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Sub-regional volumes changes of the corpus callosum in the drug naive patients with late-onset depression

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ABSTRACT

Although sub-regional analysis methods of the corpus callosum (CC) have been developed, there has been no in vivo magnetic resonance imaging (MRI) study on a sub-regional volume analysis of the CC of late-onset depression (LOD). The aim of this study was to investigate the CC volume differences between LOD subjects and healthy elderly controls using a sub-regional analysis technique. Forty subjects with LOD and thirty nine group-matched healthy control subjects underwent 3T MRI scanning, and sub-regional volumes of the CC were measured and compared between the groups. The volumes of total ($F = 5.8$, $p = 0.001$), the anterior ($F = 5.2$, $p = 0.001$) and the posterior CC ($F = 5.1$, $p = 0.001$) were significantly reduced in the LOD group as compared to the control group. We measured cognitive functions in several different domains (language functions, verbal learning, visuospatial functions, delayed recall, memory consolidation, recognition memory, and executive functions) through the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease. The anterior CC volume in the LOD group showed significant positive correlation with the Verbal Fluency scores. The posterior CC volume in the LOD group was positively correlated significantly with the Word List Memory, the Word List Recall and the Constructional Praxis scores. This study is the first to elaborate the sub-regional volume differences of the CC between controls and LOD patients. These structural changes in the CC might be at the core of the underlying neurobiological mechanisms in LOD.

1. Introduction

One of the most significant current discussions in geriatric psychiatry is late life depression (LLD), which is characterized by a significant health care risk for older adults and a major cause of disability (Crocco et al., 2010).

In a subset of LLD, late-onset depression (LOD), of which the first episode occurs later in life, could be a separate entity form early-onset depression (EOD), and exhibits certain unique clinical features (Alexopoulos et al., 1988; Krishnan et al., 1995; Krishnan et al., 1997; Schweitzer et al., 2002). LOD patients are less likely to have anxiety features, psychiatric comorbidity, or a family history of depression when compared with early-onset depression subgroups. On the other hand, the LOD patients are more associated with poorer treatment outcomes, medical comorbidity, greater cognitive deficits, increased mortality and progression to dementia (Hickie and Scott, 1998; Steffens and Krishnan, 1998).

The corpus callosum (CC), the largest white matter structure in the human brain, connects the two cerebral hemispheres. The function of the CC is not yet completely understood, but it is assumed to be involved in inter-hemispheric communication and higher cognitive function, including attention, arousal, language, emotion, and memory (Bloom and Hynd, 2005). Several researchers have studied the relationship between the CC and various neuropsychiatric symptoms including

Abbreviations: 3D-MPRAGE, three-dimensional magnetization-prepared rapid gradient-echo; BNT, Boston Naming Test; CC, corpus callosum; CERAD-K, Korean version of Consortium to Establish a Registry for Alzheimer's Disease; CP, Constructional Praxis; CR, Constructional Recall; EOD, early-onset depression; HAM-D17, 17 item Hamilton Depression Rating Scale; LLD, late life depression; LOD, late-onset depression; MINI, Mini-International Neuropsychiatric Interview; MMSE, mini-mental state examination; TIV, total intracranial volume; VF, Verbal Fluency; WLM, Word List Memory; WLR, Word List Recall; WLRc, Word List Recognition.

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depression. Ryberg and colleagues analyzed correlations between the CC areas and subjective memory complaints, mini mental state examination (MMSE) score, history of depression, geriatric depression scale score, subjective gait difficulty, history of falls, walking speed, and total score on the short physical performance battery (Ryberg et al., 2007). The authors showed that MMSE was significantly correlated with the total CC area and CC isthmus volume reductions. In addition, the authors identified that the CC volume alteration was not significantly correlated with a history and severity of depression of subjects. Several studies have showed the relationship between neuropsychological functions and the CC, but there is still insufficient data generalizing and delineating the associations between neuropsychological functions and sub-regions of the CC. Jokinen and colleagues reported that anterior CC atrophy was related to the frontal-lobe-mediated executive functions and attention (Jokinen et al., 2007). Brambilla and colleagues suggested a specific role of anterior transcallosal disconnectivity in underlying positive symptoms of schizophrenia patients (Brambilla et al., 2005).

In studies of LLD, impairments in the integrity of the CC have been reported (Alexopoulos et al., 2008; Yuan et al., 2010). In addition, sub-regions of the CC topographically map various cortical areas that have been involved in LLD in a study on mapping callosal morphology in early- and late-onset elderly depression (Ballmaier et al., 2008a). In these regards, structural abnormalities of the CC might be a useful candidate for exploring the neurobiological mechanisms of LLD.

Although several studies have tried to show structural abnormalities of major depressive disorders, the results were rather inconsistent. In terms of younger depression patients, a study previously reported larger anterior and posterior CC in EOD patients as compared to controls (Wu et al., 1993). Another study showed smaller genu of the CC in EOD patients (Macmaster et al., 2013). Moreover, the previous diffusion tensor imaging studies could not determine any abnormalities of white mater integrities of the CC in LLD as compared to controls (Guo et al., 2012). However, a study by Ballmaier et al. showed the 'thickness' and 'area' changes of the mid-sagittal CC and its relationship with verbal memory in LLD. They proposed that the effect is age of onset-specific: they reported genu specific thinning in early-onset depressed patients but evidence of thinning of both the genu and splenium in LOD (Ballmaier et al., 2008a). However, they did not show volumetric changes of the sub-regions of the CC, or their relationships with various clinical measures, such as depression severity and duration of illness and various cognitive functions, e.g. visuospatial memory. Considering the characteristics of cognitive impairment of LOD, determination of the relationship between cognitive functions assessed through a full battery of test and the CC volume changes might need to understand LOD. In addition, most of the other previous studies used arbitrary rule as criteria for defining sub-regions of the CC (genu, body, isthmus and splenium), which does not reflect the real connectivity between several cortical regions and the CC. In this regard, adoption of the CC sub-regions classification based on anatomical and functional connectivity between cortical areas might be needed to explore subtle volume changes in the CC sub-regions in LOD.

The aim of this study was to compare the CC sub-region volume differences between controls and drug naïve LOD subjects, using the CC sub-region classification method proposed by Hofer and Frahm. In addition, we tried to explore the distinctive relationship between the CC sub-region volumes and various neuropsychological functions.

2. Materials and methods

2.1. Subjects

Seventy seven subjects took part in this study (40 with LOD and 39 healthy elderly controls). They were recruited from the Catholic Geriatric Brain MRI Database which was built through the outpatient psycho-geriatric clinic of Seoul St. Mary's Hospital located in Seoul and St. Vincent's Hospital located in Suwon, South Korea from October 2009 to November 2012. The inclusion criteria of the patient group were as follows; (i) aged more than 60 years; (ii) DSM-IV TR diagnosis of a major depressive disorder established with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) (iii) the first depressive episode of major depression after the age of 60 years (iv) 17 item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$), with a total score higher than 10 (Hamilton, 1967) (v) Korean version of MMSE score higher than 26 (Park and Kwon, 1990) (vi) global Clinical Dementia Rating Score of 0 (Morris, 1993).

The exclusion criteria for the patient group were as follows: (i) patients with a presumptive diagnosis of dementia and other neurological or medical conditions which diminish cognitive function (e.g. hypothyroidism); (ii) a history or current diagnosis of other psychiatric disorders (e.g. schizophrenia, delusional disorder, substance abuse); (iii) unstable medical conditions (e.g. poorly controlled hypertension, angina or diabetes); and (iv) any clinically relevant abnormal electrocardiograms or laboratory findings or brain MRI findings (e.g. serious deep white matter hyper intensities, lacuna infarction or brain tumors) (v) patients taking any psychotropic medications (e.g. antidepressant, benzodiazepines and antipsychotics).

Subjects were screened with a self-report health questionnaire that reviewed demographic data and medical history. Depression duration was assessed in an interview by using life-chart methodology. Depression severity at the time of the scan was measured with $HAM\text{-}D_{17}$. Cognitive functioning of all subjects was assessed with the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K), including Verbal Fluency (VF), 15-item Boston Naming Test (BNT), Mini Mental Status Examination (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.

Thirty-seven healthy control participants were recruited within the community through advertisement within a local newspaper. Control subjects were matched to the patients on age, handedness, and level of education. Furthermore, control subjects were given the same self-report health questionnaire as the patients, enabling matching on health status. 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 and medication use. A clinical neuroradiologist (W.S.J.) examined brain MRIs of all subjects, and no gross abnormalities were reported in any participant, and showed normal white matter (Huang et al., 2007) defined by normal signal intensity on standard T1-weighted, T2-weighted, and FLAIR images. All subjects were right-handed. Psychometric evaluations and clinical diagnosis were performed by 2 board-certified psychiatrists (H.K.L. and C.U.L.).

The study was conducted in accordance with the ethical and safety guidelines set forth by the local 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 = 2.46 ms; TR = 1900 ms; inversion time (TI) = 900 ms; FOV = 225 × 240 mm; matrix = 240 × 256; resolution = 0.9375 × 0.9375 × 1.0 mm^3; and 160 total sagittal sections without intersection gaps.