Journal of Psychiatric Research 57 (2014) 149–156

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Depressive symptoms and cognitive performance in older adults

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ARTICLE INFO

Article history:
Received 2 January 2014
Received in revised form
21 May 2014
Accepted 6 June 2014

Keywords:
Cognitive test
BDNF
Brain atrophy
Hippocampus
Geriatric depression scale
Elderly

ABSTRACT

Many longitudinal studies have found that older adults with depressive symptoms or depression have increased risk of cognitive impairment. We investigated the relationships between depressive symptoms or depression, cognitive function, serum brain-derived neurotrophic factor (BDNF), and volumetric MRI measurements in older adults. A total of 4352 individuals aged 65 years or older (mean age 72 years) participated in the study. We investigated medical history and geriatric depression scale-15 (GDS-15) items to determine depression and depressive symptoms. Cognitive tests included the mini-mental state examination (MMSE), story memory, word list memory, trail-making tests, and the symbol digit substitution task. Of the 4352 participants, 570 (13%) fulfilled the criteria for depressive symptoms (GDS-15: 6 + points) and 87 (2%) were diagnosed with depression. All cognitive tests showed significant differences between the 'no depressive symptoms', 'depressive symptoms', and 'depression' groups. The 'depressive symptoms' and 'depression' groups showed lower serum BDNF ($p < 0.001$) concentrations than the 'no depressive symptoms' group. The 'depressive symptoms' group exhibited greater atrophy of the right medial temporal lobe than did the 'no depressive symptoms' group ($p = 0.023$). These results suggest that memory, executive function, and processing speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms and depression. Serum BDNF concentration and atrophy of the right medial temporal lobe may in part mediate the relationships between depressive symptoms and cognitive decline.

1. Introduction

An epidemiological study estimated that up to half of Alzheimer's disease (AD) cases worldwide (17.2 million) might be attributable to potentially modifiable risk factors. If the prevalence of all these risk factors were 10% lower, it is estimated that there would be as many as 1.1 million fewer AD cases worldwide; if risk factor prevalence were 25% lower, AD prevalence could potentially be reduced by over 3.0 million cases worldwide (Barnes and Yaffe, 2011).

Persons with cognitive decline are at increased risk for progressing to mild cognitive impairment (MCI) and dementia. Findings from numerous epidemiologic and clinical studies suggest that multiple biological, behavioral, psychosocial, and environmental factors may contribute to the risk of cognitive decline (Plassman et al., 2010). Also, many longitudinal studies have found that older persons with depressive symptoms or depression have an increased risk of cognitive decline, MCI, and dementia (Barnes et al., 2006; Berger et al., 1999; Devanand et al., 1996; Geerlings et al., 2000; Green et al., 2003; Verdelho et al., 2013; Wilson et al., 2002; Yaffe et al., 1999). In fact, depressive symptoms are common in dementia patients, with a prevalence of approximately 30% in people with dementia (Lyketsos et al., 2002). It is important to clarify which cognitive domains are associated with depressive symptoms or depression and to identify potential mediators between depression and cognitive decline to design strategies for the prevention of dementia in older adults.

Previous studies have reported that serum brain-derived neurotrophic factor (BDNF) levels are reduced in major depressive disorder and depressive symptoms (Cunha et al., 2006; Karege et al., 2002; Shimizu et al., 2003; Terracciano et al., 2011). BDNF has neurotrophic and neuroprotective properties (Barde, 1994; Lindvall et al., 1994) and can affect functions that underlie brain plasticity (Altar and DiStefano, 1998; Lu and Chow, 1999; McAllister

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http://dx.doi.org/10.1016/j.jpsychires.2014.06.004
0022-3956/

et al., 1999; Schinder and Poo, 2000). The neurotrophin hypothesis of depression is based on these functions of BDNF and postulates that depression results from stress-induced decreases in BDNF expression (Duman et al., 1997; Duman, Malberg, Nakagawa, & D'Sa, 2000). However, the majority of these studies have a small sample size or the design compares patients with major depression with healthy people. Extensive research is needed to determine the exact relationships between depressive symptoms and serum BDNF levels adjusted or controlled for potential confounders using large samples to examine the prevention strategies of depression in later life.

Another key factor that might affect the relationship between depression and cognition is age-related brain structural changes, especially hippocampal volume loss. Previous research has demonstrated reduced right hippocampal volume in older adults with depression (Bell-McGinty et al., 2002); moreover, depressed older adults with hippocampal volume loss were at greater risk of cognitive decline (Steffens et al., 2011). In addition, BDNF plays a role in regulating hippocampal plasticity: BDNF is presumed to be important for the integrity of the hippocampus and the maintenance of cognition. Normal aging appears to be associated with decreased BDNF signaling capacity in the brain. BDNF levels are decreased in hippocampal pyramidal neurons and dentate granule cells during aging in monkeys (Hayashi et al., 2001). These evidences suggest that a loss of BDNF plays a major role in the pathophysiology of depression, and that the neurotrophin hypothesis of depression appears to be valid especially when considered with relation to hippocampal function. However, it is not clear which cognitive categories are altered in patients with depressive symptoms and how BDNF levels might be associated to these and to hippocampal volume changes. The primary objective of this study was to examine which cognitive domains are associated with depressive symptoms and whether serum BDNF and brain atrophy are potential mediators between depression and cognitive decline in older adults.

2. Methods and materials

2.1. Participants

Our study assessed 5104 individuals who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE) (Shimada et al., 2013). Each individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. Each participant was 65 years or older at the time of examination (2011 or 2012), resided in Obu city, and had not participated in another study. We excluded participants who had been diagnosed with stroke ($n = 280$), Parkinson's disease ($n = 22$), or AD ($n = 8$); we also excluded those who had certified long-term care insurance needs ($n = 119$), functional decline in activities of daily living ($n = 11$), severe cognitive decline, i.e., mini-mental state examination (MMSE) 20 points or fewer ($n = 121$), or missing BDNF data or characteristics ($n = 191$). Ultimately, 752 of the 5104 participants were excluded and 4352 older adults (mean age 71.7 ± 5.3 years, range 65–97 years, 2085 men, 2267 women) were included in this study. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol.

2.2. Measurements: depressive symptoms and depression

The self-report screening instruments available to detect depression were deemed suitable for use in this community-based study. The 15-item version of the geriatric depression scale (GDS-15) has been validated as a screening tool for depressive symptoms in older people (Sheikh and Yesavage, 1986). A cut-off point of ≥ 5 on the GDS-15 has a pooled sensitivity of 88% and specificity 64%, and a cut-off point of ≥ 6 has a pooled sensitivity of 79% and specificity of 77% for diagnosing depression in older people (Dennis et al., 2012). A recent longitudinal study, which used GDS-15 and a cut-off score of 6, identified that MCI and subjective memory impairment were associated with incident depression (Weyerer et al., 2013). Participants were screened for depressive symptoms using the GDS-15 and a cut-off value of ≥ 6 to indicate clinically critical depressive symptoms. All participants completed a face-to-face interview including medical history by licensed and well-trained nurses. Depression was defined as follows: diagnosed as having depressive disorder by a family doctor and having received medication for depression.

2.3. Measurements: cognitive performance

Well-trained study assistants conducted assessments of cognitive functions. Prior to commencing the study, all staff received training from the authors in the correct protocols for administering the assessment measures. Cognitive tests were conducted using the MMSE (Folstein et al., 1975) and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) (Makizako et al., 2013; Shimada et al., 2013). The computerized multidimensional neurocognitive task battery, the NCGG-FAT, comprises several cognitive domains: story memory (delayed recognition), word list memory (delayed recall), attention and executive function (tablet version of trail-making test, parts A and B), and processing speed (tablet version of symbol digit substitution task). In story memory, the participants heard a short story (approximately 1 min in length) through an auditory system using headphones. They were instructed to remember the details of a story, and then select the correct answer that described the details of the story from four choices after 20–30 min. All 10 questions in each task were shown and we calculated the total number of correct answers. Word list memory involved delayed recall of a 10-word target list. The participants were instructed to recall the 10 target words after approximately 20 min. The tablet version of trail-making test consists of part A and B, as well as the original written version of trail-making test. We recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s in the tablet version of symbol digit substitution task, nine pairs of numbers and symbols were provided at the top of the display. A target symbol was shown at the center of the display. Participants then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s. One point was given for each correctly chosen number completed within the time limit. High test–retest reliability and moderate-to-high validity were confirmed in community-dwelling older adults for all task components of the NCGG-FAT (Makizako et al., 2013).

2.4. Measurements: potential correlates

With reference to the review articles by Cole and Dendukuri (2003) and Plassman et al. (2010), we selected four demographic variables, three physiological variables, two health status indicators, two blood biomarkers, and four behavioral variables as possible confounding factors of depressive symptoms and depression and cognitive decline (Table 1) (Cole and Dendukuri, 2003; Plassman et al., 2010). We selected four demographic variables—age, sex, educational level, and living alone—as possible correlates in determining the association between depressive syndromes and cognitive decline.