Psychiatry Research 251 (2017) 168–175

Contents lists available at ScienceDirect

Psychiatry Research

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

The characteristic of cognitive dysfunction in remitted late life depression and amnestic mild cognitive impairment

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ARTICLE INFO

Keywords:
Remitted late life depression
Amnestic mild cognitive impairment
Core cognitive impairment
Executive function

ABSTRACT

Remitted late life depression exhibits persistent cognitive impairments and enhances the risk of dementia. This study aimed to examine the characteristics of cognitive dysfunction in remitted late life depression and amnestic mild cognitive impairment (MCI). Remitted late life depression (n=61), amnestic MCI (n=61) and age-education-matched controls (n=65) were evaluated with a battery of neuropsychological tests grouped into executive function, memory, processing speed, attention and visuospatial domains. Compared with control subjects, amnestic MCI individuals showed more severe cognitive impairments in all domains, while remitted late life depression individuals performed worse in executive function and memory. The pattern of cognitive profiles significantly differed between remitted late life depression and amnestic MCI groups, which might be mainly attributed to worse impairments in memory and executive function in amnestic MCI individuals. Executive function was the core impaired cognitive domain mediating the influence of predictors on other cognitions in both remitted late life depression and amnestic MCI groups, which indicated a possible etiopathogenic mechanism underlying the conversion to dementia.

1. Introduction

Late life depression, characterized by a pervasive and persistent low mood in elderly people (60 years or older), is invariably accompanied by multiple cognitive impairments, including executive function, memory, processing speed, attention and visuospatial skill domains (Butters et al., 2004; Koenig et al., 2015; Kohler et al., 2010; Yeh et al., 2011). In recent years, late life depression has been considered a part of the preclinical course of Alzheimer's disease (AD) (Mahgoub and Alexopoulos, 2016; Osorio et al., 2014) and was associated with a 2–5-fold increased risk of developing AD compared with healthy aging individuals (Saczynski et al., 2010; Wilson et al., 2002). Amnestic mild cognitive impairment (amnestic MCI), a MCI subtype characterized by memory deficit, is a transitional stage between normal aging and AD. Patients with amnestic MCI have been reported an 8.6-fold higher conversion risk to AD compared with patients reporting memory problems without objective impairments on neuropsychological testing (Lehrner et al., 2005). The classification and pattern of the cognitive deficits in remitted late life depression and amnestic MCI may shed light on the pathogenesis of their conversion to dementia.

To date, the majority of studies have demonstrated that processing speed deficit is the core cognitive impairment followed by executive function in the acute phase of late life depression, meaning that changes in these two cognitive domains were sufficient to mediate changes in other cognitive domains (Butters et al., 2004; Delaloye et al., 2008; Kohler et al., 2010; Nebes et al., 2000; Sheline et al., 2006). However, a 5 -year follow-up study only partially agreed with the previous findings, as it showed that executive function and memory deficits, but not processing speed deficit, were potential predictors of the late life depression conversion to dementia during acute depression (Potter et al., 2013). Moreover, the symptom spectrum of cognitive impairments varied substantially from the acute to the remitted stage of patients with late life depression. Most cognitive dysfunction in the acute depressive phase might improve, although not return to normal levels, after depressive symptoms are reduced (Herrera-Guzman et al., 2010). For instance, the processing speed deficits observed at baseline in late life depression patients had largely recovered at the 18-month follow-up (Kohler et al., 2010). Executive function and memory impairment were reported to persist in 28.5% patients with amnestic MCI and 23.8% with non-amnestic MCI in remitted late life depression

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http://dx.doi.org/10.1016/j.psychres.2017.01.024
Received 3 February 2016; Received in revised form 5 December 2016; Accepted 9 January 2017
Available online 12 January 2017

(Yeh et al., 2011). The executive function and memory impairments persisting in the long duration of remitted late life depression might importantly contribute to the progression of other cognitive decline. Therefore, it is valuable to investigate the characteristic profiles of cognitive impairment in remitted late life depression, which might help elucidate the persistent cognitive deficits most relevant to the conversion to dementia.

Bearing some similarity to late life depression, amnestic MCI patients also suffered with multiple cognitive domain impairments including memory deficit, executive dysfunction and processing speed deficit (Blanco et al., 2016; Chang et al., 2015; Haworth et al., 2016). Memory deficit has been considered the earliest and primary characteristic in amnestic MCI patients, which might be closely related to the deterioration of overall cognition into AD (Marra et al., 2015). However, the relationship between memory deficit and other cognitive domains in amnestic MCI patients remains largely unclear. It also remains to be clarified whether certain central and basic cognitive deficits in amnestic MCI patients could predict impairment in other cognitive domains and influence the strength and breadth of the associations with other cognitive domains. Additionally, late life depression and amnestic MCI might have different conversion outcomes during their progression to dementia. While amnestic MCI is thought to be relevant to AD, late life depression was associated with an increased risk of all-cause dementia, in which the risk of vascular dementia (VD) was significantly higher than that of AD (Diniz et al., 2013). Therefore, it would be interesting to characterize the common and different patterns of cognitive impairments in remitted late life depression and amnestic MCI patients; this might contribute to the understanding of the potential mechanism involved in the evolution and prognosis of these two diseases. The present study evaluated participants using a battery of neuropsychological assessments measuring the domains of memory, executive function, processing speed, attention and visuospatial skill. The core cognitive domains in remitted late life depression and amnestic MCI patients were investigated using a series of statistical processes including profile analysis and multiple regression analysis. Moreover, neuroimaging studies had demonstrated abnormal grey matter volumes (Yuan et al., 2008), imbalanced functional connectivity (Shu et al., 2014) and their association with cognitive impairments in remitted late life depression subjects. Similar deficits in regional and connectivity characteristics in white matter networks were found in remitted late life depression and amnestic MCI patients (Bai et al., 2012), which may present a common mechanism of cognitive deterioration for these patients. Therefore, the present study also assessed changes in the brain grey and white matter structure and their possible influence on cognitive function in subjects with remitted late life depression and amnestic MCI.

2. Methods

2.1. Participants

A total of 187 participants aged 60–80 years old (remitted late life depression [n=61]; amnestic mild cognitive impairment, (amnestic MCI) [n=61]; healthy controls, (HC) [n=65]) participated in the present study. Subjects with remitted late life depression were recruited from geriatric psychiatry outpatient centers at the Affiliated ZhongDa Hospital, Southeast University, and the Affiliated Brain Hospital, Nanjing Medical University. Amnestic MCI subjects and healthy controls were recruited from the community through local advertisements. The remitted late life depression individuals had been diagnosed with unipolar major depressive disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), and their current scores on the Hamilton Depression Rating Scale for Depression-17 items (HAMD-17) had been less than 7 for 2 consecutive months. The amnestic MCI individuals were diagnosed following the recommendations of (Petersen et al., 1999) and others (Winblad et al., 2004), including subjective reports of memory impairment corroborated by objective memory performance documented by the Auditory Verbal Learning Test (AVLT), with long delayed recall scores less than or equal to 1.5 standard deviations (SDs) of age- and education-adjusted norms (cutoff of ≤4 correct responses on 12 items for ≥8 years of education). The recruited remitted late life depression and amnestic MCI subjects also met the following criteria: (1) education level above ≥8 years; (2) Mini-Mental Status Examination (MMSE) scores >24, Mattis Dementia Rating Scale (MDRS) scores >120; and (3) no or minimal impairments in activities of daily living. The healthy control subjects were required to meet the following criteria: (1) AVLT long delayed recall score >4; (2) MMSE score ≥26, MDRS scores >120; and (3) education level ≥8 years. The exclusion criteria for all the subjects were as follows: (1) a past history of any other psychiatric or neurological disease or HAMD-17 scores >7; (2) presence of endocrine diseases including hyperthyroidism or hypothyroidism that affect the performance of cognitive function (Quinlan et al., 2010); (3) head injury with loss of consciousness; (4) unstable chronic medical conditions (such as instability hypertension); (5) severe vision or hearing loss; and (6) MRI contraindications. These control subjects were matched for age, gender, and level of education to the remitted late life depression and amnestic MCI subjects. All participants provided written informed consent, and the study protocol was approved by the Hospital Ethical Committee for clinical research of ZhongDa Hospital Affiliated to Southeast University in accordance with the Declaration of Helsinki.

2.2. Clinical evaluation

Demographic and clinical data were obtained from evaluations performed by highly trained research staff and included the following variables (Table 1): gender, age, years of education, age at onset of depression, duration of depression in years, current HAMD-17 scores, scores of Activity of Daily Living (ADL), and Hachinski Ischemic Score (HIS). Age at onset of depression was defined as the age at which remitted late life depression patients experienced their first episode of major depression and was determined from personal testimony and hospital records. The 17-item Hamilton Rating Scale for Depression (HAMD-17) represents current depressive symptom severity (Hamilton, 1967). The Hachinski Ischemic Score is a clinical tool to evaluate vascular factors and is helpful to differentiate major types of dementia (Kim and Kwon, 2014).

2.3. MRI acquisition and analysis

All participants underwent a MRI scan using a 3.0 T Trio Siemens scanner with a 12-channel head-coil (Siemens, USA) at Affiliated ZhongDa Hospital, Southeast University. High-resolution T1-weighted axial images covering the whole brain were acquired using a T1-weighted 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) sequence (TR=1900 ms, TE=2.48 ms, TI=900 ms, FA=9°, number of slices=176, thickness=1 mm, gap=0 mm, imaging matrix=256×256, FOV=250 mm×250 mm, acquisition duration: 4 min and 18 s). T2-weighted axial images were acquired using T2 fluid-attenuated inversion recovery (T2-FLAIR) sequences (TR=8400 ms, TE=94 ms, TI=2439 ms, FA=150°, number of slices=20, thickness=5 mm, gap=0 mm, imaging matrix=256×256, FOV=230 mm×230 mm, acquisition duration: 1 min and 59 s). The periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH), which represented white matter changes in the T2-weighted axial images, were rated using the modified Fazekas scale (Fazekas et al., 1987). Brain atrophy on the T1-weighted axial images were analyzed by optimized voxel-based morphometry (VBM8) combined with Statistical Parametric Mapping (SPM8) software, obtaining grey matter volume (GM), white matter volume (WM) and cerebrospinal fluid volume (CSF).