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Cerebral vascular burden on hippocampal subfields in first-onset drug-naïve subjects with late-onset depression

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ABSTRACT

Background: Although there is substantial evidence of associations between frontal-striatal circuits and cerebral vascular burden in late-onset depression (LOD), relationships between vascular burden and hippocampal subfields are not clear. The purpose of this study was to investigate relationships between cerebral vascular burden and hippocampal subfield volume in LOD patients.

Methods: Fifty subjects with LOD and 50 group-matched healthy control subjects underwent magnetic resonance imaging scanning. Hippocampal subfields volumes were measured and compared between the groups. In addition, association patterns between white matter hyperintensity (WMH) volumes, clinical measures and hippocampal subfield volumes were investigated in the LOD group.

Results: Subjects with LOD exhibited significant hippocampal volume reductions in the total hippocampus, cornu ammonis (CA) 1 and 3 and dentate gyrus (DG) areas compared with healthy subjects. Total WMH volume was negatively correlated with left total hippocampal volume and CA1 in the LOD group. In addition, depression severity was negatively associated with left and right CA3 volumes in the LOD group.

Limitation: Our findings of distinctive relationships between WMH and hippocampal subfields demonstrate a simple correlation, but do not prove causation

Conclusion: This study is the first to elaborate distinctive association patterns between hippocampal subfield volumes and cerebral vascular burden in LOD. These structural changes in the hippocampal CA1, CA3 and DG areas might be at the core of the underlying neurobiological mechanisms of hippocampal dysfunction in LOD. However, longitudinal studies will be needed to identify the mechanisms of these structural changes.

1. Introduction

Late life depression can be a major health problem and significant cause of disability because of serious negative consequences, such as increased risk of morbidity and mortality (Blazer, 2003; Fiske et al., 2009). Compared to late-life depression with earlier onset, late-onset depression (LOD) where the first episode occurs later in life is more likely to have medical comorbidities (Fiske et al., 2009; Krishnan et al., 2002), significant cognitive impairment (Koenig et al., 2014), and increased risk for dementia (Alexopoulos, 2005; Koenig et al., 2014). These features of LOD might be related to vascular risk factors (e.g., cardiovascular disease, stroke, and diabetes). The vascular depression hypothesis proposed that cerebro-vascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes (Alexopoulos et al., 1997). Vascular disease appears to contribute to LOD by affecting the frontal and subcortical regions involved in mood regulation (Alexander et al., 1986). Several previous studies have found associations between functional and structural changes of the frontal-subcortical circuits and cerebral vascular burden in subjects with LOD (Aizenstein et al., 2011; Lim et al., 2012b).

In addition to the frontal-subcortical circuit, the hippocampus plays an important role in understanding the pathophysiology of LOD (Butters et al., 2008). Elevation of glucocorticoids in response to stress might lead to inhibition of neurogenesis and neurotoxic effects in the brain centered in the hippocampus, which contains considerable quantities of receptors for glucocorticoids (Byers and Yaffe, 2011).

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Such damage, in turn, promotes progressive elevation of adrenal steroids and dysregulation of the hypothalamopituitary–adrenal (HPA) axis (Byers and Yaffe, 2011). Several previous studies have reported smaller hippocampal volumes in LOD, with consistent results (Sexton et al., 2013). However, there is a paucity of research about hippocampal subfield volumes (cornu ammonis (CA) 1, 2, 3 and 4, dentate gyrus (DG), and subiculum (SUB)) changes in major depressive disorder (MDD)(Huang et al., 2013; Treadway et al., 2015). A previous study in younger adults with MDD found that the number of prior depression episodes was associated with both lower reported stress levels and reduced volume in the DG (Treadway et al., 2015). Another study described lower DG volume in drug-naive MDD participants compared to controls or medicated MDD participants, as well as lower CA1–3 volume in the hippocampal body subregion in drug-naïve subjects compared to controls (Huang et al., 2013). In addition, several prior works showed that CA1 was particularly sensitive to vascular damage such as hypoxia and ischemia in the elderly (Shing et al., 2011; Zola-Morgan et al., 1986). However, studies have yet to explore the distinctive association patterns between cerebral vascular burden and hippocampal structure in LOD, despite the close link between the hippocampus and memory and emotion processing (Malykhin and Coupland, 2015). Moreover, as hippocampus is not a homogeneous but functionally subdivided structure, investigation of hippocampal subfields structural changes might help to address more subtle neurobiological mechanisms underpinning the cognitive and emotional impairment associated with LOD. Indeed, several previous studies showed that hippocampal subfields were not uniformly affected by the various psychiatric diseases (Lim et al., 2013; Treadway et al., 2015).

We previously reported hippocampal subfield volume differences between normal controls and LOD patients using an automatic segmentation algorithm provided by FreeSurfer software (Lim et al., 2012a). We showed that subjects with LOD exhibited significant hippocampal volume reductions in the total hippocampus, SUB, and CA 2–3 areas compared with healthy subjects (Lim et al., 2012a). However, the FreeSurfer segmentation algorithm had some limitations (Wisse et al., 2014). First, low resolution (1 mm^3) T1-weighted MRI images were used, and so white matter bands between the DG and the CA were not visualized. Second, the boundaries of the parcellation scheme used for FreeSurfer segmentation were mismatched with known anatomical boundaries. Finally, the FreeSurfer segmentation method was not validated against manual segmentation on lower resolution MR images.

The purpose of this study was to investigate relationships between cerebral vascular burden and hippocampal subfield volume. We recruited drug-naïve LOD patients to exclude a medication effect, because previous studies have shown that antidepressants may influence hippocampal subfield volumes (Boldrini et al., 2013; Huang et al., 2013). We hypothesized that the hippocampal subfields of CA1, CA3 and DG might be smaller and show distinctive correlation patterns with cerebral vascular burden in subjects with LOD compared with healthy controls.

2. Methods

2.1. Subjects

In this study, 50 patients with a lifetime diagnosis of MDD were recruited through the outpatient psychogeriatric clinic of St. Vincent Hospital located at Suwon, South Korea, from October 2010 to October 2014. The inclusion criteria of the patient group were as follows: (1) aged ≥60 years; (2) DSM-IV TR diagnosis of a MDD established with the Mini-International Neuropsychiatric Interview (MINI)(Sheehan et al., 1998); (3) first episode of major depression after the age of 60 years; (4) evidence of subcortical ischemic changes corresponding to a score ≥2 on the Fazeka's scale (Fazekas et al., 1993); (5) a total score of ≥10 on the 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) (Hamilton, 1967); (6) a Korean version of the Mini-Mental State Examination (MMSE) score of ≥26 (Park and Kwon, 1990); and (7) a global Clinical Dementia Rating score of 0 (Morris, 1993). The exclusion criteria for the patient group were as follows: (1) a presumptive diagnosis of dementia and other neurological or medical conditions that diminish cognitive function; (2) a history of other psychiatric disorders; and (3) use of any psychotropic medications. Cognitive functions of all the subjects were assessed with the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K), including Verbal Fluency (VF), the 15-item Boston Naming Test (BNT), MMSE, Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP), and Constructional Recall (CR) (Lee et al., 2002). All clinical measurements were carried out on the day of MRI scanning.

Through advertisement in the local newspaper, 50 age, sex, education and handedness matched healthy control participants were recruited from within the community. Exclusion criteria were similar to the patient group, with the addition of excluding those with any current or past Axis I psychiatric diagnosis, as established by the MINI, more than grade 1 of white matter hyperintensity (WMH) on the Fazeka's scale and psychotropic medication use. All subjects were right-handed and nonsmokers with no history of smoking. Psychometric evaluations and clinical diagnosis were performed by two board-certified psychiatrists (HKL and UHU). The study was conducted in accordance with the ethical and safety guidelines set forth by the institutional review board of the Catholic University of Korea. Written consent was obtained from all subjects participating in the study.

2.2. MRI acquisition

All participants underwent MRI scans on a 3-Tesla whole body scanner equipped with an 8-channel phased-array head coil (Verio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE=2.5 ms; TR=1900 ms; inversion time (TI)=900 ms; flip angle (FA)=9°; FOV=250×250 mm; matrix=256×256; and voxel size=1.0×1.0×1.0 mm^3. T2-weighted MRI sequences were as follows: TE=91 ms; TR=3700 ms; flip angle (FA)=150°; FOV=220×220 mm; matrix=448×448 in plane resolution, and 3-mm slice thickness. Fluid attenuated inversion recovery (FLAIR) MRI sequences were as follows: TE=135 ms; TR=9000 ms; inversion time (TI)=2,200 ms; flip angle (FA)=90°; FOV=220×220 mm; matrix=356×231; and voxel size=1.0×1.0×1.0 mm^3.

2.3. Image analysis

2.3.1. White matter hyperintensity (WMH) burden

White matter hyperintensity volumes were calculated and normalized using an automated localization and segmentation method by Wu et al. (2006). For each subject, the calculated WMH volume using FLAIR images was normalized to overall brain volume. The automated WMH segmentation method (Wu et al., 2006) uses an iterative algorithm that involves an automated selection of “seeds” of possible WMH lesions and fuzzy connectedness that clusters voxels based on their adjacency and affinity in order to segment WMH lesions around the seeds (Udupa et al., 1997). A fully automated WMH segmentation system was implemented in C++ and ITK.

2.3.2. Hippocampal subfield volumes

To overcome the aforementioned problems of FreeSurfer software, segmentation of the hippocampal subfields was performed with free, open-source software: the Automatic Segmentation of Hippocampal Subfields (ASHS,http://www.nitrc.org/projects/ashs/), which was validated with manual segmentation in lower resolution T1 images