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Volume of hippocampal subfields in patients with alcohol dependence

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ABSTRACT

Alcohol-induced hippocampal atrophy has been well documented in many studies and is known to affect various subfields. Given the functional heterogeneity of these subfields, we investigated the precise effects of alcohol-induced damage in these areas. Twenty-six male patients with alcohol dependence (alcohol group) and twenty-six age-matched male healthy social drinkers were recruited from a mental health hospital and the community respectively, with the aim of comparing the hippocampal subfields between groups. Each participant underwent a 3 T MRI scan. Hippocampal subfield volumes were estimated using an automated procedure and drinking history recorded using Lifetime Drinking History, Alcohol Use Disorder Identification Test, and the Brief Michigan Alcoholism Screening Test. The alcohol group showed a lower total hippocampus volume, specifically in the left presubiculum, fimbria, and bilateral subiculum. Regression analysis assessing the influence of age and group showed that group was a more significant factor than age in most subfields. Our findings suggest that alcohol dependence alters hippocampal subfield volumes. Further longitudinal studies on the interaction of structural and neurocognitive changes would improve our understanding of brain structural changes resulting from long-term alcohol consumption.

1. Introduction

It is well known that chronic alcohol consumption can affect most organs, especially the brain. Postmortem studies showed that chronic alcohol consumption results in a reduction of white matter volume with neuronal loss in the frontal lobe (Kril et al., 1997) and a reduction in hippocampal volume without neuronal loss in the cornus ammonis (CA)1 and subiculum regions (Harding et al., 1997). Brain imaging studies on alcohol dependent subjects reported cortical thinning, cortical volume reduction, ventricular and cerebral sulcus enlargements (Bühler and Mann, 2011; Sullivan and Pfefferbaum, 2005). Decrease in gray matter in dorsolateral frontal cortex and widespread white matter volume decrease were shown to be correlated with neuropsychological performance (Chanraud et al., 2007). Durazzo et al. (2011) showed cortical volume reduction in multiple regions of brain reward system like superior frontal gyrus, insula, amygdala and hippocampus in relapsers when compared to alcohol abstainers and controls. Other studies also showed recovery of cortical volume associated with alcohol abstinence (Sameti et al., 2011; Wang et al., 2016).

The hippocampus is a subcortical structure that is vulnerable to the toxic effects of hypoxia, ischemia, inflammation, and neurodegeneration (Geddes et al., 2003; Meyer et al., 2001). Most of the volumetric studies on alcohol-dependent patients reported a volume reduction of the hippocampus with varying clinical diagnosis (Agartz et al., 1999; Bleich et al., 2003; Laakso et al., 2000). The hippocampus is a brain structure associated with many cognitive functions, such as visuospatial memory (Epstein and Kanwisher, 1998), visuospatial orientation (Iaria et al., 2003), crossmodal sensory integration (Laroche et al., 2000), information consolidation, and attention (Wall and Messier, 2001). Among these functions, visuospatial learning and memory are most consistently found as cognitive sequelae in patients with alcohol dependence (Beatty et al., 1996; Bowden and McCarter, 1993). Hippocampal plasticity has been studied extensively in its potential in adult neurogenesis, in particular, regions like dentate gyrus of hippocampus, the subventricular zone of lateral ventricle and the rostral migratory stream to the olfactory bulb (Ming and Song, 2011). Cognitive deficits resulting from chronic alcohol consumption were shown to improve after short-term (Gazdzinski et al., 2008; Mann et al., 1999; Sullivan et al., 2000) and long-term (Bartels et al., 2007)

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abstinence whilst other studies showed residual deficits or no cognitive improvement (Brandt et al., 1983; Schandler et al., 1996; Yohman et al., 1985) suggestive of brain plasticity.

The hippocampus is not a homogeneous structure. It consists of several subfields, such as the CA1–4, dentate gyrus, fimbria, hippocampal fissure, presubiculum, and subiculum, each may be involved in different pathways and thus governs different aspects of the cognitive process. Studying the subfields will enable us to gain better insights into the pathways that are involved in hippocampal plasticity resulting from chronic alcohol use and abstinence. However, to date, human studies which examine the hippocampal subfields resulting from chronic alcohol consumption are scarce. Sullivan et al. (1995) observed a volume deficit in the anterior but not posterior portion of the hippocampus in chronic alcoholics and a greater volume loss was associated with age. However, the anterior hippocampus consists of multiple subfields, it is unknown which subfields were affected. Recently, Kühn et al. (2014) showed that in all the subfields examined of alcohol dependent subjects, only the bilateral hippocampal CA2+3 gray matter volume deficit was normalized after 2 weeks of alcohol abstinence.

This study aims to further examine changes in the hippocampal subfields of alcohol-dependent patients who are abstinent from alcohol. All subjects of this study are male patients with alcohol dependence (alcohol group); they are age-matched to healthy social drinkers (control group). We aim to compare the subfield specialization with age, years of regular alcohol consumption and time of abstinence prior to brain scanning between the two groups. We hypothesize that the difference in hippocampal subfields is associated with the period of abstinence.

2. Methods

2.1. Participants

Alcohol and control groups each consisted of twenty-six male subjects. All patients were recruited from an inpatient mental health hospital specializing in alcohol dependence. Group-wise age matched healthy social drinkers were recruited through advertisements in the community. The age range of all participants was 40–63 years old. They were all interviewed by a psychiatrist using the Structured Clinical Interview of DMS-IV (American Psychiatric Association, 1994). Diagnosis of alcohol dependence was according to the DSM-IV-TR. All participants of the control group were current social drinkers who did not meet the criteria for alcohol dependence. All participants with a history of previous or current drug abuse other than alcohol, nicotine, and caffeine; previous history of head trauma or neurological disease, including Wernicke's encephalopathy and Korsakoff's syndrome; and major psychiatric disorders such as schizophrenia or bipolar disorder were excluded. Furthermore, participants who had structural abnormalities in the brain shown in MR imaging, for example, space occupying lesion or significant old infarction were excluded. The Korean version of the Alcohol Use Disorder Identification Test (AUDIT-K), the Brief Michigan Alcoholism Screening Test (MAST), and the Lifetime Drinking History (LDH) were applied to all participants. Demographic and drinking data of all subjects are provided in Table 1. The study protocol was approved by the Institutional Review Board of Chungbuk National University, Cheongju, Republic of Korea.

2.2. MRI acquisition

Structural images were collected on a 3 T Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) located at the Ochang Campus of the Korea Basic Science Institute in Cheongju, Republic of Korea. All participants were scanned with the same 32-channel head coil at the same pulse sequence. A volumetric magnetization prepared a rapid gradient echo (MPRAGE) and the parameters were referenced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (TR=6.8 ms, TE=3.1 ms, field of view=256 mm, flip angle=9°, voxel size=1×1×1.2 mm, 170 slices without gaps).

2.3. Image analysis

We processed T1-weighted sagittal images with the automated FreeSurfer software package (version 5.3.0, available at http://surfer.nmr.mgh.harvard.edu/). Briefly, the processing removes non-brain tissue by using a hybrid watershed algorithm. After that, the method involves an automated Talairach transformation as well as segmentation and processing of the subcortical white matter and deep gray matter. Hippocampal formation is segmented with the FreeSurfer's standard segmentation procedure, using a probabilistic brain atlas (Fischl et al., 2002). Automated hippocampal subfield segmentation procedure includes Bayesian inference and a probabilistic atlas of the hippocampal formation, which is based on manual delineations of subfields in T1-weighted images from a number of different subjects. Seven subfield volumes are calculated and automated volume estimates of these subfields are shown to correlate with manual volume estimates (Van Leemput et al., 2009). This automated volume estimate was proved to be reliable in subjects with brain atrophy such as mild cognitive impairment or Alzheimer's disease (Khan et al., 2015; Mueller and Weiner, 2009). Fig. 1 shows the example of hippocampal subfield segmentation.

When comparing hippocampal subfields between the groups, we used corrected volumes for estimated total intracranial volume (eTIV) derived from atlas scaling factor, using the following formulation (Buckner et al., 2004):

$$\text{Volume}_{\text{adj}} = \text{Volume}_{\text{nat}} - b\,(\text{eTIV}_{\text{nat}} - \text{mean eTIV}_{\text{nat}})$$

where $\text{Volume}_{\text{adj}}$ is the corrected hippocampal volume, $\text{Volume}_{\text{nat}}$ is the hippocampal volume in native space, and b is the slope of the volume regression on eTIV. The mean eTIV is the sample mean of the eTIV. All total hippocampal volume reported in the results section are the $\text{Volume}_{\text{adj}}$.

This covariance approach (Mathalon et al., 1993) can provide advantage over other methods such as proportion method (Sanfilipo et al., 2004) and especially in the aging population (Buckner et al., 2004).

2.4. Statistical analysis

Analyses were carried out using the CRAN R statistical package version 3.1.3 (http://cran.r-project.org).

Demographic variables and subfield volumes between the two groups were analyzed using a two-sample *t*-test to compare subfield volumes between groups. Bonferroni correction was used to control for multiple testing.

Pearson correlation was used to correlate age and total hippocampal volumes, and the partial correlation test was used for age-adjusted values. Partial correlation of total hippocampal volume with numeric variables, such as weight, year of education, AUDIT-K, brief MAST, and LDH, were assessed with Pearson's *r*, and ordinal variables were assessed with Kendall's *tau*.

Scatter plots were examined, and tests for linear relationships between age, year of education, weight, AUDIT-K, MAST, LDH, and hippocampal volumes were conducted using multivariable hierarchical linear regression models. Age and weight were treated as nuisance factors that consistently affect hippocampal volumes (see Section 2.3 on formula for eTIV correction). In the preliminary test, we conducted multiple regression analyses with age, weight, and group as covariates on each hippocampal volume subfields. Although there was a significant group difference, weight was shown to be insignificant in all models tested, only age and group were significant. Therefore, the following regression model was used for the final analyses of hippo-