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Alcohol Use and Cerebral White Matter Compromise in Adolescence

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Abstract

Alcohol use is typically initiated during adolescence, a period known to be critical in neurodevelopment. The adolescent brain may be particularly susceptible to the harmful effects of alcohol. While the cognitive deficits associated with alcohol use during adolescence have been well-documented, the neural substrates underlying these effects remain inadequately understood. Cerebral white matter has been suggested as a primary site of alcohol-related damage and diffusion tensor imaging (DTI) allows for the quantification of white matter integrity *in vivo*. This review summarizes results from both cross-sectional and longitudinal studies employing DTI that indicate that white matter tracts, particularly those thought to be involved in executive functioning, continue to develop throughout adolescence and into adulthood. Numerous DTI studies reveal a positive correlation between white matter integrity and neurocognitive performance and, in adults, the detrimental effects of prolonged alcohol-dependence on white matter integrity. We provide a comprehensive review of the DTI studies exploring the relationship between alcohol use and white matter integrity in adolescents. Results from most of these studies suggest that alcohol use is associated with reduced white matter integrity, particularly in the superior longitudinal fasciculus (SLF), and some evidence suggests that this relationship may be influenced by sex. We conclude by highlighting confounds and limitations of the available research and suggesting directions for future research.

Keywords

white matter; adolescent; alcohol use; drinking; brain

1. Introduction

More than half of people in the US over the age of 12 report current alcohol use (Substance Abuse and Mental Health Services Administration, 2011). National cohort studies have

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found sharp increases in rates of current drinking from early (around 3% at ages 12–13) to late adolescence (nearly 50% by ages 18–20), indicating that alcohol use is typically initiated during this developmental period. Notably, this behavioral trend coincides with a critical period in neurodevelopment, especially involving the neocortex, which is associated with higher cognitive functions and which continues to mature through early adulthood. Heavy alcohol exposure within this critical window can thus have particularly harmful neurocognitive consequences and associated behavioral disruptions. While the neurocognitive impact of alcohol use in human adolescents has been demonstrated (e.g. Zeigler et al., 2005; Squeglia, Jacobus, & Tapert, 2009), the neuropathological substrates of the harmful effects of alcohol exposure on brain functions remain inadequately understood. Numerous studies in both adolescents and adults have pointed to cerebral white matter as a primary site of alcohol-associated brain damage (e.g. Konrad et al., 2012; McQueeny et al., 2010). While alcohol is thought to affect both gray and white matter (see Buhler & Mann, 2011 for a review), there is some evidence that suggests white matter integrity may be an early indicator of cerebral health (Hugenschmidt et al., 2008).

White matter provides the structural foundation for the complex connections that run throughout the human brain (Filley, 2010). The distinct pale appearance of white matter is attributable to its abundance of myelin created by oligodendrocytes. These cells are a type of glial cell, which wrap axons in concentric layers to form myelin sheaths. Myelin provides insulation to axons, allowing optimal conduction of electrical signals. Bundles of myelinated axons, often referred to as white matter tracts, connect distant brain regions. Some major white matter tracts include the corpus callosum, which connects the two cerebral hemispheres, the superior longitudinal fasciculus (SLF), which runs between the frontal and occipital lobes, and the corona radiata, which contains axons ascending to and descending from the cerebral cortex. See Filley, 2010 for a more complete review of the major white matter tracts. While the cerebral cortex and subcortical nuclei, comprised primarily of neuronal cell bodies and dendrites, carry out the vital information processing within the brain, cerebral white matter constitutes the complex connecting network that carries information between brain regions. The integrity of the components comprising the cerebral white matter is therefore essential to normal functioning of the brain, ranging from basic life-sustaining functions to higher-level neurocognition.

Recent developments in magnetic resonance imaging (MRI) have enabled researchers to simultaneously examine multiple aspects of cerebral white matter including both white matter volume and integrity (Schulte et al., 2012). Hugenschmidt and colleagues (2008) suggest that reduced white matter integrity may precede white matter volume loss, which could potentially relate these two indices of white matter health. Perhaps most important for the study of white matter, diffusion MRI has recently gained widespread use due to its convenient implementation on most clinical MRI scanners, and its unique ability to measure microstructural white matter integrity and brain structural connectivity *in vivo*. Measures derived from diffusion MRI data are based on the principle that water diffusion occurs in a more directional manner in intact white matter tracts, while compromised white matter tracts typically exhibit a greater overall magnitude of water diffusion (Rosenbloom, Sullivan, & Pfefferbaum, 2003). Diffusion tensor imaging (DTI), a common implementation of diffusion MRI, can provide measures of anisotropy and diffusivity. Higher anisotropy reflects more diffusion directionality typically indicative of better white matter integrity, while higher diffusivity reflects more unconstrained diffusion typically indicative of worse integrity. Optimal white matter integrity is thus typically represented by high anisotropy and low diffusivity. Fractional anisotropy (FA) and mean diffusivity (MD) are the most commonly used measures of these constructs, in addition to secondary measures including axial diffusivity (AD) and radial diffusivity (RD) (see Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010, for an overview of DTI measures). Diffusion spectrum imaging (DSI) is a more

recently developed technique for measuring white matter integrity and is thought to allow for more refined imaging of crossing white matter tracts (see Liu et al., 2010 for more detail).

This paper provides a review of the neuroimaging literature on cerebral white matter abnormalities related to alcohol use in adolescents. We will start with a review of neuroimaging studies of white matter development over the lifespan and document the association between white matter integrity and neurocognitive function. We will then provide a selective review of the relatively well-established literature in adults showing the association between alcohol use and white matter compromise. This section will be followed by a comprehensive review of the relatively limited literature on alcohol-associated white matter compromise in adolescents. The paper will then conclude with a discussion of the limitations of the available studies and suggestions for future research.

2.1 Cerebral White Matter Development

A growing body of evidence from DTI studies suggests that white matter maturation continues throughout adolescence and into early adulthood. Barnea-Goraly and colleagues (2004), for example, examined 34 children and adolescents aged 6–19. Using a cross-sectional design, they found a significant positive correlation between age and FA values in a number of white matter tracts involved in the connections between the prefrontal cortex (PFC), the basal ganglia, and the thalamus. These results suggest that these tracts, which have been implicated in cognitive control processes, are still maturing through late adolescence. Another recent study used a group comparison design to compare the white matter integrity of 114 individuals divided into children, adolescents, and adults (Asato, Terwilliger, Woo, & Luna, 2010). Findings indicated that a number of white matter tracts continue to mature throughout adolescence, many of which are believed to play a role in top-down executive control.

The results from cross-sectional studies have been corroborated by longitudinal studies designed to track white matter maturation throughout adolescence. One study followed 22 adolescents between the ages of 16 and 20 and examined changes in white matter integrity as measured by FA and MD (Bava et al., 2010b). Comparing data for each subject at two different time points, the authors found four regions in which FA increased with age and seven regions in which MD decreased with age, both consistent with increasing white matter integrity. Additionally, white matter integrity was positively correlated with performance on tasks involving attention and working memory in a number of these regions. Notably, many of the tracts that showed age-related changes, including the superior longitudinal fasciculus and superior corona radiata (SCR), are typically associated with executive functioning and information processing (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012).

A meta-analysis of the literature on white matter development in adolescence combined the results of five DTI studies (Peters et al., 2012) including both Asato et al. (2010) and Bava et al. (2010b) described above. It should be noted that four of these studies employed a cross-sectional design while the remaining study (Bava et al. 2010b) was longitudinal. The results indicate that adolescence is associated with widespread increases in FA in regions such as the SLF, inferior longitudinal fasciculus (ILF), the anterior limb of the internal capsule, and the corpus callosum. The authors observe that the largest and most consistent correlations between age and white matter integrity were observed in the bilateral SLF. Thus results from cross-sectional, longitudinal, and meta-analytic studies together provide consistent support for the continuing white matter maturation throughout adolescence and into early adulthood, particularly in regions involved in executive functioning and cognitive control.

Some evidence suggests that white matter maturation during adolescence may differ by sex. Bava and colleagues (2011), for example, examined sex differences in white matter integrity in a sample of 58 adolescents aged 12–14. Relative to male adolescents, females (n=29) displayed significantly higher FA and lower MD values in a number of white matter tracts, including the corona radiata and inferior longitudinal fasciculus (ILF). In contrast, male adolescents in this sample did not exhibit superior white matter integrity in any regions. A more recent longitudinal study, with a sample of 16 adolescents aged 13–17, corroborated these findings (Wang et al., 2012). The authors obtained DTI data from each participant at two time points spaced one year apart. Results from this study suggest that white matter integrity begins to plateau earlier in female adolescents than in male adolescents. Asato and colleagues (2010) also found evidence of earlier white matter maturation in female compared to male adolescents. The results of this study indicate that the earlier white matter maturation observed in females may be related to their earlier onset of puberty. The relationship between age, sex, pubertal status, and white matter integrity, however, remains unclear (e.g., Bava et al., 2011; Herting et al., 2012). Together, these findings indicate that with regard to white matter maturation throughout adolescence, males and females have different development trajectories.

Recent cross-sectional studies have continued to document white matter development into adulthood. One such study examined 66 adults, aged between 23 and 81, and classified them as either young adults, middle-aged adults, or older adults (Giorgio et al., 2010). The authors found significant linear decreases in FA and increases in MD, indicative of an overall decrease in white matter integrity with age through adulthood. In conjunction with the previously mentioned studies of white matter maturation in adolescents, these results suggest that white matter continues to mature during adolescence and then undergoes a process of degradation later in life.

Lebel and colleagues (2012) measured the white matter integrity of 12 distinct tracts in a large sample of 403 healthy subjects aged between 5 and 83 years old. All 12 of these tracts displayed rapid increases in white matter integrity during adolescence and young adulthood followed by more gradual decreases in white matter integrity later in life. Each of the twelve tracts reached peak levels of integrity at different time points between 20 and 45 years of age. In addition, overall volume of white matter was shown to reach its peak around age 37. In contrast to the studies previously described, this study found no significant sex differences in the trajectory of white matter maturation. This discrepancy could potentially be explained by the broader age range included in this sample, which might preclude the detection of sex differences present primarily in adolescence. It should be noted that subjects in this study as well as many of the studies described above excluded participants for any history of neurological or psychological disorder. Such exclusion criteria may lead to samples that are not necessarily representative of the entire population, especially in older participants who have had considerably more time to develop such conditions. These older participants may therefore represent a “supernormal” group. The studies described above, however, do support a model in which white matter volume and integrity continue to develop during adolescence and into adulthood, before beginning to gradually decline.

2.2 White Matter Integrity and Neurocognitive Functioning

White matter compromise has been shown to have significant impact on neurocognitive functioning (Filley, 2010). For example, multiple sclerosis, an autoimmune disease affecting myelin, has been associated with widespread neurocognitive deficits in cognitive domains including attention, information-processing, long-term memory, and executive functioning (Chiaravalloti & DeLuca, 2008). Damage to white matter tracts in individuals with HIV infection has also been associated with global neurocognitive impairment (Gongvatana et

al., 2009). In addition, white matter abnormalities have been found in a number of psychiatric disorders such as depression, schizophrenia, and obsessive-compulsive disorder (Fields, 2008). These illustrative examples demonstrate a connection between injury to white matter and cognitive deficits.

From a developmental perspective, the maturation of white matter tracts appears to be linked to the development of normal cognitive functioning. Nagy, Westerberg, and Klinberg (2004) examined the white matter correlates of visuospatial memory and reading ability in 23 healthy individuals aged between 7 and 18 years old. Significant positive correlations were found between performance on tasks of visuospatial working memory and FA values in the anterior corpus callosum and left frontal lobe. Reading ability was also positively correlated with FA values in the left temporal lobe. These results remained significant after controlling for age, further strengthening the evidence of a connection between white matter integrity and neuropsychological performance.

Another study examined a larger sample of 47 normally developing children and adolescents aged 5–18 (Schmithorst, Wilke, Dardzinksi, & Holland, 2005). Using DTI, the authors explored associations between white matter integrity and Full Scale IQ score (FSIQ) measured by the Wechsler Intelligence Scale for Children (WISC). Significant positive correlations were found between FSIQ and FA values in a number of regions encompassing portions of the arcuate fasciculus. In addition, a significant negative correlation between MD values and IQ was observed in one region in the right frontal lobe. Together these results suggest that increased white matter integrity is associated with better global intellectual functioning in children and adolescents.

Studies in older individuals yield consistent results. Perry and colleagues (2009) reported a relationship between white matter integrity and set-shifting ability in 24 healthy adults aged 21–80. A significant correlation was found between better Trail Making Task B (TMT-B) performance and higher FA values in four regions including the SLF. The authors also observed a significant decrease in TMT-B performance with increasing age. Interestingly, after controlling for FA in the four regions mentioned above, age was no longer correlated with TMT-B performance. These results suggest that reduced white matter integrity may mediate the relationship between age and set-shifting ability.

Sasson and colleagues (2012) found evidence that white matter integrity may be associated with a wide range of cognitive functions in adults. In this study, 52 healthy subjects aged 25–82 underwent a battery of neuropsychological tests designed to measure performance in executive functioning, information processing, and memory. Performance in each of these domains was significantly associated with white matter integrity but associations varied by region. Executive functioning, for example, was positively correlated with white matter integrity in the SLF, the insular cortex, and the inferior frontal gyrus. Thus, not only is white matter integrity related to neuropsychological functioning but specific white matter regions may be differentially associated with distinct cognitive domains.

The studies described above all paint a consistent picture: increased white matter integrity is associated with better cognitive functioning. White matter tracts serve as the communication pathways between spatially segregated brain regions. Refinement of these pathways during adolescence facilitates communication between regions and thus enhances neuropsychological functioning. It follows then that damage to white matter tracts either before or after their full maturation might disrupt cognitive performance. One line of evidence comes from research on cognitive effects observed in a number of white matter disorders (Filley, 2010). Another line of evidence emerges from research on the effects of alcohol abuse on brain structure and function.

3. The Effect of Alcohol Use on White Matter Integrity in Adults

Substantial evidence supports an association between patterns of alcohol use disorders and reduced white matter integrity in adult samples (Monnig, Tonigan, Yeo, Thoma, & McCrady, 2012). Four studies will be highlighted to illustrate the consistency of this well-developed literature. These studies were chosen to illustrate research from multiple groups using both whole-brain and region of interest (ROI) approaches. In one of the first studies employing DTI to examine the association between alcohol use and white matter integrity in adults, Pfefferbaum, Sullivan, Adalsteinsson, Lim, and Moseley (2000) compared the white matter integrity of 15 detoxified alcohol-dependent men to 31 male control subjects, all aged between 40 and 72 years old. Alcohol-dependent subjects differed from controls in two of the three regions studied, with lower FA in the genu of the corpus callosum and the centrum semiovale. This correlational evidence suggests that alcohol may damage white matter *integrity* in these regions, although white matter *volume* did not differ as a function of alcohol exposure in any of these three regions.

Corroboration of these findings comes from a more recent study by the same group, which focused solely on alcohol's impact on the corpus callosum, the largest white matter tract in the brain (Pfefferbaum, Adalsteinsson, & Sullivan, 2006). This study included 57 males and females with alcohol dependence and 74 controls. Relative to controls, the alcohol-dependent group had lower FA and higher MD, both signs of reduced white matter integrity, in all three regions of the corpus callosum (the splenium, the body, and the genu). In contrast with the prior study, significant decreases in white matter volume were also observed in these three regions. This discrepancy may stem from a number of factors including the increased power of this study and the inclusion of both male and female participants. The alcohol-dependent group in this study performed significantly worse on neuropsychological tests designed to evaluate various aspects of executive functioning, including working memory and visuospatial ability. Further, white matter integrity in the genu was significantly correlated with improved working memory function while white matter integrity in the splenium was associated with enhanced visuospatial ability.

Liu and colleagues (2010) extended the above findings by using a slightly different method termed diffusion spectrum imaging (DSI), which allows more refined imaging of crossing white matter fibers. The authors compared the white matter integrity of 25 subjects diagnosed with alcohol dependence to 15 control subjects. All participants were male and aged between 27–52. The authors found that the alcohol-dependent group had significantly worse white matter integrity in six out of seven identified segments of the corpus callosum. The region of the corpus callosum most affected was the segment connecting the bilateral orbitofrontal cortices. Interestingly, reduced white matter integrity in the segment of the corpus callosum connecting the bilateral orbitofrontal cortices was associated with greater levels of impulsivity. The authors suggest that the reduced white matter integrity in this region could at least in part account for the elevated impulsivity which typically accompanies alcoholism.

Alcohol's effect on white matter tracts extends beyond the corpus callosum. Recently, Konrad and colleagues (2012) found evidence of more widespread reductions in white matter integrity in a sample of 24 alcohol-dependent inpatients and 23 controls. All participants were males aged between 32 and 63 years old. Relative to controls, the alcohol-dependent group displayed significantly lower white matter integrity in eight different brain regions including the internal capsule, the cerebellum, and the insula in addition to the corpus callosum. A significant positive correlation was found between performance on two tests of visuospatial ability and white matter integrity in the SLF, right anterior cingulate, and precentral gyrus. This evidence further supports alcohol's potentially harmful effect on

white matter integrity in adults. These results may suggest that white matter mediates the relationship between alcohol and its impact on neuropsychological function.

The four studies described above are just a few of many studies (for a complete list, see Buhler & Mann, 2011) providing evidence that in adults, a history of alcohol use disorder is associated with compromised white matter integrity and that these effects are associated with neuropsychological deficits. The adult literature also suggests that women may be more susceptible to alcohol-related white matter deficits (e.g. Pfefferbaum et al., 2009; Mann et al., 2005). Given these findings, it is important to know whether alcohol consumption has observable effects on white matter and cognition in adolescents, whose drinking careers are much shorter than the alcohol-dependent adults in treatment typically studied. It is also unclear whether subclinical use patterns produce measurable impairment. To address these outstanding questions, the limited research linking alcohol use with white matter integrity in adolescents will be reviewed next.

4. Alcohol's Effect on White Matter in Adolescents

To date, only three studies have attempted to isolate the effect of various patterns of alcohol use on white matter integrity in adolescents. Two of these studies present findings on the effect of binge drinking (Jacobus et al. 2009; McQueeny et al., 2009) whereas the other focuses on adolescents with AUDs (DeBellis et al., 2008). The other studies summarized in Table 1 explore the effect of mixed substance use on white matter integrity in adolescents; they are included in the review if at least 50% of the substance-using group being diagnosed with an AUD or reported significant alcohol involvement.

It should be noted that the studies described below were conducted by only three separate research teams and often use overlapping samples. All of these studies have relatively small samples and focus on individuals aged between 13 and 20 years old. Many share a number of common limitations such as the inclusion of participants with comorbid psychiatric disorders and insufficient power to detect sex differences. These studies are also limited in their ability to untangle the effects of alcohol use from other drug use and premorbid group characteristics. These limitations will be discussed in more detail in the next section.

McQueeny and colleagues (2009) compared 14 adolescents with a history of binge drinking to 14 controls, all aged between 16 and 19 years old. The binge-drinking group was composed of adolescents with at least one binge-drinking episode in the last three months whereas individuals in the control group had no history of binge drinking. In this study, a binge-drinking episode was defined as the consumption of at least 4 or 5 alcoholic drinks in one sitting, for females and males respectively. The authors of this study focused specifically on FA as a measure of white matter integrity and hypothesized that the binge-drinking adolescents would show significantly reduced FA values compared to controls. Consistent with their predictions, they found that the binge-drinking adolescents exhibited lower FA values in 18 regions throughout the brain. These regions included the SLF, known to continue to develop throughout adolescence, as well as the corpus callosum, the superior corona radiata (SCR), the internal and external capsules. FA values in six of these 18 regions were significantly correlated with clinical variables like severity of hangover symptoms and peak BAC levels, strengthening the evidence of a link between alcohol use history and these white matter deficits. While these results are consistent with hypotheses, it should be noted that this study is limited by its relatively small sample size, which prevented the examination of possible moderating variables such as sex. Additionally, the possibility remains that the observed white matter deficits are premorbid characteristics of the binge-drinking group. Potentially, reduced white matter integrity in the identified regions could predispose adolescents to engage in binge drinking behavior. Similarly, binge-style use might interact

and exacerbate a preexisting factor in this subset of individuals, which could also contribute to the observed white matter deficits.

Bava and colleagues (2009) compared 36 adolescents between the ages of 16 and 19 years old with current heavy use of both marijuana and alcohol (MJ + ALC) and 36 controls. The MJ + ALC group had between 180–1844 lifetime marijuana use episodes and between 25–736 lifetime alcoholic drinks. Comparing these groups, the authors found that the MJ + ALC group had significantly lower FA and higher MD in ten different white matter tracts including the SLF and other tracts involved in fronto-parietal circuitry. However, this study also found areas of higher FA and lower MD in the MJ + ALC group in regions such as the occipital lobe and anterior internal capsule, suggestive of better white matter integrity. The authors suggest that these unexpected differences observed in white matter integrity are due either to compensatory mechanisms or premorbid characteristics that predispose adolescents to substance abuse. The same authors performed a follow-up study to examine the functional correlates of these white matter differences (Bava, Jacobus, Yang, Mahmood, & Tapert, 2010). No significant differences in neuropsychological performance were observed between the two groups. In some regions, however, lower FA values in the MJ + ALC group were significantly correlated with worse performance on measures of attention and working memory. Conversely, in some regions, higher FA values were significantly correlated with improved verbal learning. Thus, the MJ + ALC and control groups did not differ on measures of cognitive function but they did differ on white matter integrity, and white matter integrity was associated with cognitive functioning in the predicted directions. Interpretation of these results is challenging because it is impossible to disentangle the contributions of alcohol and marijuana use with this design.

Jacobus and colleagues (2009) attempted to isolate the effect of binge drinking from marijuana use by comparing three groups: binge drinkers (BG), binge drinkers who were also marijuana users (BG + MJ), and controls. In this study, binge drinking was defined as having at least one binge drinking episode of 4 or 5 drinks in one sitting for females and males, respectively. Marijuana users were defined by having between 180–1800 lifetime marijuana uses. Participants were 42 adolescents aged 16 to 19 years old. Compared to controls, the BG group had significantly lower FA values in 8 distinct white matter regions, again including both the SLF and SCR, consistent with a detrimental effect of subclinical binge drinking on white matter integrity. The BG + MJ group had significantly lower FA values in only 3 of these 8 regions and no regions of higher FA values when compared to the control group. These 3 regions were located in the SLF and corona radiata. Even though the BG + MJ group had significantly more lifetime drinking episodes and drinks per month than the BG group, the combined BG + MJ group had significantly higher FA values in 4 of these 8 regions compared to the BG group. Notably, compared to the BG group, the BG+MJ group had significantly lower FA values in the right inferior longitudinal fasciculus. Follow-up analyses revealed that lifetime marijuana use was positively correlated with FA in two superior corona radiata clusters and number of marijuana hits in the past 30 days was positively correlated with FA in the SLF. The authors suggest that these results could reflect a neuroprotective property of marijuana and that marijuana use could offset the harmful effects of alcohol. The study design, however, was missing a group of adolescents who used marijuana in the absence of binge drinking. Such a group could potentially help to isolate the effects of alcohol and marijuana on white matter and elucidate potential interactions. This study was similar to the study conducted by Bava and colleagues (2009) in that it compared a group of adolescents that used both marijuana and alcohol to a control group. When comparing the MJ+ALC group to controls, Bava and colleagues found evidence of lower FA in the SLF but also in more widespread areas (see above). This discrepancy could potentially be explained by differences in the drinking patterns between the two substance-using groups. For example, the MJ+ALC group in Bava et al. (2009) had an average of 52.9

drinks per months in the last three months, whereas the BG+MJ group in Jacobus et al. (2009) had an average of only 26.1 drinks per month.

De Bellis and colleagues (2008) compared the white matter integrity of 28 control subjects to 32 adolescents with alcohol use disorders who were recruited from substance abuse treatment programs. Participant ages ranged from 13 to 19. The study focused on seven different regions of the corpus callosum. The authors hypothesized that they would find decreased FA and increased MD in the AUD group but instead found only opposite results. For instance, they observed that the AUD group had higher FA and lower MD in the isthmus of the corpus callosum, actually suggestive of improved white matter integrity. Notably, a significant correlation was observed between these DTI measures in the isthmus and age of AUD onset. Specifically, earlier AUD development was associated with higher FA and lower MD in the isthmus of the corpus callosum. This finding lends credence to the idea that these differences in white matter integrity may be a cause and not an effect of alcohol use. The authors suggest that accelerated white matter development in this region could potentially increase the risk of developing an AUD. There were, however, some notable limitations to this study. The control group, for example, was significantly younger than the AUD group. Given that white matter integrity is rapidly increasing during adolescence (e.g., Bava et al., 2010a, Lebel et al., 2012), older ages could potentially explain the improved white matter integrity observed in the AUD group. Another limitation of this study was that almost all of the adolescents in the AUD group had comorbid psychiatric disorders. For example, 83% of the AUD group had previously been diagnosed with a mood disorder. 75% of the AUD group met the criteria for a cannabis use disorder. Similarly, 38% of the adolescents in the AUD group met the criteria for nicotine dependence. It is unclear what bias, if any, this high level of comorbidity may introduce.

Recently, Bava, Jacobus, Thayer, and Tapert (2013) conducted a longitudinal study in an attempt to isolate the relationship between substance use on white matter integrity in adolescents. This study, which followed a total of 92 participants over an 18 month period, provides the most direct evidence to date that alcohol use negatively impacts white matter integrity during adolescence. The substance-using group comprised 41 adolescents with greater than 100 lifetime episodes of alcohol or marijuana use while the 51 adolescents in the control group had limited substance use histories. At both Time1 and Time 2, participants underwent a battery of neuropsychological tests as well as DTI. At Time 2, the substance-using group exhibited poorer white matter integrity in seven tracts including the bilateral SLF, the right posterior thalamic fibers, and the left posterior corona radiata, as measured by FA, MD, RD, and AD. Only a subset of these tracts exhibited significant between-group differences at Time 1. More alcohol use during the interscan interval was found to be associated with higher MD in the bilateral SLF, indicative of worse white matter integrity. This relationship held true after controlling for a number of covariates such as family history of substance use disorder and age at Time 1. Marijuana use during the interscan interval did not to predict any diffusion parameters at Time 2. These results suggest that alcohol use can have detrimental effects on white matter integrity and that more severe use is associated with greater white matter damage. One limitation of this study is that the substance-using group initiated alcohol and marijuana use prior to Time 1, which means that the observed differences in white matter integrity could still be due to premorbid group characteristics.

Given the limited amount of research that isolates the effects of binge drinking or AUDS, we will also consider studies on the effect of substance use disorders (SUDs) on white matter integrity in adolescents in cases where AUDs were prominently represented in the SUD group. One such study compared 35 adolescents with SUDs to 20 control subjects (Clark, Chung, Thatcher, Pajtek, & Long, 2011). The SUD group used not only alcohol but

cannabis and other drugs as well. The authors found that the SUD group displayed no differences in white matter volume but did exhibit reduced white matter integrity in frontal and parietal regions. The SUD group also had greater levels of psychological dysregulation, which was measured with the Behavior Rating Inventory of Executive Function (Guy, Isquith, & Gioia, 2004). White matter integrity was negatively correlated with psychological dysregulation. While these results are in line with expected trends, they should be interpreted with caution. The SUD group had significantly higher rates of psychopathology symptoms as well as significantly lower IQs, which makes it difficult to isolate the independent effects of substance abuse. All members of the SUD group were recruited from intensive outpatient treatment programs, meaning these results are unlikely to be representative of the general population. With a sample like this, it is possible that the observed differences in white matter integrity and executive functioning are due to premorbid characteristics as opposed to the use of cannabis or alcohol. Additionally, it remains unclear which effects are attributable to alcohol use and which are attributable to the use of cannabis or other drugs.

Thatcher and colleagues explored the effect of in a subgroup of the sample described above, comprised of 36 adolescents aged 14–18 years old (Thatcher, Pajtek, Chung, Terwilliger, & Clark, 2010). Within this sample, 24 adolescents had SUDs (n=12 female) while the other 12 adolescents served as controls (n=6 female). The SUD group had significantly lower FA in only one cluster located in the SLF. Within this cluster, AD was found to be significantly lower and RD to be significantly higher in the SUD group compared to controls. As previously mentioned, this white matter tract is known to continue maturing throughout adolescence and is believed to be involved in executive functioning. The authors reported a significant sex by group interaction, such that within the SUD group, female adolescents had significantly lower FA than male adolescents. In the control group, however, the opposite trend was observed; males had significantly lower FA than females. This finding is consistent with evidence of slower white matter maturation in males (Bava et al., 2010b, Asato et al., 2010). These results suggest that substance use may be having a greater impact on the white matter integrity of female adolescents. The exact mechanisms behind such sex differences, however, remain unclear. This study also had a number of limitations. Lower FA in the SLF was also significantly correlated with a number of factors including cigarette use, disruptive behaviors, and depressive symptoms. Such correlations may indicate that the effect observed in the SLF is not due to alcohol use alone. This study also recruited its participants from SUD treatment programs, which is likely to make these results less applicable to the general population.

As summarized in Table 1, the studies described above all share a common message: heavy-drinking adolescents and control subjects exhibit measurable differences in white matter integrity. In all of these studies, excluding De Bellis et al. (2008), there is evidence that alcohol and/or mixed substance use is associated with reduced white matter integrity in at least some of the brain regions studied. Still, the exact nature of these associations remains unclear due to a number of methodological limitations recurring throughout this literature.

5. Methodological Limitations of Adolescent Studies

As highlighted in the previous summaries of studies exploring alcohol's impact on white matter, a number of common methodological limitations characterize this literature. These limitations have prevented isolation of alcohol's effect on white matter integrity in adolescents. A careful consideration of the following limitations should inform future study designs.

5.1 Sex Differences

The brains of male and female adolescents may be differentially affected by patterns of alcohol use consistent with binge drinking or AUDs. Medina and colleagues (2008), for example, illustrated that females with AUDs had smaller total volumes and white matter volumes in the prefrontal cortex (PFC) compared to controls. Males with AUDs, however, had larger total and white matter PFC volumes compared to controls. Squeglia and colleagues (2011) found significant interactions between the effects of sex and binge drinking on cortical thickness. While this study did not specifically examine white matter, the results indicate that female binge drinkers had thicker cortices than female controls while male binge drinkers had thinner cortices than male controls. As previously mentioned, the results of one study suggest that sex may also influence the relationship between SUDs and white matter deficits (Thatcher et al., 2010). In light of this evidence, it seems crucial to consider sex differences when exploring the relationship between alcohol use and white matter integrity in adolescents. Typically, however, the small sample sizes of these studies do not allow sufficient power for reliable detection of sex differences. It is possible, therefore, that the adverse effects of drinking on white matter integrity are being obscured by differential sex effects. Thus, it would be informative if we could evaluate the interaction between alcohol use and sex on white matter integrity during adolescence.

5.2 Marijuana and Other Drugs

The use of marijuana and other drugs in conjunction with alcohol is a common confounding factor in most of the studies described above. This confound makes isolating the effect of alcohol use challenging. The co-occurrence of marijuana use is significant because marijuana use may have mixed effects on white matter integrity. One study found that a group of adolescents defined by heavy cannabis use had reduced white matter integrity in a number of brain regions compared to controls (Ashtari, Cervellione, Cottone, Ardekani, & Kumra, 2009). However, other studies included in this review suggest that marijuana may have a neuroprotective effect on white matter integrity that could potentially mitigate the harmful effects of alcohol (Bava et al., 2009, Jacobus et al., 2009). Consistent with this interpretation, DeLisi and colleagues (2006) found that adults who had used cannabis heavily during adolescence had higher FA values in specific regions including the left anterior cingulate and left precentral gyrus compared to controls. This study, however, was limited by a relatively small sample size, with only 10 participants in each of the two groups. Additionally, Bava and colleagues (2013) found that alcohol but not marijuana use predicted Time 2 white matter integrity. The effect of marijuana use on white matter has yet to be clearly determined and its common co-occurrence with alcohol use in adolescent samples has thus far prevented sufficient isolation of the effect of either drug.

Alcohol-using adolescents commonly report significantly higher rates of cigarette smoking and other drug compared to controls (e.g., Bava et al., 2009, Jacobus et al., 2009, De Bellis et al., 2008). While these factors are often statistically controlled for, the contributions of these other drugs to deficits in white matter integrity remain unclear. Results from a recent study, for example, suggest that adolescent smokers may have *elevated* FA values in several brain regions (Hudkins, O'Neill, Tobias, Bartzokis, & London, 2012). Theoretically, then, both concurrent nicotine and marijuana use could be masking the detrimental effects of alcohol. With so much still unknown about the effects of marijuana and other drugs on white matter integrity, these potentially confounding factors must be carefully considered and controlled for when possible.

5.3 Comorbid Psychiatric Disorders

Alcohol use disorders are often comorbid with a number of other psychiatric disorders including mood disorders, anxiety disorders, and conduct disorder (APA, 1994). High rates

of these comorbid psychiatric disorders were displayed in many of the adolescent samples in the studies described above. In De Bellis et al. (2008), for example, 83% of the AUD group had a mood disorder, 83% had some form of disruptive behavior disorder, and 30% had an anxiety disorder. Similarly, in Clark et al., 2011, 31% of the SUD group was diagnosed with conduct disorder, 34% had major depression, and 40% were diagnosed with ADHD. A significant body of evidence suggests that many psychiatric disorders including major depression, bipolar disorder, PTSD, and OCD involve white matter abnormalities (Fields, 2008). The high frequency of these disorders among adolescent AUD samples may be preventing isolation of alcohol's effect on white matter integrity. A possible way to avoid this confound might be recruitment from non-clinical populations where base rates of such disorders are likely to be lower.

5.4 Premorbid Group Characteristics

One common feature shared by almost all of these studies is a cross-sectional design. Cross-sectional studies are inherently limited in their ability to detect causal relationships. In addition, longitudinal studies are most informative when the first assessment occurs prior to substance use onset (cf. Bava et al., 2013). Thus, the results of the above studies cannot clarify whether alcohol use is causing a decrease in white matter integrity or whether reduced white matter integrity is leading to more alcohol use. It is possible, for example, that decreased white matter integrity in specific brain regions could make some adolescents more prone to risk-taking behavior, resulting in greater alcohol consumption and the development of an AUD. Relevant premorbid group characteristics that could influence white matter integrity include family history and prenatal alcohol exposure.

A recent study demonstrated that alcohol-naïve youth with family histories of AUDs had reduced white matter integrity in the prefrontal cortex and posterior parietal cortex compared to controls (Wetherill et al., 2011). Similarly, Herting, Schwartz, Mitchell, and Nagel (2010) found significantly reduced white matter integrity in more widespread regions in alcohol-naïve youth with family histories of AUDs relative to controls without such a family history. These regions were found in tracts located in the prefrontal cortex, the temporal cortex, and the occipital cortex. Interestingly, this study found that a region of the corona radiata located in the parietal lobe had increased white matter integrity in alcohol-naïve youth with family histories of AUDs compared to controls. These studies suggest that a family history of AUDs may affect white matter integrity in at-risk individuals prior to any personal drinking experience. Family history should thus be considered an important factor when testing for the effect of alcohol use on white matter integrity in adolescents. While family history is often measured, it has not been consistently controlled for either statistically or by design (e.g., Bava et al., 2009, Thatcher et al., 2010). Similarly, prenatal alcohol exposure might also contribute to the observed differences in white matter integrity almong substance using teens (see Wozniak & Muetzel, 2011 for a complete review), especially in studies where this historical variable was not considered (e.g., Thatcher et al., 2011, Clark et al., 2012). DeBellis and colleagues (2008) found that substance-using teens had higher levels of both prenatal alcohol and tobacco exposure. Follow-up analyses, however, suggested that prenatal exposure to either substance did not contribute to observed differences in white matter integrity. Other studies described above excluded participants with prenatal alcohol exposure consistent with at-risk drinking (e.g., McQueeny et al., 2009, Jacobus et al., 2009).

5.5 Length of Abstinence Prior to Scanning

As displayed in Table 1, participants had variable lengths of abstinence prior to scanning in many of the studies described above. Bava and colleagues (2009), for example, report that the average number of days between last alcohol use and the DTI study in the substance-

using group was 43.0 with a standard deviation of 68.6 days. Thatcher and colleagues (2010) report an average of only 12.17 days of abstinence prior to scanning with a standard deviation of 13.07. Results such as these suggest a high degree of variability in the length of abstinence prior to scanning both between participants within each individual study and between studies themselves. This is important because alcohol-induced damage to white matter integrity may be reversible with abstinence. Sorg and colleagues (2011), for example, found that adult alcoholics who resumed heavy alcohol use after treatment had decreased white matter integrity compared to alcoholics who remained abstinent. A recent meta-analysis of the adult literature on the relationship between alcohol use and white matter volume suggests that days abstinent prior to scanning is positively correlated with white matter volume (Monnig et al., 2012). In other words, subjects who were abstinent for longer periods of time prior to scanning had significantly greater white matter volume. While rates of recovery may vary, accumulating evidence suggests that prolonged abstinence is associated with predictable white matter recovery (e.g., Mon, Delucchi, Durazzo, Gazdzinski, & Meyerhoff, 2011). Together, these results suggest that alcohol's effect on both white matter integrity and volume may be reversible with sustained abstinence. Variable periods of abstinence between participants in a single study and between studies might therefore prevent the detection of alcohol-related impairment. Good practice requires sufficient abstinence prior to imaging to ensure no acute intoxication. However, to maximize sensitivity, days abstinent prior to scanning should be carefully considered and controlled for when designing future studies.

5.6 DTI Limitations

A number of issues should be considered when interpreting measures derived from DTI. Inherent to the diffusion tensor model is the assumption of a single primary diffusion direction within each imaging voxel. This can results in inaccurate estimation of diffusion characteristics in areas where heterogeneous fiber tracks cross or converge, as fibers with different orientations passing through the same voxel are essentially averaged together. Novel analytical methods including high angular resolution diffusion imaging (HARDI) and DSI have been developed to address this issue by explicitly modeling multiple intravoxel fiber populations (Weeden et al., 2008; Tuch et al., 2002), and studies applying such methodologies in clinical populations including alcoholism are under way. Another potential complication involves the current state of understanding of the neurobiological basis driving changes in DTI measures of anisotropy and diffusivity. A number of studies have linked changes in FA and MD to more direct microstructural cellular measures such as axonal diameter and density and myelin integrity (Le Bihan & Johansen-Berg, 2012), although additional evidence is still required to further elucidate this point. Novel MRI methods such as those recently proposed to provide measures of myelin integrity (Glasser & Van Essen, 2011; Deoni et al., 2011) when applied concurrently with DTI may help to clarify interpretations of FA and MD values. Finally, recent investigators have questioned whether higher anisotropy measure always reflect better brain integrity, especially in cases where compensatory processes may be at play (Hoeft et al., 2007), although such findings remain to be replicated.

6. Future Research Directions

Future research exploring the effect of alcohol on white matter integrity in adolescents should attempt to better address the confounds and limitations described above. First, more carefully designed studies are needed to isolate the effect of alcohol from comorbid psychiatric disorders and the effects of other drugs. If study groups differ both on alcohol use and other characteristics that might have an impact for white integrity, clear conclusions cannot be drawn. This issue could be addressed by more clearly defining inclusion and exclusion criteria used to create study groups (cf., Bava et al., 2013), by matching control

groups on variables of interest unrelated to alcohol use, or by using larger sample sizes to more effectively statistically control for these confounds.

Second, longitudinal designs are necessary in order to disentangle the effects of alcohol use from premorbid group characteristics. Such studies would help to clarify whether the observed differences in white matter integrity lead to increased alcohol consumption, whether they are the result of prolonged alcohol use, or a combination of both. Additional longitudinal studies could also serve to elucidate the relationship between alcohol use and trajectories of white matter maturation during adolescence.

Third, future studies should attempt to identify whether sex is a major modifying factor of alcohol's effect, which might require larger sample sizes. Extant data suggest that female adolescents may be more vulnerable to the detrimental effects of alcohol on white matter integrity. Research is needed to investigate how the effects of alcohol use interact with the different developmental trajectories of male and female adolescents.

Fourth, we know little about alcohol's effect on white matter integrity in young adult drinkers (18–25). While drinking is known to increase rapidly through adolescence, rates of alcohol use and binge drinking peak at ages 21–25 (Substance Abuse and Mental Health Services Administration, 2011). In this age range, about 70% of individuals report being current drinkers and almost 50% engage in binge drinking behavior. In compiling this review, however, no studies were found documenting the relationship between white mater integrity and alcohol use in this period immediately after adolescence. DeBellis and colleagues (2005) examined the relationship between alcohol use and white matter *volume* in participants aged 13–21. Results indicated that participants with AUDs had smaller prefrontal cortex white matter volumes than control subjects, which may provide further justification for exploring the effects of alcohol use on white matter integrity in this older age range.

Fifth, if we have evidence to suggest that alcohol use is damaging white matter in adolescents, future research should address whether such effects are reversible with sustained abstinence. In this regard, a recent study demonstrated that adult alcoholics had both improved white matter integrity and neurocognitive functioning after one year of abstinence (Alhassoon et al., 2012). Such findings are in line with the large body of evidence supporting the notion of brain plasticity and offers hope that alcohol-induced damage to white matter in nonclinical samples of drinkers can be reversed by reducing alcohol consumption.

Sixth, the studies described above have been carried out by a limited number of research groups. The samples in these studies often overlap which means these results cannot be treated as independent data. Further replication of these findings by separate research teams is needed in order to better understand the effect of alcohol use on white matter integrity in adolescence.

Finally, future studies could use novel imaging techniques that allow for accurate analysis of crossing white matter fibers (e.g., Weeden et al., 2008; Tuch et al., 2002) as well as more direct measures of myelin integrity (e.g., Glasser & Van Essen, 2011; Deoni et al., 2011). Combining DTI with these techniques and others (e.g., fMRI) with may provide more insight into the effects of alcohol use on white matter in adolescents (Schulte et al., 2012).

7. Conclusions

White matter tracts are the pathways of communication between regions of the human brain. The integrity of these pathways has been shown to correlate reliably with

neuropsychological functioning, highlighting the importance of these tracts in normal cognitive development. Evidence suggests that maturation of white matter tracts continues throughout adolescence and into early adulthood. The prolonged nature of its development might make white matter susceptible to the deleterious effects of alcohol during this period. In support of this idea, patterns of alcohol use consistent with binge drinking and AUDs during early adolescence have been associated with both reduced white matter integrity and impaired cognitive functioning. Decreased white matter integrity could therefore serve as the mechanism underlying alcohol's effects on neurocognitive function. The limited amount of research in this area and a number of recurring confounds, however, preclude strong conclusions on the functional relationship between white matter and alcohol consumption in adolescence.

Future research exploring the effect of alcohol use on white matter integrity in adolescents could provide insight into the processes leading to the development of AUDs (Nixon & McClain, 2010). A body of evidence indicates that initiation of alcohol use during adolescence increases the likelihood of AUD development later on in life (e.g., Guttmannova et al., 2011, Dawson, Goldstein, Chou, Ruan, & Grant, 2008). Casey and Jones (2010) suggest that alcohol use may disrupt the development of the top-down pathways between the prefrontal cortex and striatum, resulting in impaired cognitive control and increased susceptibility to the temptation of alcohol. The literature just reviewed highlights the SLF as a white matter tract undergoing significant development during adolescence. The SLF is also one of the tracts most consistently affected by alcohol use in the studies summarized in Table 1, including the longitudinal study that provides the most direct evidence of a causal effect. Given the data suggesting that the white matter integrity of the SLF is directly correlated with executive functioning, it possible that alcohol-induced damage to this tract could impair executive functioning and eventually lead to increased alcohol consumption (Giancola, 1998). Such a positive-feedback loop could contribute to the development of alcohol addiction. This idea is supported by two recent studies. First, Chung, Pajtek, and Clark (2012) found that reduced white matter integrity was associated with more alcohol-related problems at a 6-month follow-up in a sample of adolescents in treatment for substance use. Second, Jacobus and colleagues (in press) showed that in substance-using adolescents, reduced white matter integrity predicted more alcohol consumption and risk-taking behaviors at a 1.5 year follow-up. The results of both of these studies provide support for a model in which heavy alcohol use during adolescence leads to reduced white matter integrity, which in turn may lead to more alcohol use.

White matter integrity may be the link between alcohol use and cognitive functioning and a key component in the development of alcohol addiction. A better understanding of the relationship between alcohol use and white matter in adolescence could potentially inform future interventions, perhaps calling for a focus on brain effects incurred by alcohol in younger drinkers. Adolescence might therefore represent not only a period of increased susceptibility to alcohol-induced damage to white matter but also an opportune time for effective interventions.

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Highlights

- White matter continues to develop throughout adolescence and into early adulthood.
- White matter compromise can relate to poor cognition.
- In adults, heavy alcohol use is linked to white matter damage.
- The effect of alcohol use on white matter integrity is less clear in adolescents.
- Better-designed and longitudinal studies are needed to clarify this relationship.

Table 1

Summary of Studies Evaluating the Relationship between Alcohol Use on White Matter Integrity in Adolescents

Article	Sample	Sex (%F)	Age Range	Average Number of Days Since Last Alcohol Use M(SD)	Method	Results		Study Limitations
						FA	MD	
McQueeny et al. (2009)	14 BG vs. 14 C	14.3	16–19	30.29(10.53) for BG	Whole brain	BG < C in 18 regions	Not reported	• Small sample size
Bava et al. (2009)	36 MJ + ALC vs. 36 C	27.8	16–19	43(68.6) for MJ+ALC group	Whole brain	MJ+ALC < C in 10 regions MJ+ALC > C in 3 regions	MJ+ALC < C in 1 region MJ+ALC > C in 1 region	• Variable periods of abstinence before scanning • Cannot differentiate between effects of MJ and ALC use
Jacobus et al. (2009)	14 C, 14 BG, 14 BG+MJ	16.3	16–19	30.2(10.5) for BG group, 26.1(15.6) for BG + MJ group	Whole brain	BG < C in 8 regions, BG < BG+MJ in 4 regions	No significant differences observed	• BG and BG + MJ groups differed significantly on long-term and recent drug use • No MJ only group to compare
De Bellis et al. (2008)	32 AUD vs. 28 C	30	13.3-19.3	63.7(88.2) for AUD group	ROIs	AUD > C in 2 regions of CC	AUD < C in 1 region of CC	• AUD group older than controls • AUD group had more comorbid psychiatric disorders • AUD group had more cannabis use disorders • AUD group had more SUD family history
Bava et al. (2013)	41 SU vs. 51 C	31.5	16–20	Not reported	Whole brain	SU > C in 3 regions	SU < C in 5 regions	• SU group significantly older than controls • Results may be in part due to premorbid characteristics
Clark et al. (2011)	35 SUD vs. 20 C	49.1	14–19	Not reported	ROIs	SUD < C in PFC and parietal lobe	Not reported	• Cannot untangle effects of different drugs • SUD group had significantly lower IQs
Thatcher et al. (2010)	24 SUD vs. 12 C	50	14–18	12.17(13.07) for SUD group	Whole brain	SUD < C in SLF	No significant differences observed in SLF	• SUD group used multiple substances • SUD group had significantly higher rates of rates of depressive symptoms and disruptive behaviors

Note: Sample in Thatcher et al. (2010) was a subsample of Clark et al. (2011). Jacobus et al. (2009) includes the same sample as McQueeny et al. (2009) but with an additional BG + MJ group. Participants in McQueeny et al. (2009) were a subset of the controls in Bava et al. (2009). The participants in Bava et al. (2013) overlap with the participants in McQueeny et al. (2009), Bava et al. (2009), and Jacobus et al. (2009), with an additional measurement event 1.5 years later. %F = percent female, BG = binge drinkers, C = control subjects, FA = fractional anisotropy, MD = mean diffusivity, MJ + ALC = marijuana and alcohol users, AUD = alcohol use disorder, CC = corpus callosum, ROIs = regions of interest, BG + MJ = binge drinkers who are also marijuana users, SU = substance-using adolescents, SUD = substance use disorder, PFC = prefrontal cortex, SLF = superior longitudinal fasciculus