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Research paper

White matter microstructural changes are associated with alcohol use in patients with panic disorder

Borah Kim [a,1], Won.-Suk. Shin [b,1], Min.-Kyoung. Kim [a], Sang.-Hyuk. Lee [a,*]

[a] Department of Psychiatry, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea
[b] CHA University, School of Medicine, Pocheon, Republic of Korea

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ABSTRACT

Background: A close relationship between panic disorder (PD) and alcohol use disorder (AUD) has been suggested. We aimed to investigate alterations in white matter (WM) volume or integrity in patients with PD comorbid with AUD.

Methods: Forty-nine patients with PD, free of comorbid AUD (PD−AUD), and 20 patients with PD comorbid with AUD (PD+AUD) were investigated. All subjects were assessed using the Panic Disorder Severity Scale, Anxiety Sensitivity Inventory-Revised (ASI-R), Beck Depression Inventory, and CAGE questionnaire. Voxel-based morphometry and tract-based spatial statistics were used for imaging analysis.

Results: Increased fractional anisotropy (FA), as well as decreased mean diffusivity and radial diffusivity were observed in multiple WM tracts, including the body and splenium of the corpus callosum and the retrolenticular part of the internal capsule, in the PD+AUD group compared to the PD–AUD group. CAGE scores in the PD+AUD group and ASI-R scores in the PD−AUD group were significantly correlated with FA values for the corpus callosum. No WM volume differences were found.

Limitations: The present study should be considered preliminary due to relatively small sample size.

Conclusions: Our findings revealed microstructural changes in multiple WM tracts, including the corpus callosum and internal capsule, suggesting they could be significant neural correlates of AUD in patients with PD.

1. Introduction

A relationship between panic disorder (PD) and alcohol use disorder (AUD, alcohol abuse and dependence) has been suggested, but it is not clearly understood. A previous study reported odds ratios of 12-month associations between PD and AUD ranging from 2.1 to 2.7 (Hasin et al., 2007). Moreover, patients with AUD have a higher prevalence of PD (20−30%) compared to the general population (2−5%) (George et al., 1988). In addition, AUDs can increase the severity and persistence of comorbid anxiety disorders and result in poor treatment response (Smith and Randall, 2012).

One explanation for the co-occurrence of PD and AUD is the role of AUD as an attempt to self-medicate for obtunding anxiety (Otto et al., 1992). Although alcohol acts acutely to reduce symptoms of PD, it has anxiogenic effects over the long term (Kushner et al., 1996). In contrast, AUD can precede panic symptoms. Since alcohol withdrawal is associated with increased central nervous system excitability (Becker, 1998), alcohol sensitized limbic areas are implicated in the pathophysiology of PD. Thus, panic attacks occur at first during withdrawal, but eventually also during periods of sobriety (Cowley, 1992).

A few studies have reported the relationship between brain structural characteristics and comorbid AUD in other mental illnesses. Compared to patients with bipolar disorder that do not abuse alcohol, patients with bipolar disorder and alcohol abuse show significantly altered white matter (WM) integrity in the left uncinate fasciculus (Versace et al., 2008). The greatest severity of shape abnormalities in the hippocampus, thalamus, striatum, and globus pallidus have been demonstrated in patients with

Abbreviations: AD, axial diffusivity; ASI-R, anxiety sensitivity inventory-revised; AUD, alcohol use disorder; BDI, beck depression inventory; FA, fractional anisotropy; GM, gray matter; ICV, intracranial volumes; MD, mean diffusivity; PD, panic disorder; PDSS, panic disorder severity scale; PD−AUD, panic disorder free of comorbid AUD; PD+AUD, panic disorder comorbid with AUD; RD, radial diffusivity; WM, white matter

* Correspondence to: Department of Psychiatry, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang, Seongnam 463-712, Republic of Korea.
E-mail address: leesanghyuk@yahoo.com (S.-H. Lee).

[1] These authors contributed equally to this work.

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schizophrenia with AUD as compared to those without AUD or healthy controls (Smith et al., 2011). In patients with post-traumatic stress disorder, abnormal WM integrity within the frontal regions have been found in a subgroup with severe AUD (Maksimovskiy et al., 2014). Thus, it could be suggested that comorbid AUD in psychiatric disorders is associated with brain structural characteristics.

According to brain structural imaging studies of PD, significant WM volume reduction of various brain regions, including the fronto-limbic, thalamo-cortical, and cerebellar pathways (Konishi et al., 2014), as well as the alteration of multiple WM tracts, including the corpus callosum, cingulum, and internal capsule (Kim et al., 2014; Lai and Wu, 2013), have been reported. Other studies have shown that increased fractional anisotropy (FA) in patients with PD and comorbid conditions, such as depression and suicidality, could be associated with the comorbid conditions in patients with PD (Kim et al., 2013; Kim et al., 2015). However, there are no studies of brain WM structural characteristics associated with comorbid AUD in patients with PD.

We hypothesized that the patients with PD and comorbid AUD would show WM microstructural changes (increased FA) in the widespread regions, including the fronto-limbic pathways, compared to the patients with PD without comorbid AUD. Comparisons of WM volume and integrity between patients with PD and AUD and those without AUD were also performed. In addition, we aimed to identify the relationship between clinical symptoms and structural characteristics of the brain regions showing a group difference.

2. Materials and methods

2.1. Subjects and clinical assessment

Forty-nine patients with, PD free of comorbid AUD (PD − AUD), and 20 patients with PD, comorbid with AUD (PD+AUD), were recruited from the outpatient units of the Department of Psychiatry, CHA Bundang Medical Center, CHA University. Subjects were 17-55-year-old patients who primarily met the DSM-IV criteria for PD with or without agoraphobia, as diagnosed by experienced psychiatrists (S.H. Lee and B. Kim) using the structured clinical interview to assess DSM-IV Axis I disorders (SCID-I) (First et al., 1996). We defined the presence of AUD via a diagnostic interview by experienced psychiatrists (S.H. Lee and B. Kim) using AUD criteria in the SCID-I. In the PD+AUD group, seven patients were diagnosed with comorbid alcohol dependence, and 13 patients were diagnosed with comorbid alcohol abuse. The diagnosis of primary PD preceded (duration of illness: 9.10 ± 4.69 months) comorbid AUD (duration of illness: 6.55 ± 4.49 months) among all subjects in the PD+AUD group. There was no prior history of treatment for AUD among our patients.

All subjects were of Korean descent and right-handed. Exclusion criteria for all subjects included any current diagnosis or lifetime history of schizophrenia, substance use disorder other than AUD, substance-induced anxiety disorder, mental retardation, serious medical or neurological disorders, or contraindications to magnetic resonance imaging (MRI) including metal implants or pregnancy. At the time of the scan, the majority of patients were taking a selective serotonin re-uptake inhibitor (SSRI), which included paroxetine, escitalopram, or duloxetine (n=63), and benzodiazepines as anxiolytics, which included alprazolam or clonazepam (n=67), even though durations of medication were relatively short (mean ± SD, 6.32 ± 7.09 days).

Subjects were assessed for clinical severity of panic symptoms and AUD. Panic and depressive symptoms were assessed in each patient using the Panic Disorder Severity Scale (PDSS) (Lim et al., 2007b; Shear et al., 1997), the Anxiety Sensitivity Inventory-Revised (ASI-R) (Lim et al., 2007a; Taylor and Cox, 1998), and the Beck Depression Inventory (BDI) (Beck et al., 1961). The CAGE questionnaire was also administered and subsequently assessed (Mayfield et al., 1974) for each patient to assess alcoholism. CAGE is the acronym for the questions: Have you ever felt you should *cut down* on your drinking? Have people *annoyed* you by criticizing your drinking? Have you ever felt bad or *guilty* about your drinking? Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*eye-opener*)? The score is the number of questions answered with 'yes'. The scores on all four scales were determined within 3 days before or after MRI.

All study procedures complied with CHA Bundang Medical Center Institutional Review Board regulations, the Declaration of Helsinki, and the principles of Good Clinical Practice. After a complete description of the study was given to potential subjects, written informed consent was obtained prior to enrollment.

2.2. MRI procedures

All scans were performed on the same 3 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA), which was equipped with an eight-channel phase array head coil at CHA Bundang Medical Center, CHA University. Parameters for three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) images were as follows: repetition time (TR) 16 ms, echo time (TE) 4.3 ms, flip angle 10°, slice thickness 1 mm, field of view (FOV) 25.6 cm, 256×256 matrix, isotropic voxel size $1 \times 1 \times 1$ mm^3. Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: TR 17,000 ms, TE 108 ms, FOV 24 cm, 144×144 matrix, slice thickness 1.7 mm, voxel size $1.67 \times 1.67 \times 1.7$ mm^3. A double echo option was used to reduce eddy-current-related distortions. To reduce the impact of EPI spatial distortions, an 8-channel coil and array spatial sensitivity encoding technique (ASSET, GE Healthcare) with a sensitivity encoding (SENSE) speed-up factor of 2 was used. Seventy axial slices parallel to the anterior commissure–posterior commissure (AC–PC) line covering the whole brain were acquired in 51 directions with b=900 s/mm^2. Eight baseline scans with b=0 s/mm^2 were also acquired. Diffusion-tensor images (DTIs) were estimated from the diffusion-weighted images using the least-squares method.

2.3. Data processing and analyses

2.3.1. Voxel-based morphometry (VBM) analysis of WM volumes

Image processing for WM volume analysis was performed on Statistical Parametric Mapping (SPM) 5 software (Wellcome Trust Center for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) using the VBM 5 toolbox (http://vbm.neuro.uni-jena.de/vbm) run on MATLAB 7.9 (MathWorks, Natick, MA, USA). Two-dimensional DICOM files of each brain were organized into volumetric three-dimensional files as NIFTI-1 (http://nifti.nimh.nih.gov) format using the MRIcron software package (http://www.sph.sc.edu/comd/rorden/mricron). In VBM preprocessing, the converted files of T1 images were segmented and normalized using the unified model (Cuadra et al., 2005). Then, voxel values were modulated by the Jacobian determinants derived from the spatial normalization, which allowed brain structures that had their volumes decreased after spatial normalization to have their total counts decreased by an amount proportional to the degree of discounted volume. The final voxel resolution after normalization was 1 mm^3. Finally, modulated WM partitions were smoothed with a 12-mm full width at half-maximum Gaussian kernel, and used for statistical analysis. Additionally, total intracranial volumes (ICV) were computed using the native-space tissue maps of each