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White Matter Integrity in Adolescents with Histories of Marijuana Use and Binge Drinking

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Abstract

Structural brain abnormalities have been observed in adolescents with alcohol use disorders but less is known about neuropathological brain characteristics of teens with subdiagnostic binge drinking or the common pattern of binge drinking combined with marijuana use. The goal of this study was to examine white matter integrity in adolescents with histories of binge drinking and marijuana use.

Diffusion tensor imaging (DTI) was conducted with 42 adolescents (ages 16−19) classified as controls, binge drinkers, or binge drinkers who are also heavy marijuana users. Tract based spatial analysis identified shared fiber structure across individuals and facilitated voxelwise comparisons of fractional anisotropy (FA) and mean diffusivity (MD) between groups.

Significant between group differences were found in FA in eight white matter regions (*p*s ≤ .016) between the binge drink-only group and controls, including superior corona radiata, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and superior longitudinal fasciculus. Interestingly, in 4 of these same regions, binge drinkers who are also heavy marijuana users had higher FA than binge drinkers who did not use marijuana (*p*s < .05). MD did not differ between groups.

Findings are largely consistent with research suggesting less neuropathology in adolescents without histories of substance use. However, binge drinkers who also use marijuana did not show as consistent

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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a divergence from non-users as did the binge drink-only group. Detection of white matter alterations may have implications in identifying early cognitive dysfunction in substance using adolescents.

Keywords

Adolescence; Brain Imaging; Marijuana Abuse; Alcohol Abuse; White Matter; Diffusion Tensor Imaging

1. Introduction

Alcohol use in adulthood is associated with neurotoxic molecular and metabolic changes in the brain. Animal and human studies have shown that chronic alcohol exposure leads to structural and chemical brain alterations [24,45,74], functional brain changes [2] and neurocognitive impairments [31,89,96]. Neuroimaging studies have noted prominent macrostructural (e.g., volume) and microstructural (e.g., fiber density, compactness, coherence) white matter changes in adults with alcohol use disorders [70,72], which may predict deteriorating cognitive performance [21,73]. Less is known about the detrimental effects of alcohol use on the adolescent brain.

As in adulthood, heavy alcohol use during adolescence has been linked to abnormalities in white and grey matter tissue volume [26,27,58,59,65], brain function [4,83,91,93], and neuropsychological performance [17,80,92,110]. Adolescent drinking is particularly important given its potential to interfere with maturational processes such as myelination and synaptic organization that continue throughout adolescence and into early adulthood [13,33-35,71].

Few studies have expanded on the macrostructural information provided by structural magnetic resonance imaging (MRI) in adolescent alcohol users. In addition to changes in overall white matter volume, the microstructural properties of white matter tissue at different stages of myelin development are important for the smooth, efficient, and integrated white matter fiber pathways necessary for neuronal transmission. Several studies have found differences in microstructural white matter indices of the corpus callosum between adolescents with and without alcohol use disorders [28,95], but less is known about white matter in adolescents who engage in sub-diagnostic drinking behaviors. Underage drinking is common [47], and most alcohol consumed by teens is in a binge or heavy episodic fashion. The National Institute on Alcohol Abuse and Alcoholism defines binge drinking as a pattern of alcohol consumption that brings blood alcohol concentration levels to .08 or above, which typically corresponds with consuming ≥ 5 drinks or ≥ 4 drinks on an occasion for boys and girls, respectively [66,88,106]. Sub-diagnostic binge drinking can be associated with changes in neurocognition and altered brain structure in youth and adults [41,48,56,77,98].

The second most widely used intoxicant among teens is marijuana [47], which is frequently used in combination with alcohol [61], but the potential additive, interactive, or protective role of concomitant marijuana use on any neural effects of adolescent binge drinking is unknown. Adolescent marijuana use has been linked to abnormalities in neurocognition and brain function [42,57,67,81,94], and the use of both substances appears related to anomalous brain function [59,82]. However, little is known about how the common pattern of use of these two substances together may relate to adolescent white matter development. Examining white matter tissue in adolescents who engage in binge drinking and marijuana use will help us better understand the neuropathological effects of the most common substance intake behaviors of teens.

Despite the documented negative cognitive effects of heavy marijuana use in adolescence [42,50,57], animal studies examining potential neuroprotective effects of cannabinoids (the active ingredient in marijuana) on toxic insults suggest antioxidant properties and reductions in glutamate excitotoxicity in the brain by inhibition of glutamate transmission [37,38,55, 102]. As excitotoxicity and oxidative stress are suggested mechanisms of alcohol-related brain injury [24,25], cannabinoid exposure could potentially mitigate ethanol-induced changes[36]. However, a study of neonatal rats found that activation of endocannabinoid CB1 receptor, in combination with alcohol administration, may modulate glutamate and GABAergic neurotransmission, and prime the brain to suffer cell death by suppressing synaptic activity important for developmental processes. This could indicate that alcohol and marijuana use together may lead to worse neural outcomes, specifically in the developing brain [40].

This study expands on the current literature by examining the quality of white matter fiber structure in relation to adolescent binge drinking in the context of marijuana use. We used diffusion tensor imaging (DTI) to evaluate microscopic white matter change *in vivo* by estimating the diffusion of water molecules in neural tissue. Brain regions that are rich in fiber tracts have greater restriction in the directionality of water molecule movement [51], so diffusion measurements visualize the white matter bundles and describe the microscopic architecture of white matter tissue [9,51]. DTI exams were performed on: (1) adolescents with no substance use history, (2) those with a history of binge drinking, and (3) those with a history of concomitant binge drinking and marijuana use. We compared between groups two common scalar diffusion measurements: fractional anisotropy (FA), which reflects the directionally-dependent movement of water molecules along fiber tracts, and mean diffusivity (MD), reflecting the degree of overall displacement of water molecules in localized tissue [51,75]. Based on literature examining combined effects of alcohol and cannabinoids on neural toxicity in the immature brain [40] and data from our lab showing abnormal brain functioning in abstinent adolescent marijuana users [81,94] and binge drinkers [56], we hypothesized that histories of binge drinking alone and in combination with marijuana would be linked to poorer white matter fiber tract coherence and organization (i.e., lower FA) compared to controls. We further hypothesized that in regions where FA was low in users, MD values would be higher, reflecting tissue loss or potential demyelination.

2. Methods

2.1 Participants

Adolescents ages 16 through 19 years were recruited from local high schools and colleges. Comprehensive screening interviews [53,57] were administered to adolescents and their guardians. Inclusionary criteria required adolescents to have a parent or legal guardian to provide consent and a medical and psychiatric history. Exclusionary criteria were history of: (1) Diagnostic and Statistical Manual for Mental Disorder –Fourth Edition (DSM-IV) [3] Axis I disorder other than alcohol or cannabis use disorder, (2) use of psychoactive medications, (3) chronic medical illness, (4) neurological condition (e.g., migraine), (5) head trauma with loss of consciousness >2 minutes, (6) prenatal alcohol (> 3 drinks in a day or > 6 drinks in a week) or drug exposure, (7) complicated or premature birth (< 33 weeks gestation), (8) learning disability or mental retardation, (9) left handedness, (10) noncorrectable vision, colorblindness or hearing impairments, (11) parental history of bipolar I or psychotic disorder, and (12) non-fluency in English for youth.

All participants under 18 years of age and their parents or guardians underwent written informed consent (or assent for minors) in accordance with the University of California, San Diego Human Research Protections Program. Participants over age 18 consented for their own participation, and their parents consented for a collateral interview. Teens were classified as: (1) binge drinkers (BG; n=14) with histories of at least one episode of ≥ 4 drinks on one occasion

for females and ≥ 5 drinks for males; (2) binge drinkers and marijuana users (BG+MJ; *n*=14) with history of lifetime marijuana use between 180 to 1800 times and binge drinking history as above; and (3) control teens with very limited if any substance use history (CON, *n*=14). Groups were statistically similar on age, gender, household income, general intellect, externalizing and internalizing behaviors, and mood (see Table 1).

All participants received urine toxicology to confirm self-report and parent report of adolescent's abstinence from marijuana and other drugs, and Breathalyzers (Intoximeter, St. Louis, MO) to confirm abstinence from alcohol. BG+MJ teens were abstinent from marijuana at least 23 days (range 23−61) on the day of brain imaging. Histories of marijuana use were reported by six BG (no more than 9 episodes) and three CON (no more than 5 episodes) participants, with 30 to 1076 days since last use. Abstinence from alcohol was an average of 26 days (range 3−45 days) for BG+MJ teens, 30 days (range 13−52 days) for BG teens, and ranged from 90 to 998 days for CON, who had an average of 4 lifetime drinking episodes. Total lifetime drinking episodes in BG and BG+MJ groups ranged from 12 to 405 (see Table 1).

2.2 Measures

Substance use was assessed with the Customary Drinking and Drug Use Record [16], an interview that obtains information on lifetime and past 3-month use of alcohol, marijuana, nicotine, and eight other classes of illicit drugs in addition to DSM-IV abuse and dependence criteria, hangover/withdrawal symptoms, and negative consequences associated with substance use. The Child Behavior Checklist [1] obtains reports from parents regarding child behavior concerns. This measure has shown good reliability and validity on reports of internalizing and externalizing behavior [14]. The Beck Depression Inventory [12] assessed depressive symptoms on the day of scanning. The Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Vocabulary subtest was administered by trained psychometrists to assess premorbid intellectual functioning [105]. Parental socioeconomic status was assessed with the two-factor Hollingshead scale that combines education and occupation [43]. Family history of psychiatric disorders was assessed with the Family History Assessment Module [76].

2.3 Procedures

2.3.1 DTI Data Acquisition and Processing—All DTI scans were performed on a General Electric 3.0-T magnetic resonance imager at the University of California, San Diego. Data with whole brain coverage were collected through a single-shot dual spin echo excitation with TE = 93.4 ms, TR = 12,400 ms, field of view = 24 cm, slice thickness = 3.0 mm, image matrix = 128 × 128, and b-value = 2000 s/mm^2. Diffusion-weighted images were acquired in 15 diffusion directions, in addition to the normalization image with no diffusion encoding (b=0) [32]. Four volumes were acquired and averaged for each direction. Each two-dimensional slice was Fourier transformed and re-gridded to rectilinear space prior to the following processing steps.

Tract-Based Spatial Statistics (TBSS) [85] was used for voxel-wise comparisons of FA and MD values between groups. TBSS attempts to correct for inaccuracies that complicate interpretation of other voxelwise methods (e.g., voxel-based morphometry), such as weaknesses in alignment, smoothing, and localization of brain tissue [85]. Diffusion measurement images (FA and MD) were derived from the *3dDWItoDT* program of the Analysis of Functional NeuroImages package (AFNI) [23], which fits the diffusion weighted data to a tensor model using a non-linear least squares approach to compute the three orthogonal eigenvectors and corresponding eigenvalues necessary for calculating the scalar FA and MD indices based on standard formulas [68]. Additional processing procedures used Oxford Centre

for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Package tools (FSL) [86].

Two pre-alignment processing steps were conducted: a six-degree of freedom affine motion correction for head motion; and a 2D, six degree of freedom alignment to reduce the effects of gradient coil eddy currents (FLIRT) [44]. Each image was inspected for quality, and non-brain voxels were removed from analysis by AFNI 3dAutomask, then manually refined as needed. A representative diffusion image from the control group was selected as the target image for registration. All subjects were aligned by nonlinear transformation to the selected target image and then the whole dataset was affine-aligned to MNI-152 space [30]. These transformed data images (FA and MD) were averaged to create a mean FA or MD image. Next, a white matter tract skeleton was created from the mean FA or MD image to represent the centers of large white matter tracts in the dataset. This skeleton was generated by identifying lines (within white matter tracts) in the mean image with the largest diffusion values. Finally, each participant's transformed FA and MD image was projected onto the diffusion skeleton. This procedure helped achieve alignment between the common skeleton and the tract center of individual FA and MD images. For each point on the skeleton, voxelwise statistics were conducted across individual subjects [85].

2.3.2 Statistical Analysis—A whole brain one-way ANOVA was used to examine the between-group differences in both FA and MD on a voxel-by-voxel basis. Type I error was controlled using intensity and cluster based thresholding (family-wise $p<.05$). A Monte Carlo simulation with a *alpha* =.05 and connectivity of 1 mm [85] determined that clusters comprised of at least 27 contiguous voxels would have a 5% chance of occurring under the null hypotheses. Thus, only clusters consisting of ≥27 microliters with each voxel differing at $p<.05$ were interpreted. Follow-up analyses determined which groups were responsible for significant ANOVAs.

3. Results

3.1 Demographic Information

Groups did not differ on any demographic characteristic (*p*s > .05, see Table 1). The BG+MJ group had more lifetime drinking episodes than BG or CON groups ($p<.005$), so this variable was used as a covariate in follow-up analyses. The BG+MJ reported more lifetime illicit drug use episodes (other than alcohol, marijuana, or nicotine) compared to BG and CON ($p<.05$). In particular, the BG+MJ group reported more lifetime ecstasy use episodes than other groups (see Table 1; $p<.05$), although no one in any group used it more than once. Groups did not differ on lifetime amphetamine, hallucinogen, barbiturates, benzodiazepine, cocaine, opiate, ketamine, GHB, or inhalant use (*p*s>.05).

3.2 Between group comparisons

A whole brain ANOVA revealed significant between-group FA differences in 8 separate fiber tract regions: 4 clusters in the left superior corona radiata, 1 cluster in the right inferior longitudinal fasciculus, 1 cluster in the left inferior fronto-occipital fasciculus, 1 cluster in the left middle cerebellar peduncle, and 1 cluster in the left superior longitudinal fasciculus (see Table 2 and Figure 1; clusters ≥ 27 contiguous voxels each at $p<.05$). Follow-up pair-wise comparisons controlling for lifetime drinking episodes indicated that BG displayed lower FA than CON in all 8 clusters (*p*s ≤ .016, see Table 2). BG+MJ displayed lower FA than CON in 2 of the corona radiata clusters and in the superior longitudinal fasciculus cluster (*p*s ≤ .01, see Table 2). Interestingly, BG demonstrated significantly lower FA than the BG+MJ group in 4 of the 8 regions: 1 of the superior corona radiata clusters, inferior fronto-occipital fasciculus, middle cerebellar peduncle, and the superior longitudinal fasciculus (*p*s .014 to .043). Results

were unchanged when lifetime drinking episodes were not controlled for, except that BG+MJ now showed lower FA than CON (p = .029) in the middle cerebellar peduncle as well. Whole brain analysis revealed no significant between group differences for MD.

Groups did not differ on any other class of illicit substances except lifetime ecstasy use episodes, therefore we conducted pairwise comparisons controlling for reported ecstasy use. Results were unchanged in 6 of the 8 regions, and differed in 2 regions as follows. In 1 of the 4 superior corona radiata regions, the FA difference between BG+MJ and CON no longer reached significance (p = .08), but BG now had lower FA than BG+MJ in this region (p = .03). In the middle cerebellar peduncle, the FA difference between BG and BG+MJ no longer reached significance (p = .16), but BG+MJ now had lower FA than CON (p = .028) after controlling for ecstasy use.

3.3 Bivariate relationships

Relationships between FA in regions that differed by group and measures of lifetime and recent (past 3 month) marijuana and alcohol use were examined among the two user groups (BG and BG+MJ, n = 28). As lifetime marijuana use increased, FA values in two left superior corona radiata clusters also increased (rs = .38 to .41, ps = .03). Further, more marijuana hits in the past three months was linked to higher FA in the superior longitudinal fasciculus (r = .51, p = .006). Similarly, those with more lifetime drinking occasions had higher FA in the superior longitudinal fasciculus (r = .43, p = .02). Lifetime drinking occasions and number of hits smoked in the past three months were not significantly correlated (p>.05). Alcohol drinks consumed in the past three months was not associated with FA in any of the 8 clusters that differed between groups.

4. Discussion

The aim of this study was to look at how adolescent binge drinking behavior affects white matter in the context of marijuana use. White matter integrity, indexed by FA, differed between groups in eight clusters located in both association fiber pathways (e.g., fronto-occipital fasciculus, superior longitudinal fasciculus) as well as the corona radiata. These particular association and projection white matter fiber tracts, often implicated in neurocognitive functioning in both adults and children, continue to develop throughout adolescence and are considered important for connecting sensory structures to the frontal lobes [8,10,52,79,99,103,104].

Overall, we found that teens reporting histories of binge drinking alone and with concomitant marijuana use displayed lower FA compared to controls. Teens reporting binge drinking behaviors alone had significantly lower FA than controls in all eight clusters, whereas teens reporting both binge drinking and marijuana use had lower FA than controls in only three of the eight clusters: two clusters located in the corona radiata and one cluster in the inferior longitudinal fasciculus. In seven clusters (excluding the right inferior longitudinal fasciculus), teens reporting both marijuana and binge drinking had higher FA values than teens who reported binge drinking only (statistically significant in four of the eight clusters: corona radiata, fronto-occipital fasciculus, middle cerebellar peduncle, superior longitudinal fasciculus).

Interestingly, we observed increasing FA values with more marijuana use in white matter fiber tracts such as the left superior longitudinal fasciculus and the left superior corona radiata. In the superior longitudinal fasciculus, FA values and marijuana use episodes in the past three months were positively related. Also in this region, we found an unexpected positive relationship between lifetime drinking occasions and FA values, even though marijuana use and lifetime drinking frequency were not correlated.

No MD differences between groups were seen in any of the 8 clusters that showed between-group FA differences, or anywhere else in the brain, suggesting the potential mechanism of white matter change in this sample may be alterations in the highly organized fiber structure, as compared to tissue loss or demyelination, although this remains uncertain [7,11,54]. Although the pathological relationship between these diffusion indices (e.g., FA and MD) is not entirely understood due to the complicated geometry of white matter tracts in the brain, correlations between MD and FA may point to contributions to the breakdown in microstructural integrity of white matter (e.g., changes in intra/extra cellular fluid, axonal density, disorganization of fiber structure) [72]. Our results propose a relationship between both adolescent binge drinking and marijuana use and subtle white matter tissue microstructural abnormalities in varying projection and association fiber pathways (e.g. superior longitudinal fasciculus) that are important for healthy adolescent neural and cognitive development [19, 63,64,87].

Notably, our results highlight the possible neural consequences of subdiagnostic binge drinking behavior in adolescents, independent of marijuana or other drug use. In support of this hypothesis, animal and human studies have shown that the pathophysiological effects of binge drinking include rate changes in excitatory and inhibitory neurotransmitters in many forebrain structures (e.g., hippocampus, nucleus accumbens), neurochemical metabolite changes, and cell death by inflammatory processes [60,69,84,90,97]. Cellular apoptotic death is even suggested to occur with very small doses of alcohol [109]. Recently, Crews and Nixon (2008) found that ethanol intoxication during binge drinking, as opposed to ethanol withdrawal episodes, may lead to proinflammatory cytokines and increases in oxidative stress. Although the mechanism of white matter change in this sample is complex and not entirely understood, we hope that our findings will build on the current literature exploring the neuropathological consequences of binge drinking on adolescent brain tissue.

While the effects of alcohol use independently on the brain are better understood, the effects of marijuana use remain less clear. Some studies have found evidence of structural and functional brain abnormalities [5,6,20], while other neuroimaging studies report no differences in the brains of heavy marijuana users compared to non-using controls [15,22,29,39,49,100, 108]. In previous studies, our group has found between-group differences in cognition and brain activity in heavy marijuana using adolescents compared to controls [67,81,94]. In this sample, white matter tracts in adolescents who binge drink and use marijuana were more coherent than in adolescents reporting only binge drinking. These findings are unexpected, as recent animal studies have found that rats receiving the psychoactive principal component of marijuana (THC) along with alcohol show an enhanced susceptibility of the developing brain to incur alcohol-related apoptotic neuronal cell death [40].

However, our lab has found similar findings looking at macrostructural changes in adolescent hippocampal volumes. We found reduced hippocampal volumes and abnormal asymmetry in adolescent drinkers compared to controls, but did not observe volume or asymmetry abnormalities in teens reporting *both* alcohol and marijuana use [59]. It is possible that marijuana may have some neuroprotective properties in mitigating alcohol-related oxidative stress or excitoxic cell death as suggested in animal models of alcohol-induced neuronal death and cell regeneration [24,37,101,102]. Although research on the neuroprotective role of cannabinoids is not completely understood, studies have identified several potential neuroprotective molecular mechanisms. For example, activation of cannabinoid receptors may reduce inflammatory activity and excess glutamate neurotransmission that can lead to toxic cell death due to influx of intracellular calcium ion concentrations. Marijuana may also prevent toxicity through anti-oxidative benefits that prevent damage to cellular lipids and proteins, and which may not require cannabinoid-receptor mediated action [18,36,78]. Research on the role of cannabinoids in animal models of binge drinking has found evidence for cannabinoids as a

neuroprotectant against binge alcohol toxicity in hippocampal regions when both substances are administered concurrently [36]. Furthermore, binge alcohol-related modulation of cannabinoid receptors may also contribute to the cellular mechanisms of neuroprotection. Binge alcohol consumption in animals has been found to initially down-regulate CB1 receptors (after 2 days of withdrawal), then up-regulate CB1 receptors later, after 40 days of withdrawal [62]. Given how widely used cannabis and alcohol are alone and in combination, a greater understanding of their interactive, neuroprotective, and neurotoxic effects is important.

Several limitations in this study should to be noted. Although we did not find differences on demographic variables, these three groups of adolescents could differ on a variable not assessed. Since analyses were not longitudinal, we cannot ascertain if changes resulted from substance use or were preexisting. Lastly, we used a nonprobability sampling approach, and our sample was fairly small precluding the ability to examine continuous relationships between FA, alcohol, and marijuana use within each user group separately. Future studies examining the effects of combined alcohol and marijuana use on microstructural integrity of white matter will need larger samples.

In this study, we found that concomitant binge drinking and marijuana use was not associated with better white matter compared to controls, but higher FA values compared to adolescents reporting only binge drinking. Findings suggest that binge drinking may lead to microscopic disruption of white matter fibers. Although not evaluated in this study, alcohol-related diffusion changes in white matter tissue have been linked with altered cognitive performance in adult samples [73]. Studies on cognitive and behavioral consequences of binge drinking have found differences in executive functions including decision-making, which may be related to changes in neural circuitry [46,107]. Gender effects have even been suggested, with female bingers performing worse on neurocognitive tasks compared to male bingers and controls [98]. In future studies, we plan to examine how white matter changes in these adolescents over 18 and 36 month follow-up periods as well as how these changes relate to drug use and risk taking behavior.

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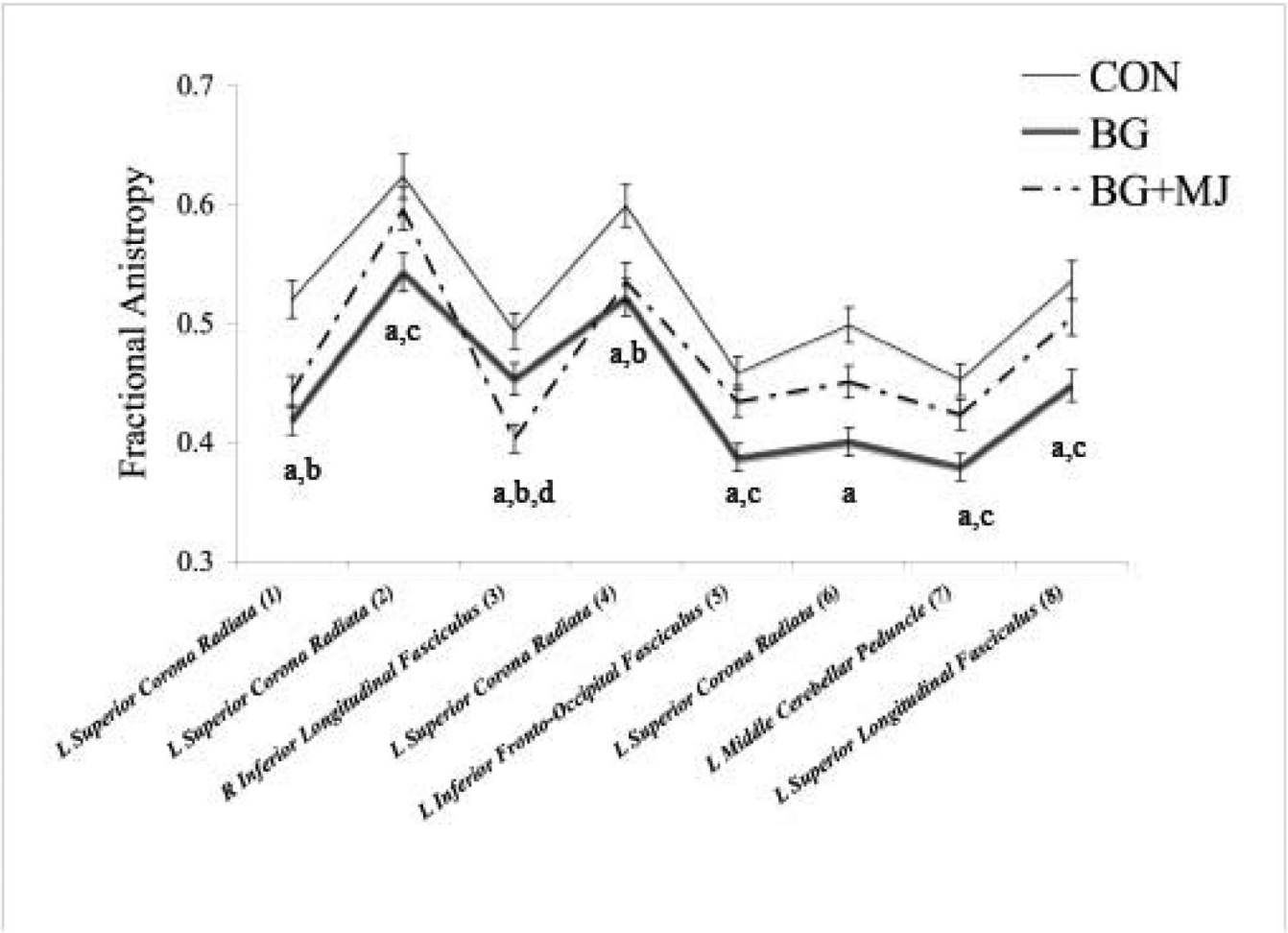

Figure 1.
Between Group FA Differences, a = CON > BG; b = CON > BG+MJ; c = BG < BG+MJ; d = BG > BG+MJ; all $p < .05$