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Decreased white matter integrity in fronto-occipital fasciculus bundles: Relation to visual information processing in alcohol-dependent subjects

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ABSTRACT

Chronic alcohol abuse is characterized by impaired cognitive abilities with a more severe deficit in visual than in verbal functions. Neuropathologically, it is associated with widespread brain structural compromise marked by gray matter shrinkage, ventricular enlargement, and white matter degradation. The present study sought to increase current understanding of the impairment of visual processing abilities in alcohol-dependent subjects, and its correlation with white matter microstructural alterations, using diffusion tensor imaging (DTI). To that end, a DTI study was carried out on 35 alcohol-dependent subjects and 30 healthy male control subjects. Neuropsychological tests were assessed for visual processing skills and deficits were reported as raw dysfunction scores (rDyS). Reduced FA (fractional anisotropy) and increased MD (mean diffusivity) were observed bilaterally in inferior and superior fronto-occipital fasciculus (FOF) fiber bundles. A significant inverse correlation in rDyS and FA values was observed in these fiber tracts whereas a positive correlation of these scores was found with the MD values. Our results suggest that FOF fiber bundles linking the frontal lobe to occipital lobe might be related to visual processing skills. This is the first report of an alteration of the white matter microstructure of FOF fiber bundles that might have functional consequences for visual processing in alcohol-dependent subjects who exhibit no neurological complications.

Introduction

Chronic alcoholism is known to impair performance in a variety of cognitive functions. Previous studies have reported that up to 75% of detoxified alcoholics have some kind of cognitive or memory disturbance (Trivedi et al., 2013). Attention, working memory, visuospatial abilities, executive functions, and verbal fluency have all been shown to be impaired in alcoholism (Ambrose, Bowden, & Whelan, 2001; Demir, Uluğ, Lay Ergün, & Erbaş, 2002; Fama, Pfefferbaum, & Sullivan, 2004; Oscar-Berman & Marinković, 2007; Stavro, Pelletier, & Potvin, 2013; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003). Chronic alcohol consumption also leads to diffuse brain shrinkage (Baker, Harding, Halliday, Kril, & Harper, 1999; Kril, Halliday, Svoboda, & Cartwright, 1997; Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000; Sullivan, Rosenbloom, Serventi, Deshmukh, & Pfefferbaum, 2003), with the frontal lobes showing the earliest and most extensive shrinkage (Kubota et al., 2001; Moselhy, Georgiou, & Kahn, 2001; Pfefferbaum et al., 1995).

Alcohol-dependent individuals often exhibit distinct impairments in visual processing abilities whereas the verbal functions are relatively preserved (Fabian, Parsons, & Sheldon, 1994; Stavro et al., 2013; Wegner, Günthner, & Fahle, 2001). The visual processing deficits have classically been associated with impaired function of occipital lobes, but more recently, also with alterations within the fronto-occipital circuitry (Hermann et al., 2006; Modi et al., 2011; Schmahmann & Pandya, 2007). The occipital and frontal lobes are anatomically distinct and separately located, yet evidence suggests that they are functionally integrated to generate some of the most complex behaviors. Disruption of this fronto-occipital connectivity might lead to brain dysfunction manifested as impaired visual processing in alcohol-dependent individuals. Postmortem and structural magnetic resonance imaging (MRI) techniques have also reported that alcohol abuse is damaging predominantly to cerebral white matter (de la Monte, 1988; Harper, Kril, & Holloway, 1985). In support of these findings, postmortem RNA analyses of superior frontal lobe samples found that genes

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related to myelin structure were down regulated in alcohol-dependent individuals (Lewohl et al., 2000).

The performance of cognitive tasks engages a network of brain regions connected by white matter fiber bundles (Chanraud, Reynaud, et al., 2009; Trivedi et al., 2013). Previous investigations on alcoholism have provided evidence of alcohol-related changes in various brain regions, namely, prefrontal lobe, cingulate cortex, amygdala, hippocampus, and cerebellum (Chanraud, Leroy, et al., 2009; Makris, Oscar-Berman et al., 2008; Pfefferbaum et al., 2000; Trivedi et al., 2013; Wobrock et al., 2009). Studies have also shown an association between white matter structural damage and certain components of executive functions, e.g., working memory and attention skills (Pfefferbaum et al., 2000; Trivedi et al., 2013), inhibitory control (Schulte, Müller-Oehring, Salo, Pfefferbaum, & Sullivan, 2006), emotional processing (Schulte, Müller-Oehring, Pfefferbaum, & Sullivan, 2010), and cognitive flexibility (Chanraud, Reynaud, et al., 2009).

Diffusion tensor imaging (DTI), an MRI methodology, has been extensively used for analyzing brain white matter integrity in alcohol-dependent subjects (Pfefferbaum & Sullivan, 2002). DTI assesses the directional orientation and coherence of myelin within white matter microstructure by quantifying the magnitude and orientation of water mobility on a voxel-by-voxel basis in a tissue. Fractional anisotropy (FA) and mean diffusivity (MD) are the commonly derived measures of DTI data. FA is defined as the inverse of the 3 eigenvectors that describe the potential diffusion of water in nerve bundles (Alexander, Lee, Lazar, & Field, 2007). The primary eigenvector describes water diffusivity in the direction of the fiber tract and is called the axial diffusivity (AD), which assesses the axonal function (Mac Donald, Dikranian, Bayly, Holtzman, & Brody, 2007). Diffusion of water perpendicular to axons is defined by 2 eigenvectors and reported as the radial diffusivity (RD). RD has been associated with demyelination, neuroinflammation with edema, or macrophage infiltration (Harrison et al., 2012; Kumar et al., 2011). Mean diffusivity (MD) is the average of the AD and 2 RD eigenvectors and quantifies the magnitude of diffusion (Catani, 2006; Grignon, Mainard, Delion, Hodez, & Oldrini, 2012; Le Bihan, 2003).

With the possibility of noninvasive mapping of inter-regional white matter fiber connections, we performed a DTI study in order to explore the yet largely unknown relationship between white matter characteristics in the fronto-occipital circuit and visual processing in alcohol-dependent subjects. The fronto-occipital fasciculus (FOF) is a long association fiber tract of the cerebral white matter. It is a distinct fiber bundle that courses above the body and head of the caudate nucleus, medial to the corona radiata, and lateral and ventral to the fibers radiating from the corpus callosum (Forkel et al., 2012; Schmahmann & Pandya, 2007). FOF is a true association fasciculus linking the parieto-occipital regions with the dorsolateral premotor and prefrontal areas and is thought to play a role in visual aspects of cognitive processing (Catani & Schotten, 2012; Schmahmann & Pandya, 2007).

We hypothesized that microstructural alteration in white matter fiber bundles linking frontal and occipital brain regions would be related to visual processing deficits in these subjects.

Materials and methods

Subjects

The study included 35 alcohol-dependent subjects and 30 healthy control subjects. All study participants were men, between 30 and 45 years of age and non-smokers. The alcohol-dependent subjects were recruited from an army rehabilitation center, and met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for alcohol substance dependence, and had abstained from drinking alcohol for approximately 2 weeks (median = 17 days). All participants were free of neurological and psychiatric conditions suspected to affect cognition or brain morphology. Control participants were recruited from the local community. Control participants were interviewed to confirm that they did not meet the criteria for alcohol dependence or abuse (World Health Organization criteria). Additionally, all subjects were evaluated using the Alcohol Use Disorders Identification Test (AUDIT; Reinert & Allen, 2002; see Table 1). The groups did not differ in their socioeconomic status. Imaging studies were carried out at our institute.

Table 1
Demographic data and neuropsychological test results of the study subjects.

	Alcohol dependent subjects ($n = 35$)	Healthy subjects ($n = 30$)
Age (years)	36.5 ± 5	35.2 ± 3.7
Body mass index (kg/m^2)	24.5 ± 4.1	24.6 ± 3.5
Education (years)	10.5 ± 1.9	10.3 ± 1.7
AUDIT	30.2 ± 4.6	0.2 ± 1.3[a]
Neuropsychological tests		
MMSE score	28.52 ± 1.67	29.51 ± 1.22
Koh's block design[b]	15.42 ± 7.3	1.66 ± 2.65[a]
Bender–Gestalt (BG) test[c]	12.09 ± 0.29	0.83 ± 1.83[a]
Nahor–Benson (NB) test[d]	4.314 ± 1.43	0.366 ± 0.88[a]

AUDIT, alcohol use disorders identification test.
Data are presented as mean ± SD.
[a] p-value ($\leq$0.05) for between-group comparisons performed using two-sample t-test.
[b] Range for raw dysfunction scores (0–50).
[c] Range for raw dysfunction scores (0–34).
[d] Range for raw dysfunction scores (0–8).

The inclusion criteria for alcohol-dependent patients were 1) less than 3 withdrawal periods (Duka, Townshend, Collier, & Stephens, 2003), and 2) detoxification for at least 2 weeks and abstinence as assessed by normal levels of gamma glutamyl transferase (GGT) (Table 2). The GGT test is widely used as a marker for alcohol intake. Elevated levels of GGT indicate excessive alcohol consumption. The exclusion criteria included 1) signs or symptoms of malnutrition, and 2) signs of liver dysfunction: aspartate aminotransferase/alanine aminotransferase ratio greater than 2 (Cohen & Kaplan, 1979).

All participants were examined to identify the following exclusion criteria: history of non-alcohol substance dependence, CNS trauma (such as loss of consciousness for greater than 30 min, seizures not related to alcohol withdrawal, degenerative disease), serious medical condition (such as insulin-dependent diabetes or hepatic disorder), or mood disorder. All participants were volunteers and gave written informed consent obtained according to institutional review board guidelines. The study was approved by a local ethics committee.

Table 2
Characteristics of the alcohol-dependent subjects.

Patient characteristics	Value	Laboratory norms
Alcohol consumption[a]	153.3 ± 19.2	
Duration of dependence (years)	4.43 ± 1.3	
Abstinence (weeks)	17.47 ± 4.39	
Age (years) at first drinking	23.7 ± 3.1	
Age (years) at the onset of dependence	33.2 ± 6.2	
Biological variables:		
g-Glutamyl-transferase	51.3 ± 2.1	≤53
Alanine aminotransferase (U/l)	26.4 ± 14.1	≤38
Aspartate aminotransferase (U/l)	27.3 ± 16.1	≤40
Aspartate aminotransferase/alanine aminotransferase	1.03 ± 0.27	≤2

[a] Consumption was defined as grams of pure alcohol/day during three months preceding detoxification.