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Research paper

Association of subjective memory complaint and depressive symptoms with objective cognitive functions in prodromal Alzheimer's disease including pre-mild cognitive impairment

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ABSTRACT

Background: Subjective memory complaints (SMC) and depressive symptoms (SDS) are common in the elderly population. However, the relationship among SMC, SDS, and cognitive function remains unclear. We investigated these associations in the elderly from cognitively normal (CN), pre-mild cognitive impairment (MCI), and amnestic MCI (aMCI) groups.

Methods: Participants (CN, 299; pre-MCI, 106; aMCI, 267) underwent comprehensive clinical and neuropsychological assessment. and self-report SMC and SDS questionnaires. SMC and SDS were administered in a self-report format. For each neuropsychological test z-score, stepwise multiple linear regressions were performed to assess the relative contribution of SMC, SDS, and their interactions.

Results: SMC are associated with lower objective memory, while SDS are associated with lower psychomotor speed. Interactions between SMC and SDS were significant for tests of memory, executive function, psychomotor speed, and global cognition. Additional analyses revealed that SDS moderated the SMC-cognition relationship such that only individuals with higher SDS showed significant SMC-cognition associations.

Limitations: Due to the cross-sectional design, associations among SMC, SDS, and cognitive function was rather weak, albeit significant. Additionally, future biomarker studies, such as those assessing amyloid burden, are needed to explore the mechanisms underlying the relationship among SMC, SDS, and cognitive function.

Conclusion: Early identification of individuals at risk for developing abnormal cognitive changes is critical. Our findings from the study involving a large sample of carefully selected participants suggest that SMC and SDS could be used as early detection markers of Alzheimer's disease.

1. Introduction

Both subjective memory complaints (SMC) and depression are common in the elderly population. Previous studies on the relationship between SMC and objective cognitive function or Alzheimer's disease (AD) pathology have been controversial. Some studies reported significant relationships between SMC and objective cognition (Jonker et al., 2000; Scheef et al., 2012; van Oijen et al., 2007) or AD-related brain pathology (Perrotin et al., 2012; Schultz et al., 2015; Snitz et al., 2015; Stewart et al., 2008). However, individuals with SMC seem to be rather heterogeneous. Not all individuals with SMC show objective cognitive impairment or clinical progression. A recent longitudinal study reported that 76.5% of the individuals with SMC died without developing cognitive impairment (Kryscio et al., 2016). Although some of these individuals may represent the very early stages of AD, a considerable number of them are only “worried well”. Other reports have suggested that SMC are not associated with objective cognitive function (Harwood et al., 2004; Howieson et al., 2015; Jungwirth et al., 2004). It has also been reported that SMC are associated with negative emotions such as depression rather than actual neuropsychological

Abbreviations: SMC, Subjective Memory Complaints; SDS, Subjective Depressive Symptoms; AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; Pre-MCI, Pre-Mild Cognitive Impairment; CN, Cognitively Normal; CDR, Clinical Dementia Rating; BNT, Boston Naming Test; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test; TMT, Trail Making Test; MMSE, Mini Mental State Examination

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performance (Alegret et al., 2015; Chin et al., 2014; Hanninen et al., 1994; Mendes et al., 2008). A recent meta-analysis of 53 studies indicated SMC explained, albeit significantly, less than 1% of the variance in objective memory and that depressive symptoms had significant moderating effects (Crumley et al., 2014).

Depression is a well-known risk factor and one of the prodromal symptoms of AD (Byers and Yaffe, 2011; Enache et al., 2011; Ownby et al., 2006). Recent AD biomarker studies have reported that depression is associated with beta-amyloid burden (Babulal et al., 2016; Roe et al., 2013; Wu et al., 2014). Previous studies have consistently reported that depression has a negative impact on cognitive function (Potter and Steffens, 2007). Although depression-associated cognitive domains were various across studies, psychomotor speed, executive function, memory, and global cognition have been consistently reported (Kohler et al., 2010; Manning et al., 2015; Morimoto and Alexopoulos, 2013; Steffens and Potter, 2008). Given that the association between SMC and objective cognitive function is still controversial and that SMC is related to depression, it is plausible that depression may act as a moderator of the relationship between SMC and objective cognitive function. Although several studies have explored relationships among these factors (Alegret et al., 2015; Chin et al., 2014; Mendes et al., 2008), very few studies have examined the moderating role of depression in the SMC-cognition relationship. One study statistically analyzed whether depression moderated the SMC-cognition relationship and failed to find a significant influence of depression (Cook and Marsiske, 2006). Small sample sizes and very low levels of depressive symptoms may have led to the negative result. It is important to evaluate the possibility that depressive symptoms moderate the SMC-cognition relationship using a larger study sample.

Pre-mild cognitive impairment (pre-MCI) is an intermediate state between cognitively normal (CN) and MCI. Previous investigations have reported that more than 90% of the participants in the pre-MCI group exhibited AD neuropathology (Morris et al., 2001; Storandt et al., 2006). Recent research has also found that cognitive functions such as executive function are already altered in the pre-MCI stage (Seo et al., 2016). Investigating pre-MCI in the AD continuum is important for the early detection of AD in the population.

Therefore, this study aimed to investigate whether SMC or depression are associated with objective cognitive function in a large group of elderly participants with CN, pre-MCI, and amnestic MCI (aMCI). In addition, we explored if the relationship between SMC and objective cognitive functions varies with the levels of depression symptoms.

2. Methods

2.1. Participants

A total of 299 CN elderly, 106 individuals with pre-MCI, and 267 individuals with aMCI were recruited from a pool of individuals registered in the National Research Center for Dementia (NRCD), Gwangju, Korea from January 2014 to April 2016. Elderly people aged 60 and more volunteered to participate in the NRCD and after screening procedure with strict inclusion and exclusion criteria they were included in the study. Requests for volunteers were made through the local newspapers and posters placed on a bulletin board at public health centers and senior centers. All the subjects were community-dwelling and fully informed regarding study participation and provided written informed consents by themselves or by their legal guardians. All the participants were examined by a clinical interview, which included the assessment of the clinical dementia rating (CDR). CN participants had a clinical dementia rating (CDR) score of 0. They had a normal range of cognitive function and good general health with no evidence of brain atrophy, white matter changes, multiple lacunae, infarction, or other focal brain lesions on magnetic resonance imaging (MRI) scans. The Pre-MCI participants received a CDR score of 0.5 and their neuropsychological test z-scores were above −1.5 according to age-, education-, and gender-specific norms. They had good general health with no extensive white matter changes, multiple lacunae, infarction, or other focal brain lesions or atrophy other than suspected incipient AD on MRI scans. All the aMCI participants met the Petersen criteria (Petersen, 2004) and received a CDR score of 0.5. Their neuropsychological tests z scores were below −1.5 on at least one of six memory tests according to the age-, education-, and gender-specific norms. The exclusion criteria were (1) illiteracy, (2) severe vision or hearing loss, (3) evidence of focal brain lesions on MRI including multiple lacunae and white matter hyperintensity lesions of grade 2 or more according to the Fazeka scale, (4) any type of dementia, (5) any significant neurological, medical, or psychiatric disorders that could affect cognitive function, and (6) the current use of psychoactive medication. The Institutional Review Board of the Chosun University Hospital approved the study.

2.2. Clinical and neuropsychological assessment

All participants were examined by a clinical interview. Their medical history, including stroke or family history of dementia, were also assessed. Clinical diagnosis including CDR designation was made after reviewing all the available information in consensus case conferences. SMC were assessed using 14 items of the subjective memory complaints questionnaire (Youn et al., 2009). Subjective depressive symptoms (SDS) were assessed using 30 items of the geriatric depression scale (Kim et al., 2008). The cut-off scores of 16/17 for major depressive disorder, and 15/16 for minor depressive disorder were suggested (Kim et al., 2008). Both these tests were administered in a self-report format.

Comprehensive neuropsychological assessment was performed using the Seoul Neuropsychological Screening Battery (SNSB), which covers five major cognitive domains (Kang et al., 2003). The attention domain was assessed using a forward and backward digit span test. The language domain was assessed using a shortened version of the Boston Naming Test (BNT; 15 item version). The visuospatial domain was assessed using a copying test from the Rey Complex Figure Test (RCFT). The memory domain was assessed using six measures, including the Seoul Verbal Learning Test (SVLT) trials 1–3 total recall as immediate recall (SVLT_irl), 20-min delayed recall (SVLT_drl), yes-no recognition (SVLT_rcg), RCFT immediate recall (RCFT_irl), 20-min delayed recall (RCFT_drl), and yes-no recognition (RCFT_rcg). The frontal/executive domain was assessed using the animal fluency test, Stroop test (Stroop_W: word reading, and Stroop_C: color naming in a color-word incongruent condition), and Trail Making Tests (TMT) A and B. The global cognition was assessed using the Mini Mental State Examination (MMSE).

2.3. Statistical analyses

The demographic and clinical data were compared between groups using separate one-way analysis of variance (ANOVA) and χ^2 tests for continuous and categorical variables, respectively. Post-hoc analysis with the Tukey's method was conducted for the main effects that were significant in the ANOVA test at $p < 0.05$. Stepwise multiple linear regression analysis was performed in the total group to assess the relative contributions of SMC, SDS, and their interactions on each neuropsychological z-score according to age-, education-, and gender-specific norms. To examine whether the relationship between neuropsychological performance and SMC was influenced by the level of depression, the sample was divided into groups with less and more SDS using the median value of the study sample. For the neuropsychological z-scores which that had a significant interaction effect, simple linear regression analysis was separately performed for the two subgroups. All the statistical analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL); results with p-values less than 0.05 were considered significant.