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Abnormal white matter integrity in long-term abstinent alcohol dependent patients

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ABSTRACT

A number of diffusion tensor imaging (DTI) studies have reported substantial white matter (WM) abnormalities in alcohol-dependent patients. These studies were usually performed in recovering alcohol-dependent patients who had been abstinent for days to several weeks. The current study was designed to examine WM microstructure and decision-making in a sample of long-term abstinent alcohol-dependent patients. The study included 12 subjects with alcohol dependence who had been abstinent for at least 6 months before testing and scanning and 13 healthy control subjects. The Iowa Gambling Task (IGT) was used to measure decision-making. We found that the long-term abstinent alcohol-dependent group had significantly higher radial and axial diffusivity (RD and AD, respectively) values in frontal, temporal and parietal WM than was found in the healthy control group despite showing no difference in fractional anisotropy (FA) values in comparison to controls. In conclusion, we found widespread WM changes in long-term abstinent alcohol-dependent patients compared with healthy controls. Our findings suggested that AD and RD should be included in analyses of DTI data in addition to the more commonly studied FA. In the current study, FA values of the detoxified alcoholics had recovered and were comparable to those of the controls, whereas significant changes in AD and RD were still observed in some clusters in the frontal, parietal and temporal lobes of detoxified alcoholics even after 27.8 months.

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1. Introduction

A number of diffusion tensor imaging (DTI) studies have reported substantial white matter (WM) abnormalities in alcohol-dependent patients (Pfefferbaum and Sullivan, 2005; Harris et al., 2008; Yeh et al., 2009; Sorg et al., 2012; Zorlu et al., 2013). These studies were usually performed in recovering alcohol-dependent patients who had been abstinent for days to several weeks. However, structural brain damage seems to be partially reversible during abstinence (Gazdzinski et al., 2005; Agartz et al., 2003). To our knowledge, only one study examined whole brain WM microstructure in long-term abstinent alcohol-dependent patients. Monnig et al. (2013a) found that alcohol-dependent patients who had been abstinent for at least 1 year had lower fractional anisotropy (FA) values in bilateral parietal regions relative to healthy controls. Monnig et al. (2013a) recruited a long-term abstinent alcohol-dependent patient sample with comorbid mood, anxiety and substance use disorder. However, the role of comorbidity in WM deficits was not evaluated. WM abnormalities in mood, anxiety and substance use disorders have been reported in a number of studies (Moeller et al., 2007; Bora et al., 2012; Cole et al., 2012; Zhang et al., 2013). The advantage of studying subjects abusing various substances in Turkey is that there are groups of subjects with single substance abuse, particularly alcohol. Hence, we recruited long-term abstinent alcohol-dependent patients who abused only alcohol to date and who did not have any axis I psychopathology, to rule out the effects of both multi-drug use and comorbid psychopathology.

Decision-making involves the outcome of cognitive processes leading to a choice between alternative courses of action. Poor decision-making has been described as “deciding against one's best interests and inability to learn from previous mistakes, with repeated decisions leading to negative consequences” (Bechara and Damasio, 2005). A commonly used measure of decision-making is the Iowa Gambling Task (IGT) (Bechara et al., 1994). The IGT simulates real-life decision-making with uncertainty concerning premises and outcome as well as reward and punishment. The IGT was specifically developed to measure decision-making in patients with lesions of the ventromedial prefrontal cortex. Such patients often take part in risky

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behaviors that are immediately gratifying while ignoring negative future outcomes. Similarly, alcohol abusers persist in behaviors that have short-term benefits despite long-term major negative consequences. Studies have shown that currently active or recently detoxified alcohol-dependent patients exhibit impaired decision-making on the IGT (Mazas et al., 2000; Bechara and Damasio, 2002; Lawrence et al., 2009a). Fein et al. (2004) showed that, after long-term abstinence, alcohol-dependent patients still had poorer decision-making performance than controls.

DTI is a magnetic resonance imaging (MRI) technique that is suitable to quantitatively investigate WM axonal integrity in vivo. Fractional anisotropy (FA) is a measure of the degree to which water diffusion is constrained in the brain and is widely used as a general index of axonal integrity (Kubicki et al., 2002). Damage to WM or demyelination along neuronal axons results in more isotropic water movement and is manifested as relatively low FA values. A problem with DTI is the interpretation of changes in FA. Therefore, the component measures from which FA is derived, the so-called first ($\lambda1$) and second ($(\lambda2+\lambda3)/2$)) eigenvalues measuring axial and radial diffusion (AD and RD, respectively) to the primary axis of the axon, can provide additional insights regarding the nature of WM deficits. An increase in RD values is thought to signify increased space between fibers suggesting demyelination or dysmyelination (Harsan et al., 2006), whereas a decrease in AD values suggests axonal injury (Lazar et al., 2003).

In a previous study, we examined the relationship between WM integrity and decision-making in recently detoxified alcohol-dependent patients (Zorlu et al., 2013). To our knowledge, this was the first study to explore the relationship between whole brain WM integrity and decision-making in alcohol-dependent patients. We found that WM integrity was significantly correlated with impaired decision-making for all subjects (alcohol-dependent patients and controls). The current study was designed to examine WM microstructure in a sample of long-term abstinent alcohol-dependent patients who have been abstinent for a minimum of at least 6 months. We also tested whether there was any relationship between WM integrity and decision-making. In the present study, we applied Tract Based Spatial Statistics (TBSS) to study WM changes in long-term abstinent alcohol-dependent patients compared with healthy controls. The skeleton-based approach of TBSS may overcome potential problems with the registration and alignment of WM between subjects to facilitate cross-subject statistical analysis (Smith et al., 2006).

2. Methods

The study included 12 patients with alcohol dependence and 13 healthy control subjects. The alcohol-dependent patients met DSM-IV (American Psychiatric Association, 1994) criteria and had been abstinent for at least 6 months before testing and scanning. The alcohol-dependent patients had been in sustained remission for an average of 27.8 months. All participants were male and right-handed. The groups were matched for age and years of education. Controls were recruited by means of local advertisements and snowball communication among adult people from the community.

Exclusion criteria for the alcohol-dependent group were as follows: (1) any lifetime substance use other than alcohol (except nicotine); (2) current or past history of any DSM-IV Axis I psychiatric disorders except not current but past history of alcohol-induced mood disorder with depressive features; (3) current or past history of any significant neurological disorders; (4) history of loss of consciousness more than 30 min; (5) any severe hepatic, endocrine, renal disease; and (6) any contraindications for MRI scanning (e.g., metal implants, pacemakers). Healthy controls met the same criteria as patients, except for the history of alcohol dependence. All participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997) to exclude participants with past or current comorbid Axis I diagnoses and to confirm the diagnosis of alcohol dependence in the clinical group. The long-term abstinent alcohol-dependent patients were interviewed to determine the age they started drinking, the duration of alcohol dependence and the time since the last drink. All participants were active smokers.

All of the participants were medication-free, and none of them had any comorbid conditions at the time of the study. We did not specifically test the participants for alcohol use, Hep-C and other medical conditions. Our data were based on participants' self-report, clinical examination and available medical records. All participants gave written informed consent to participate in the study. The study was approved by local research and ethics committees.

2.1. Decision-making

The IGT was used to measure decision-making (Bechara et al., 1994). All participants completed the IGT within 3 days of the MRI examination.

Briefly, participants sat in front of four decks (A, B, C and D) of cards equal in appearance and size, and the goal was to win as much money as possible. The participants were told that the game required a long series of card selections, one card at a time, from any of the four decks, until they were told to stop. Each deck consisted of 40 cards, but participants did not know that the amount and probability of punishment varied across decks. Two of the four decks gave high rewards, but also high losses, and resulted in a net loss in the long run (disadvantageous decks A and B). The two other decks resulted in low rewards, but also rendered lower losses, and resulted in a net gain in the long run (advantageous decks C and D). The task ended when the participant had selected a total of 100 cards. Scoring for the IGT's 100 choices were divided into five blocks of 20 choices each. A net score was calculated within each block by subtracting the number of cards selected from the two disadvantageous decks (A+B) from the number selected from the two advantageous decks (C+D). Higher scores reflected more advantageous decision-making performance on the task. In line with the literature, raw scores for the IGT variables were used in all analyses.

2.2. Imaging protocol

MRI was performed using a 1.5 T MR system (GE Signa HDxt, General Electric Medical Systems, Milwaukee, WI, USA). Diffusion imaging data were acquired in 32 diffusion gradient directions (b-value$=1000$ s/mm^2) plus one $b=0$ reference images using a sequence optimized to collect diffusion weighted images (repetition time$=6500$ ms, echo time$=90$ ms, voxel size$=1.1\times1.1\times4$ mm^3).

2.3. DTI data analysis

DTI data were analyzed using FMRIB's (Oxford Centre for Functional MRI of the Brain) Diffusion Toolbox, which is part of FSL (FMRIB Software Library) (Smith et al., 2004). Motion and eddy current artifacts were corrected using FSL EDDY_ CORRECT. A brain mask of the non-diffusion-weighted image was created using FSL's Brain Extraction Tool (Smith, 2002). The diffusion tensor was then calculated with FSL DTIFIT for whole brain volumes, and the resulting FA maps together with the AD ($\lambda1$) and RD ($(\lambda2+\lambda3)/2$) maps, were used in subsequent TBSS analysis.

Voxel-wise statistical analysis of the data was performed using TBSS (Smith et al., 2006). All individual FA maps were nonlinearly registered to the template and then affine-transformed into standard Montreal Neurological Institute (MNI) space. A mean skeleton map of WM tracts was generated based on the mean FA image of all participants. Each participant's aligned FA image was projected onto the FA skeleton, resulting in a skeletonized FA map for each individual. TBSS analyses of RD and AD were conducted in the same manner and aligned to the FA skeleton.

2.4. Statistical analyses

To identify FA, AD and RD differences between long-term abstinent alcohol-dependent patients and controls, the skeletonized FA data were fed into the voxel-wise statistical analysis which was based on a non-parametric approach using permutation test theory (randomize tool in FSL) (Nichols and Holmes, 2002). The Threshold-Free Cluster Enhancement (TFCE) method was used to define the clusters (Smith and Nichols, 2009). Results were considered significant for $p<0.05$ and clusters greater than 200 voxels were reported. The most probable anatomical localization of each significant cluster was determined using publicly accessible white matter atlases (http://www.dtiatlas.org).

For clusters where significantly higher RD values in the long-term abstinent alcohol- dependent group were observed, the mean AD values of each cluster mask for each subject were extracted. The function “fslmeants” from FSL was used to extract means of AD values from these masks. Between-group differences for AD values in these regions of interest were analyzed using the Mann–Whitney U-test. The same procedure was conducted for RD values in clusters where significantly higher AD values in the long-term abstinent alcohol-dependent patients group were observed.

Demographic measures were compared between groups using Mann–Whitney U-test. We conducted a mixed-design analysis of variance (ANOVA) (two-group: long-term abstinent alcohol-dependent patients vs. controls×5 IGT blocks) to examine possible differences between groups on their performance on the IGT.

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