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Less depressive symptoms are associated with smaller hippocampus in subjective memory impairment

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ABSTRACT

Although individuals with subjective memory impairment (SMI) tend to be at an increased risk for dementia and the majority of them have depressive symptoms, it remains unclear whether SMI with depression is associated with an increased or decreased risk of dementia. The purpose of this study was to investigate the relationship between depressive symptoms and hippocampal/amygdalar volume, a reliable biomarker in the prediction of progression to dementia in SMI. Ninety subjects with SMI participated in the study, and 28 healthy participants without memory complaints served as a normal control (NC) group. 3-D T1-weighted structural MRI scans were completed in all subjects. When the volumes of hippocampus and amygdala were compared among the groups, the SMI group showed significantly smaller volumes than the NC group. When multiple regression analysis was conducted in all subjects, neither hippocampal nor amygdalar volume showed significant interaction effect between group and Geriatric Depression Scale (GDS). However, when the analysis was conducted within each group, lower GDS score was associated with smaller hippocampal volume in the SMI group, and higher GDS score was associated with smaller amygdalar volume in the NC group. Thus, individuals with SMI and less depressive symptoms tend to have smaller hippocampus, which could be associated with more risk of dementia, than normal individuals.

1. Introduction

Subjective memory impairment (SMI) is a subjective complaint of memory decline among old people in the absence of any objective memory disturbance (Abdulrab & Heun, 2008). Although it remains unclear, individuals with SMI are generally considered to be at an increased risk of developing dementia in the future than those without SMI (Elfgren, Gustafson, Vestberg, &Passant; Jessen et al., 2010; Mol, van Boxtel, Willems, & Jolles, 2006; Schofield et al., 1997). The association with risk of dementia appears to be stronger among hospital-based SMI groups than in community-based groups (Jonker, Geerlings, & Schmand, 2000; Mitchell, 2008), and it has also been reported that SMI among the highly educated old people are more likely to be associated with the development of dementia (Jonker et al., 2000).

Subjective memory problems are also common among elderly individuals with depressed mood (Reid & MacLullich, 2006), and particularly among those self-referred to memory disorder clinics (Jonker et al., 2000; Mol et al., 2006). However, it remains unclear whether depression accompanied by SMI is associated with either an increased or decreased risk of developing dementia including Alzheimer's disease (AD). In a previous cross-sectional study, the degree of SMI was not correlated with their objective memory performance but was correlated with their depressive symptoms (Bolla, Lindgren, Bonaccorsy, & Bleecker, 1991), which may suggest that depressive symptoms significantly contributes to individual subjective perceptions of memory impairment even if they don't have significant memory impairment. In contrast, it has also been suggested that depression is a risk factor or an early manifestation of degenerative dementia. In particular, recent studies showed that a history of depression is associated with both of an increase in AD-related neuropathological changes in the hippocampus (Rapp et al., 2006) and an increase of risk developing clinically significant AD

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(Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008). Previous research also proposed that in certain subsets of old patients, late-life depression, mild cognitive impairment (MCI), and dementia could represent a possible clinical continuum (Panza et al., 2010).

Given that hippocampal and amygdalar volumes are believed to be reliable biomarkers of a predisposition for dementia in cognitively intact elderly individuals (den Heijer et al., 2006; Ikram et al., 2010), these measurements may also be useful in investigating the association between severity of depressive symptoms and the risk of developing dementia in individuals with SMI. A number of studies using volume-based or three-dimensional surface analyses have shown that hippocampal volumes as well as amygdalar volumes are smaller among individuals with SMI compared to those of typical elderly individuals without SMI (Stewart et al., 2008; Striepens et al., 2010; Tepest et al., 2008; van der Flier et al., 2004).

In the current study, hippocampal and amygdalar volumes in subjects with SMI (recruited from a memory disorder clinic) were initially compared with those in normal subjects without memory complaints. More specifically, the association between hippocampal/amygdalar volume and the degree of depressive symptoms measured by the Geriatric Depression Scale (GDS) (Yesavage et al., 1982–1983), the most widely used instruments for screening old individuals with depression, was analyzed in each group as well. Through these, we aimed to know whether subjects with SMI have smaller volumes of the hippocampus or amygdala compared to normal control (NC) subjects and whether their depressive symptoms are associated with the differences in volume.

2. Materials and methods

2.1. Subjects

As there is no consensus on the standard criteria, SMI was defined for the purposes of this study as self-reported memory impairments accompanied by normal performance on tests of cognitive abilities including memory. Normal memory performance was defined operationally as scores greater than the lowest 16th percentile (−1 standard deviation) of those in 447 normal subjects on neuropsychological tests of visual and verbal memory after being adjusted for age, sex, and education level. The Rey-Osterrieth Complex Figure Test (RCFT) was used as a measure of visual memory, and the Seoul Verbal Learning Test (SVLT) (Kang & Na, 2003) was used as an indicator of verbal memory.

The SMI group included self-referrers who sought medical attention for memory impairment but showed normal level of performance on neuropsychological tests at the memory disorder clinic of the Department of Neurology at the Samsung Medical Center in Seoul, Republic of Korea between April 2000 and February 2008. A total of 396 individuals visited the clinic during that period, and 107 visitors out of them were identified as SMI subjects. Subjects were excluded if they had any history of diagnosis or medication on neurological or psychiatric diseases. The NC subjects were recruited from healthy elderly individuals who visited the outpatient clinic of the Samsung Medical Center for the sake of a health promotion examination during the same period as the SMI groups. The NC subjects were confirmed not to have any subjective cognitive impairments, history of neurological or psychiatric diseases, or objective impairments on neuropsychological tests. All participants underwent a diagnostic assessment that included a history of cognitive, behavioral, and functional impairments, as well as a full neurological examination. The absence of medical problems was confirmed with laboratory tests including those for vitamin B12/folate level, syphilis serology, and the thyroid function. Conventional MRI confirmed the absence of territorial cerebral infarctions, brain tumors, and other structural lesions or abnormalities. In addition, those who had significant white matter hyperintensities on MRI according to the modified Fazekas' criteria: cap or band $\geq$ 10 mm or deep white matter lesion $\geq$ 25 mm were excluded (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). Among 107 SMI subjects, 8 subjects with errors in their MRI data, 2 subjects with old lacunar infarcts on MRI, and 7 subjects with significant white matter hyperintensities were excluded. Eventually, 90 subjects were included in the SMI group, and 28 healthy elderly individuals were included in the NC group. The demographic and clinical characteristics of these groups are presented in Table 1.

Table 1
Demographic and clinical characteristics of the participants.

	NC (n = 28)	SMI (n = 90)	p value
Age (years)	70.7 ± 5.5	65.8 ± 8.5	0.001
Male gender, N (%)	10 (35.7)	28 (31.1)	0.65
Education (years)	12.3 ± 4.4	10.4 ± 5.1	0.07
MMSE[a]	29.1 ± 1.2	28.6 ± 1.6	0.40

NC, normal control; SMI, subjective memory impairment; MMSE, Mini-Mental State Examination.
[a] The comparison was conducted with adjustment for age and education.

All participants provided a written informed consent regarding the scientific evaluation of their data. The present study was approved by the Institutional Review Board of Samsung Medical Center.

2.2. Neuropsychological tests and depressive symptom scale

All participants completed a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery (SNSB) (Kang & Na, 2003). This battery includes tests of attention, language, praxis, Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these assessments, scorable tests included Digit Span (forward and backward), the Korean version of the Boston Naming Test (Kim & Na, 1999), the RCFT (copying, immediate and 20-min delayed recall, and recognition), the SVLT (three learning-free recall trials of 12 words, 20-min delayed recall trial for these 12 items, and a recognition test), the Controlled Oral Word Association Test (COWAT), semantic category fluency test (animal and supermarket items) and the Stroop Test (word and color reading of 112 items during a 2-min period).

Participants' depressive symptoms were assessed using the Korean version of the GDS (Bae & Cho, 2004), which is based on the original version of the GDS (Yesavage et al., 1982–1983) and has been proved to be valid and reliable in screening major depression of elderly patients in Korea. The scale involves 30-item easy-to-administer inventory, and patients should respond "yes" or "no" for each question. A score of 16 is suggested as the optimal cutoff point of the Korean version of the GDS for screening major depression (Bae & Cho, 2004).

2.3. MR imaging for volumetric analysis

2.3.1. Image acquisition

Brain MRI was performed with a 1.5-T MRI scanner (GE Signa, Milwaukee, WI, USA). Three-dimensional, T1-weighted spoiled gradient (SPGR) echo images were obtained using the following imaging parameters: coronal slice thickness, 1.5 mm; echo time, 7 ms; repetition time, 30 ms; number of excitations, 1; flip angle, 45°; field of view, 22 × 22 cm; and matrix size, 256 × 256 pixels.