional NeuroImages' (Cox, 1996) diffusion plug-in *3dDWItoDT* (Cox & Glen, 2006). FA and MD were examined with whole-brain voxelwise analysis using Tract-Based Spatial Statistics (TBSS; (Smith et al., 2006)).

Statistical analyses

Voxelwise statistics of FA and MD data were carried out in AFNI using independent sample *t*-tests. Type I error control for multiple comparisons was achieved with a combination of individual voxel probability and cluster size thresholding, requiring that any significant group difference was comprised of 54 contiguous voxels, each differing at $p < .05$. Monte Carlo simulations determined that this yielded a brain-wise probability of a false positive at $p < .01$. Thirteen such FA clusters and 2 MD clusters represented significant differences between users and controls (Bava et al., 2009). Clusters showing significant group differences in FA or MD were correlated with neuropsychological test scores using Pearson's *r* correlation coefficients ($\alpha = .05$). Significant correlations were subjected to hierarchical regressions to assess the unique

influence of FA on neuropsychological performance for each group, with mean FA and group status entered on step 1 and their interaction term on step 2. If the interaction was nonsignificant ($p>.05$), results from the first step were interpreted.

Follow-up analyses—For FA and MD clusters that significantly predicted neuropsychological test scores ($\alpha=.05$), hierarchical regressions examined mean FA/MD and substance use (i.e., lifetime marijuana use, marijuana use days per month, lifetime alcohol use, drinks per month) and their interaction as predictors of neuropsychological test score to determine whether the extent of substance use moderated the relationship between WM quality and neuropsychological performance in users ($n=36$). Further, to evaluate the potential influence of premorbid characteristics on neuropsychological performance, mean FA/MD and parental history of SUD were examined with regression analyses, where parental SUD was entered on step 1, average FA or MD of the significant cluster entered on step 2, and neuropsychological performance as the dependent variable.

Results

Groups did not significantly differ on demographic variables including age, gender distribution, ethnic composition, and socioeconomic status (Hollingshead, 1965) (see Table 1). Measures of emotional functioning and psychopathology were similar between groups and within normal limits. Estimated premorbid IQ and academic reading achievement were also comparable between groups, typically falling in the average to high average range. As expected, MJ+ALC youths were more likely to have a parental history of substance use disorder ($p<.05$), and more nicotine ($p<.05$) and other drug ($p<.001$) use than controls, so these variables were included as covariates in statistical analyses.

FA and MD Group Differences

As reported in our previous study, independent samples *t*-tests, corrected for multiple comparisons with intensity and cluster-based thresholding, revealed 10 clusters (≥ 54 μl) in which MJ+ALC teens showed significantly lower FA than controls (Bava et al., 2009). The most prominent areas of decreased FA for users were found in the left SLF, left postcentral sensory gyrus, and bilateral crus cerebri ($p<.001$). Temporal regions including the right superior temporal gyrus ($p<.001$), projection fibers of the left temporo-thalamic tract ($p<.01$), and right ILF ($p<.01$) also showed lower FA in MJ+ALC users, as did association fibers in right inferior frontal ($p<.001$), left occipital-frontal ($p<.01$), and splenium ($p<.01$) regions (*p*-values refer to group difference in FA averaged across each cluster). Interestingly, in three right hemisphere clusters, MJ+ALC users had *higher* FA than controls ($p<.001$): the cuneus region of the occipital lobe, anterior limb of the internal capsule, and arcuate portion of the right SLF.

Within clusters of significant FA discrepancy, MD values did not differ between groups. However, a whole-brain analysis of MD revealed significant differences in two areas: Inferior to the right occipital-cuneus and adjacent the lingual gyrus (users had higher MD than controls, $p<.01$) and in the left ILF (users showed *lower* MD than controls, contrary to hypotheses, $p<.01$).

To evaluate the influence of potential confounds, group differences were examined in an ANCOVA ($N = 72$). Specifically, lifetime cigarettes smoked, Fagerstrom Test for Nicotine Dependence score, lifetime other drug use instances, and parental history of SUD were greater in MJ+ALC users than controls. Group differences in FA and MD reported above persisted after controlling for these variables ($F_{(12,54)} = 6.50$, $p < .001$). Mean FA and MD did not relate to estimated premorbid IQ or gender in either group.

Neurocognitive Correlates of White Matter Anomalies

Neuropsychological performance—Groups did not significantly differ on measures of neurocognitive functioning, with the exception of WAIS-III Digit Symbol, where users evidenced poorer performance than controls ($t_{(70)} = 2.39$, $p = .02$).

Fractional anisotropy—For users (n=36), FA in the right ILF, a cluster where FA was lower than that of controls, was positively correlated with Digit Span total scaled score ($r = .38$, $p = .02$) and Digit Symbol total scaled score ($r = .35$, $p = .03$) (see Table 2). Conversely, clusters in which users' FA exceeded that of controls showed bidirectional associations. CVLT-II List A Trial 1 ($r = .47$, $p = .004$) and D-KEFS TMT Switching ($r = .55$, $p = .001$) were positively associated with FA in the occipital-cuneus region, whereas Digit Span total ($r = -.33$, $p = .04$) showed a negative relationship with FA in the anterior limb of the internal capsule.

Hierarchical regression analyses of FA in the right occipital region (MJ+ALC FA > Control FA) indicated a significant FA × group interaction in predicting performance on D-KEFS TMT Switching ($\beta = 3.85$; $p < .001$). Simple effects analyses revealed that higher FA was associated with better performance on TMT Switching in the MJ+ALC group ($\beta = .55$; $p < .01$) (see Figure 1). Concomitant with this finding, an interesting trend emerged suggesting that higher FA in this region was associated with poorer performance on TMT Switching in controls ($\beta = -.32$; $p = .06$). When predicting CVLT-II List A Trial 1 scores, a significant FA × group interaction ($\beta = 2.16$; $p < .05$) indicated that for users only, increased FA in the right occipital region was associated with better Trial 1 performance ($\beta = .47$; $p < .01$). Controls did not show a significant relationship between FA in this region and Trial 1 performance. FA in the right anterior limb of the internal capsule, another cluster in which FA in MJ+ALC users exceeded that of controls, predicted performance on WMS-III Logical Memory II delayed recall for both groups ($\beta = -.31$; $p < .05$). The group main effect and FA × group interaction were nonsignificant.

Regression analyses also revealed important findings in temporal brain regions. FA in the right superior temporal gyrus ($\beta = .30$; $p < .05$) and the right ILF ($\beta = .31$; $p < .01$) predicted performance on WAIS-III Digit Symbol total scaled score in both groups. The group main effects and FA × group interactions were nonsignificant. In addition, a significant FA × group interaction ($\beta = 3.8$; $p < .05$) indicated that increased FA in the right ILF predicted better performance on WAIS-III Digit Span total scaled score for MJ+ALC users ($\beta = .38$; $p < .05$), whereas controls showed no relationship between FA and Digit Span performance (see Figure 1).

Mean diffusivity—Correlation analyses indicated consistent and strong negative relationships between MD in the ILF (MJ+ALC < Control) and performance on measures of complex attention (CVLT-II List A Trial 1, Digit Span total scaled score, Digit Span backward) and verbal retention (Logical Memory II delayed recall) for users only. In contrast, MD in the occipital-lingual region (MJ+ALC > Control) was positively associated with performance on measures of complex attention (Digit Span total scaled score, Digits Backward, PASAT 2-second trial) in controls only (see Table 2). Hierarchical regression analyses of MD did not reveal significant findings.

Follow-up Analyses

To examine whether the extent of substance use moderated the relationship between FA and neuropsychological performance, hierarchical regressions examined mean FA and substance use (i.e., lifetime marijuana use, marijuana use days per month, lifetime alcohol use, drinks per month), and their interaction as predictors of neuropsychological test score. Analyses were conducted after outliers (>2.5 SD) on substance use were removed. Regression analyses examining the significance of FA in the right anterior limb of the internal capsule and lifetime

marijuana use in predicting performance on WMS-III Logical Memory delayed recall (n = 32) indicated that increased use was associated with decreased performance on delayed recall (β = -.53; p <.01). The main effect of FA and the FA × use interaction were nonsignificant. Extent of marijuana use did not significantly moderate the relationship between FA and test performance in other regions. In addition, there were no significant main effects of alcohol use (lifetime or drinks per month) or FA × alcohol use interactions in predicting test performance.

The influence of premorbid characteristics on neuropsychological performance was examined using bivariate correlations of parental history of SUD with FA and MD and entered into regression analyses if significant (p <.05). FA in the right ILF was positively correlated with parental history of SUD (r = .39, p = .02). Regression analyses indicated that parental history of SUD did not predict neuropsychological performance beyond FA. No significant findings were found between MD and parental history of SUD.

Discussion

The goal of the present study was to examine the neurocognitive correlates of WM quality differences in MJ+ALC users. Previous findings showed decreased FA in frontal-parietal circuitry comprising fibers of the inferior frontal region, splenium of the corpus callosum, postcentral gyrus, and left SLF as well as areas of increased FA in three right hemisphere regions, including the cuneus region of the occipital lobe, anterior limb of the internal capsule, and arcuate portion of the SLF.

A number of findings supported our initial hypotheses that regions of decreased FA in users would be associated with lower performance on neurocognitive measures, whereas areas of increased FA would be linked to better performance, presumably due to compensatory processes. In temporal brain pathways comprising the right ILF and superior temporal gyrus, where FA was *lower* in the user group, performance on measures of speeded processing declined as FA decreased. Similarly, low FA in the ILF was associated with poorer scores on a measure of attention and working memory in users. Considering that this tract shows significant increases in FA from childhood to adolescence (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Schmithorst, Wilke, Dardzinski, & Holland, 2002), the current findings implicate weaknesses in cognitive functioning in users that may be linked to diminished fiber integrity. By comparison, in the right occipital region, where users demonstrated *higher* FA than controls, visuomotor switching performance and first trial verbal list learning improved with increasing FA, and suggests the possibility of a coincident compensatory process occurring in MJ+ALC users during this developmental period.

Similar compensatory mechanisms are suggested in previous studies (Tapert et al., 2007), where adolescents with histories of chronic marijuana use show increased BOLD response compared to controls in areas connected to the occipital-cuneus (i.e., occipital gyri). Likewise, findings of greater brain activation in adult MJ+ALC users is thought to be associated with regional brain compensation (Chang & Chronicle, 2007; Pfefferbaum et al., 2001).

One unexpected finding indicated that FA in the anterior limb of the internal capsule, a region of higher FA in users, was associated with poorer performance on a measure of contextual verbal memory. This relationship departs from the compensatory model and suggests that elevated anisotropic diffusion may have adverse impact on brain function and neurocognitive performance. Higher FA in adolescent substance users, with primary MJ+ALC dependence, has been reported previously and related to premature myelination (De Bellis et al., 2008). The mechanism proposed is one wherein accelerated development could interfere with the formation or efficiency of typical functional networks. As such, increased FA in the anterior

limb of the internal capsule may hinder connections with prefrontal, cingulate and thalamic fibers (Parent, 1990) and prove disadvantageous for cognitive performance.

The specific relationships between FA in regions such as the temporal lobe or crus cerebri to performance on measures of verbal learning and memory and visuomotor processing, respectively were not supported by the current findings. It is possible that traditional structure-function relationships may be altered by ongoing maturational processes, or that anisotropic changes have not reached the extent to which these cognitive functions would be impacted.

In this study, we explored the relationship between adolescent marijuana and alcohol use, WM quality, and neurocognitive performance. The present results link performance on standardized neurocognitive measures with WM diffusion properties in substance users. We found decreased FA in temporal brain areas in adolescents with histories of marijuana and alcohol use that was related to poorer attention, working memory, and speeded processing. These findings implicate substance-related alterations in WM with corresponding functional weakness. Conversely, in occipital brain regions, we found evidence for possible compensatory mechanisms in the user group. Specifically, users displayed higher FA that was associated with better working memory and complex sequencing performance. Higher FA and lower MD in this region did not correlate with enhanced cognitive performance in the control group, suggesting that changes in this region may optimize performance in the user group only. Another area of increased FA in users, in the internal capsule, was associated with poorer verbal memory performance indicating that neuroadaptive processes may not simply be additive or subtractive, but may be complicated by interfering or competing maturational processes.

A number of study limitations should be addressed in future work. Composite analysis of neuropsychological domains and WM quality may yield more power in assessing areas of neurocognitive vulnerability. In addition, future research should assess neurocognitive functioning in adolescents before they initiate MJ+ALC use to better understand the contribution of premorbid characteristics to substance-related WM changes. Although structural abnormalities appear to persist after sustained abstinence, delineation of the acute and chronic effects of MJ+ALC on brain structure is of interest in future work. The frequent comorbidity of marijuana and alcohol use makes it difficult to examine the separate and combined effects of these substances on brain structure and function. It is possible that the use of one substance can mitigate or potentiate the neurotoxic effects of the other and this mechanism should be further explored in follow-up studies. Finally, protocols that employ higher angular resolution (Frank, 2002) can provide more detailed assessment for exploration of circuitry disruption.

Marijuana and alcohol are two of the most widely used substances in adolescence. Understanding their role in neurodevelopment may help inform assessment of substance-related cognitive weaknesses and contribute to skill-based training and interventions to optimize cognitive development. The current findings suggest differential influences of white matter development on cognition in MJ+ALC using adolescents than in non-using peers. Neuroadaptation may reflect additive and subtractive responses to substance use that are complicated by competing maturational processes. Additional studies are needed to determine the long-term impact of MJ+ALC use on neurobehavioral functioning, particularly in light of preliminary work indicating a possible reversibility of WM changes with long-term abstinence (Delisi et al., 2006). Longitudinal studies of WM quality in adolescent substance users will also be important for assessing how neurobiological adaptations influence cognitive functioning throughout adolescence and into early adulthood.

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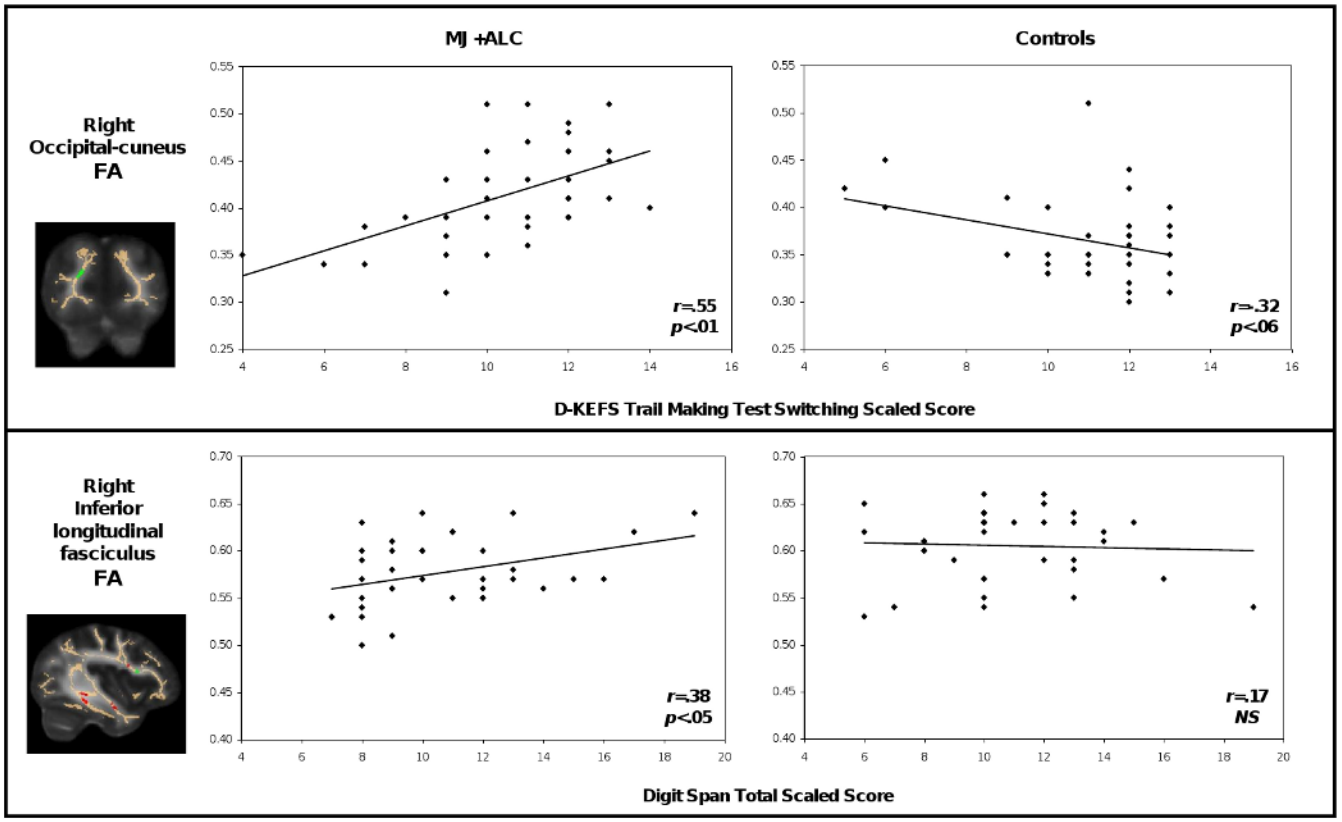

Figure 1.

Neuropsychological correlates of fractional anisotropy (FA) in marijuana+alcohol users (MJ +ALC) (*n*=36) and controls (*n*=36). Significant clusters are superimposed on the fiber skeleton (beige) and overlaid on a standardized FA template. Red indicates *decreased* FA in MJ+ALC users. Green indicates *increased* FA in MJ+ALC users. D-KEFS=Delis-Kaplan Executive Function System Inventory

Table 1

Demographic and substance use characteristics of participants.

	MJ+ALC (*n* = 36) M (SD) or %	Controls (*n* = 36) M (SD) or %
Years of age (range 16.3-19.0)	17.9 (0.9)	17.8 (0.8)
Female	27.8 %	27.8 %
Caucasian	61.1 %	62.9 %
Annual household income (thousands)	141.7 (128.3)	115.9 (60.2)
Hollingshead socioeconomic level	28.8 (13.7)	30.4 (16.2)
WRAT-3 Reading standard score	106.7 (8.0)	109.7 (6.6)
WASI Vocabulary *T*-score	58.4 (8.7)	58.7 (8.7)
Beck Depression Inventory Total	3.2 (3.2)	2.6 (2.7)
Spielberger State Anxiety *T*-score	39.5 (6.7)	37.7 (7.0)
Child Behavior Checklist Internalizing *T*-score	46.1 (10.0)	44.8 (7.9)
Child Behavior Checklist Externalizing *T*-score	49.7 (9.4)	45.2 (10.3)
Age of first weekly marijuana use	14.7 (3.1)	-
Lifetime marijuana use episodes **	551.7 (481.2)	1.4 (2.3)
Marijuana use days per month **	11.6 (8.4)	0.1 (0.3)
Days since last marijuana use **	52.1 (69.6)	355.4 (330.3) [a]
Age of first weekly alcohol use	15.5 (1.7)	16.0 [b]
Lifetime alcohol drinks **	195.3 (152.7)	25.0 (38.6)
Drinks per month **	52.9 (52.4)	8.2 (12.4)
Days since last alcohol use	43.0 (68.6)	86.9 (118.2) [a]
Cigarettes per smoking day *	1.2 (3.8)	0.0 (0.2)
Fagerstrom Test for Nicotine Dependence score *	0.3 (0.7)	0.0 (0.0)
Lifetime other drug use instances **	10.5 (11.2)	0.5 (2.2)

* $p<.05$

** $p<.001$

[a] For controls with history of any marijuana (n=14) or alcohol (n=12) use

[b] (n=1)

Notes: MJ+ALC, Marijuana and alcohol user. WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). WRAT-3, Wide Range Achievement Test, 3rd edition (Wilkinson, 1993).

Table 2

otropy (FA) and mean diffusivity (MD) to neuropsychological test performance in marijuana+alcohol users and controls

	D-KEFS TMT Number Sequencing		D-KEFS TMT Switching		CVLT-II Trial 1		WAIS-III Digit Symbol		WAIS-III Digit Span		WAIS-III Digits Backward		WMS-III Logical Memory II		WMS-III Logical Memory Recognition		PASAT 2-second Trial	
ifference	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT	MJ+ ALC	CT
LC<CT																		
LC<CT																		
LC<CT				-.36*								-.34*						
LC<CT		-.37*																
LC<CT																		
LC<CT							.35*		.38*									
LC<CT								.41*										
LC<CT																		
LC<CT																		
LC<CT																		
LC>CT									-.33*					-.34*				
LC>CT																-.33*		
LC>CT			.55**		.47**													
LC<CT					-.43**				-.45**		-.44**		-.34*					
LC>CT										.39*		.35*						.34*

L=Left; R=Right; MJ+ALC=marijuana+alcohol user; CT=Control; TMT=Trail Making Test; CVLT-II=California Verbal Learning Test-II (Delis et al., 2000); PASAT=Paced Auditory Serial Addition Test (Gronwall, 1974); D-KEFS=Delis-Kaplan Executive Function System (Delis et al., 2001); WAIS-III= Wechsler Adult Intelligence Scale – III (Wechsler, 1997b); WMS-III, Wechsler Memory Scale – III (Wechsler, 1997a).