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White matter microstructure, alcohol exposure, and familial risk for alcohol dependence

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ABSTRACT

Offspring from families with alcohol dependence (AD) have been shown to exhibit brain morphological alterations that appear to be related to their familial/genetic risk for AD. Greater susceptibility for developing AD may be related to structural underpinnings of behavioral traits that predispose to AD. We examined white matter (WM) integrity in 81 individuals with either a high density of AD in their families ($N=44$) or without a family history for either alcohol or drug dependence ($N=37$). Magnetic resonance images were acquired on a Siemens 3 T scanner with fractional anistropy (FA) and the apparent diffusion coefficient (ADC), along with radial diffusivity (RD) and longitudinal (axial) diffusivity calculated for major white matter tracts in both hemispheres. Extensive personal histories of alcohol and drug use were available from longitudinal collection of data allowing for reliable estimates of alcohol and drug exposure. We found that the interaction of personal exposure to alcohol and familial risk for AD predicts reduction in WM integrity for the inferior longitudinal fasciculus (ILF) and the superior longitudinal fasciculus (SLF) in the left hemisphere and the forceps major tract. Only one tract showed a significant difference for exposure alone, the anterior thalamic radiation.

1. Introduction

The neurotoxic effects of alcohol consumption have been evident since the time that Victor et al. (1971) published their classic work. Using autopsy data, it was shown that the debilitating behavioral and neurocognitive effects of long-term alcohol use seen in Wernicke–Korsakoff patients, who have among other deficits a profound short-term memory loss, were associated with significant neuropathological changes in a number of subcortical regions.

It is now clear from numerous reports focused on individuals with chronic alcohol dependence that long-term consumption of alcohol is associated with brain morphological changes (Chanraud et al., 2010), as well as neurocognitive changes (Sullivan and Pfefferbaum, 2005; Oscar-Berman and Marinkovic, 2007). Although alcohol diffuses throughout the brain, there is evidence that not all regions are equally affected by alcohol. Regional changes have been suggested by work showing impairment in frontal and parietal networks in long-term alcohol dependence (Pfefferbaum et al., 2010) and a tendency for lateralized effects to be seen, with the right hemisphere showing greater impairment (Oscar-Berman and Marinkovic, 2007; Pfefferbaum et al., 2009) in association with the neurotoxic effects of alcohol.

There is an intriguing possibility that some of the observed variation in structural and functional characteristics of individuals who are heavy consumers of alcohol may have existed prior to the initiation of drinking and that some of these characteristics may actually be markers of vulnerability. Structural differences have been observed family-history-positive youth selected for a high density of familial alcohol dependence. These include reduced volume of the right amygdala (Hill et al., 2001), reduced volume of the right orbitofrontal cortex (Hill et al., 2009a), and greater volume of cerebellum for age (Hill et al., 2007a; Hill et al., 2011a) suggesting a slower rate of neural pruning of grey matter in those with a family history of alcohol dependence. Also, youth with parental alcoholism have been reported to have smaller total brain volume (Gilman et al., 2007). Electrophysiological differences between family-history-positive and-negative youth were first identified using event-related potential (ERP) recordings in boys without any significant drinking history (Begleiter et al., 1984). Reduction in the P300 component of the ERP was seen in those with a family history. Several other studies have found similar effects (for reviews, see Polich et al., 1994; Hill, 2010). These deficits may reflect an inability to reach age-appropriate levels of P300 in high-risk youth (Hill et al., 1999) and, importantly, slower trajectories of P300 change are related to childhood psychopathology (Hill and Shen, 2002).

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A variety of functional imaging paradigms have been used to address possible differences between high- and low-risk youth. Although the paradigms and functions have varied across studies (for review see Tessner and Hill, 2010), the general tendency has been to see reduced activation in frontal regions associated with attentional tasks (Spadoni et al., 2008) and with tasks requiring inhibition of a prepotent response (Schweinberg et al., 2004). Functional imaging studies that have focused on brain connectivity using functional magnetic resonance imaging (fMRI) in family-history-positive and -negative youth have reported weaker fronto-parietal connectivity (Wetherill et al., 2012) and weaker fronto-cerebellar connectivity (Herting et al., 2011) in family-history-positive youth.

Attempts to differentiate what is cause and what is consequence are complicated by the fact that youth from families with a history of alcohol dependence have a higher risk for developing an alcohol use disorder (AUD) or related substance use disorder (SUD) than do youth without such a history (Milberger et al., 1999; Merikangas et al., 2009). Follow-up of youth from multiplex, multigenerational families with multiple cases of alcohol dependence is associated with a four-fold increase in risk for substance use disorder (SUD) (Hill et al., 2008, 2011b). In addition, youth with a positive family history of alcohol dependence tend to start using alcohol at an earlier age than do those without a history (McGue et al., 2001; Hill and Yuan, 1999; Hill et al., 2000). Because of this earlier onset of substance use, those with a family history may be at greater risk for incurring alcohol- and drug-related exposures that could potentially affect brain morphology.

Magnetic resonance (MR) diffusion tensor imaging (DTI) provides an opportunity to investigate white matter microstructure often revealing disruption that is not apparent upon macrostructural inspection (Pfefferbaum and Sullivan, 2002). DTI studies are possible because of characteristics of water diffusion in the brain. Diffusion that is unconstrained is isotropic as is seen in the cerebrospinal fluid whereas anisotropy results from constraints imposed by fiber tracts. The metrics of DTI include fractional anistropy (FA) and the apparent diffusion coefficient (ADC), which can be decomposed into two components, the transverse (radial) diffusivity (λT), and the longitudinal (axial) diffusivity (λL). (Beaulieu, 2002). Specifically, FA reflects the tendency for water to diffuse along an axis parallel to the fiber tract such that higher values of FA are associated with more intact white matter microstructure. Radial diffusivity (RD), which measures water diffusion perpendicular to the tract, is associated with disruption of white matter integrity so that higher values are indicative of greater disruption. These DTI metrics provide a method for assessing the likelihood that white matter integrity has been affected. Radial diffusivity (RD) increases with loss of myelin integrity. Longitudinal diffusivity can be altered where disruption of axonal integrity or axonal deletion is present. Typically, disruption of white matter through breakdown of the myelin sheath is associated with decreased FA and increased radial diffusivity RD (Song et al., 2002).

Among the applications of DTI methodology are assessments of whether white matter integrity has been compromised by exposure to substances, whether neurodegenerative conditions may be taking place, or whether white matter variation might be the result of a familial/genetic characteristic of the individual. Evidence that FA may also vary due to inborn characteristics comes from recent studies showing a substantial heritability of FA in related healthy individuals (Jahanshad et al., 2010). FA values change during development, typically with changes in mean diffusivity. In their review of 30 studies that have addressed DTI in child, adolescent, young adult, and older adult samples, Schmithorst and Yuan (2010) conclude that there is an overall tendency for FA values to rise during childhood, adolescence and young adulthood, peaking at about 40 years of age and then declining. The rise in FA seen during this period is mirrored by a decrease in mean diffusivity, declining until age 40 and then rising again.

DTI studies have provided evidence that white matter microstructural disruption occurs in alcohol-dependent men and women in the corpus callosum and spenium and in multiple white matter tracts (Pfefferbaum et al., 2006, 2009). DTI can reveal regional white matter disruption and assess white matter tracts (Lehericy et al., 2004). Applying quantified fiber tracking, Pfefferbaum et al. (2009) showed that alcoholism affected FA and diffusivity of several fiber bundles with frontal and superior regions most affected (frontal forceps, longitudinal fasciculi, internal and external capsules, fornix and superior cingulate). Curiously, more posterior and inferior structures were relatively spared.

Although there is substantial evidence that exposure to alcohol and drugs is associated with white matter microstructural changes (Sullivan and Pfefferbaum, 2005; Pfefferbaum et al., 2009), it is unclear if some of these microstructural changes may have been present in those with a family history of alcohol dependence before they started drinking. Only a few studies have examined white matter microstructure in youth with and without a family history of alcohol dependence (Medina et al., 2008; Bava et al. 2009, 2010; De Bellis et al., 2008; Herting et al., 2010; Wetherill et al., 2012). One study reported reduced FA for the inferior longitudinal fasciculus and right optic radiation in family-history-positive youth (Herting et al., 2010), while another (Wetherill et al., 2012) did not find altered white matter microstructure in tracts connecting the frontal and parietal regions, though they did find evidence for reduced frontoparietal connectivity using fMRI. Bava et al. (2009) reported a family history effect for the right crus cerebri, though no other regions showed an association. Exposure to marihuana and alcohol predicted FA above and beyond parental history, though no interaction between family history and exposure was seen. However, in a later report, Bava et al. (2010) found FA in inferior longitudinal fasciculus (right) to be significantly correlated with parental SUD.

Alcohol or marihuana exposure during adolescence and young adulthood appears to have an adverse effect on white matter microstructure (Medina et al., 2008; De Bellis et al., 2008; McQueeny et al., 2009; Bava et al., 2009; Thatcher et al., 2010). Three of the studies that evaluated exposure effects also evaluated family history (Bava et al., 2009; Medina et al., 2008; De Bellis et al., 2008) with one reporting no effect of familial risk for alcohol dependence background (Medina et al., 2008), the other showing minimal effect (Bava et al., 2009), while the third found an unexpected increase in FA (De Bellis et al., 2008).

Because of the possibility that both familial loading for alcohol dependence and exposure to alcohol or drugs of abuse might affect white matter tracts, this study was designed to address these issues in a sample that varied in familial loading for alcohol dependence and for whom extensive data were available for personal exposure to alcohol, marihuana, and cigarettes. Based on results from previous studies that have assessed alcohol exposure, we predicted that subjects with heavier alcohol exposure would have reduced FA and increased ADC (either axial or transverse diffusivity) reflecting loss of white matter integrity. With previous reports of reduced FA in those with a family history of alcohol dependence, we predicted that individuals with multiplex family history would have reduced FA. It was also hypothesized that those with a multiplex family history who were among the heavier consumers of alcohol might have the greatest decline in FA and the largest increases in radial or longitudinal diffusivity. Our first goal was hypothesis-driven and was designed to assess whether or not previously identified changes in specific tracts (inferior longitudinal fasciculi and superior longitudinal fasciculi) would be seen in association with multiplex