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Executive dysfunction and gray matter atrophy in amnestic mild cognitive impairment☆

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ABSTRACT

Recent studies have shown that impairment in executive function (EF) is common in patients with amnestic mild cognitive impairment (aMCI). However, the neuroanatomic basis of executive impairment in patients with aMCI remains unclear. In this study, multiple regression voxel-based morphometry analyses were used to examine the relationship between regional gray matter volumes and EF performance in 50 patients with aMCI and 48 healthy age-matched controls. The core EF components (response inhibition, working memory and task switching, based on the EF model of Miyake et al) were accessed with computerized tasks. Atrophic brain areas related to decreases in the three EF components in patients with aMCI were located in the frontal and temporal cortices. Within the frontal cortex, the brain region related to response inhibition was identified in the right inferior frontal gyrus. Brain regions related to working memory were located in the left anterior cingulate gyrus, left premotor cortex, and right inferior frontal gyrus, and brain regions related to task shifting were distributed in the bilateral frontal cortex. Atrophy in the right inferior frontal gyrus was most closely associated with a decrease in all three EF components in patients with aMCI. Our data, from the perspective of brain morphology, contribute to a better understanding of the role of these brain areas in the neural network of EF.

1. Introduction

Amnestic mild cognitive impairment (aMCI) is associated with an increased rate of conversion to Alzheimer's disease (AD) and is generally considered to represent a transitional state between normal aging and AD (Petersen et al., 2001). Although the impairment of memory is regarded as a hallmark of aMCI, recent studies have demonstrated that deficits in executive function (EF) may also be present (Brandt et al., 2009; Johns et al., 2012; Liu-Ambrose et al., 2008; Marshall et al., 2011; Saunders and Summers, 2011; Zheng et al., 2012a). In the study by Johns et al., all patients with aMCI, independent of whether they were of single domain or multiple domain subtype, showed deficits in at least one sub-domain of EF (Johns et al., 2012). Deficits in EF for patients with aMCI are not only a key contributor to the impairment of everyday function (Marshall et al., 2011) but are also strong predictors of a conversion to AD (Chapman et al., 2011).

The neuroanatomic bases of executive dysfunction in patients with aMCI remain unclear. It is well known that the prefrontal cortex (PFC) plays a crucial role in EF (Funahashi, 2001), and there is substantial evidence that different areas of the PFC exert different roles in executive controls (Kesner and Churchwell, 2011; Petrides, 2005). Numerous studies have demonstrated that aMCI-related regional gray matter (GM) atrophy is most significant in the medial temporal lobes (MTLs) and, to a lesser extent, in other brain structures, including the frontal cortex (Barbeau et al., 2008; Dos et al., 2011; Hamalainen et al., 2007a, 2007b; Schmidt-Wilcke et al., 2009; Spulber et al., 2012; Tondelli et al., 2012; Whitwell et al., 2008). We hypothesized that the EF deficits of patients with aMCI would be correlated with the morphological changes in the PFC in patients with aMCI. In addition, deficits of different core EF components might be associated with GM loss in distinct brain areas.

To test these hypotheses, we first evaluated the three core EF components (i.e., response inhibition, working memory and task switching) in patients with aMCI and age-matched healthy controls using computerized tasks. Next, high-resolution brain magnetic

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resonance (MR) scans were performed in all of the participants. Voxel-based morphometric (VBM) analysis was performed to explore the brain regions where atrophy might be associated with the declines of the core EF components in patients with aMCI, which was the main aim of this study. Using multiple regression analyses between performance on cognitive tests and aspects of local morphology, VBM studies in patients with aMCI and AD have shown correlations between the GM volume of MTLs and the patients' performance in memory (Barbeau et al., 2008; Dos et al., 2011; Leube et al., 2008; Sarazin et al., 2010; Schmidt-Wilcke et al., 2009) and clock drawing tests (CDT) (Thomann et al., 2008). In this study, we performed VBM analyses on EF in patients with aMCI and reveal data that provide a deeper understanding of the neural network of EF from a morphological perspective.

2. Methods

2.1. Participants

This study included 50 patients with aMCI and 48 age-matched healthy controls who were recruited from the memory disorders clinic and the health examination center of Shengjing Hospital of China Medical University using advertisements between June 2010 and February 2013. A detailed evaluation, including medical history, physical and neurological examinations, psychiatric and cognitive evaluations, laboratory tests, and brain magnetic resonance imaging (MRI) were performed in the participants. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the Chinese version of the Activities of Daily Living Scale (Lawton and Brody, 1969), the Clinical Dementia Rating scale (CDR) (Hughes et al., 1982), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) Beijing version, the Chinese version of Auditory Verbal Learning Test (Guo et al., 2007) and the 30-item Geriatric Depression Scale (Yesavage et al., 1982) were used in the psychiatric and cognitive evaluations. Laboratory follow-ups included in the following: a complete blood count and differential; serum electrolyte and glucose measures; liver and renal function tests; thyroid function tests; HIV and syphilis screening; and serum B12 and folate levels. All of the participants metthe following criteria: (1) no history or evidence of psychiatric or neurological disease, cardiovascular disease, diabetes, thyroid disease, vitamin B12 deficiency, alcoholism, or drug abuse; (2) an educational level of no less than 6 years; (3) right-handedness; and (4) no significant changes in conventional MRI of the brain, such as a cerebral infarct, hydrocephalus, or leukoaraiosis. In addition, all of the patients with aMCI received CDR scores of 0.5 and met Petersen's criteria (Petersen, 2004) for amnestic MCI, which included the following: (1) memory complaint by the patient or a reliable informant; (2) objective memory impairment as demonstrated by scores of more than 1.5 SDs below the normative age and education values and; (3) no global cognitive impairment and no significant effect on daily functions. For the normal control participants, further inclusion criteria included a CDR score of 0 and scores within normal ranges on all of the neuropsychological tests. The demographic characteristics and neuropsychological assessments of the patients and control participants are presented in Table 1, including their performances on the 4 EF-related tests in MoCA (Alternating Trail Making—an analog of the Trail Making Test part B (TMT-B); the Clock Drawing Test (CDT); Abstraction and Verbal fluency) which had shown good discriminating power for EF in normal individuals (Zheng et al., 2012b).

The study was approved by the Ethics Committee of the Shengjing Hospital of China Medical University. Written informed consent was obtained from all of the participants.

Table 1
Demographic characteristics and neuropsychological assessments of patients with aMCI and normal controls

Participant demographics	aMCI (n = 50)	Controls (n = 48)	t or χ^2	p
Age, y	69.8 (6.8)	69.2 (5.1)	0.536	0.594
Sex (male/total)	16/50	19/48	0.613	0.528
Education, y	9.8 (3.5)	10.4 (3.2)	−0.968	0.335
MMSE	27.9 (1.5)	29.5 (0.7)	−6.608	<0.001
ADL	20.2 (0.5)	20.1 (0.3)	1.682	0.099
GDS	6.3 (1.2)	5.5 (1.0)	3.688	<0.001
AVLT				
Total immediate recall	15.2 (2.6)	18.6 (1.9)	−7.037	<0.001
Long delayed recall	3.5 (0.6)	6.7 (1.3)	−15.314	<0.001
MoCA total score	21.0 (2.9)	27.2 (1.7)	−12.957	<0.001
Executive items of MoCA				
Alternating Trail Making	0.6 (0.5)	0.9 (0.3)	−2.803	0.006
Clock Drawing Test	2.7 (0.5)	2.8 (0.4)	−1.567	0.121
Abstraction	1.0 (0.6)	1.1 (0.6)	−1.613	0.110
Verbal fluency	0.9 (0.3)	1 (0.1)	−1.345	0.183

Data are Mean (standard deviation).
Key: ADL, Activitiesy of Daily Living; aMCI, amnestic mild cognitive impairment; AVLT, Auditory Verbal Learning Test; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

2.2. Evaluation of core EF components

Unlike previous studies of EF in patients with aMCI, in which the EF components examined were determined empirically, our study investigated the core EF components based on the model of Miyake et al. Using latent-variable analysis, Miyake et al. verified that although the three basic executive functions were moderately correlated with one another, they were still distinct. Although there is controversy regarding the Miyake model, it has been validated by several studies using different sets of EF tasks in various ages of participants (Hedden and Yoon, 2006; Vaughan and Giovanello, 2010). EF tasks were intentionally selected to be sensitive and specific for the evaluation of a single core EF component: response inhibition was assessed with a stop-signal task, working memory was assessed with a keep track task, and task switching was assessed with a more-odd shifting task. These tasks were programmed with E-prime 2.0 (Psychology Software Tools, Pittsburg, PA). The responses were logged using the buttons or vocal keys of the E-prime serial response box. All of the stimuli in the experimental task were presented in font size 48 on a white background in the middle of a standard 15-inch CRT computer screen, and all of the participants were individually tested in a quiet room. The participants sat at a comfortable distance from the screen ($\sim$ 60 cm). The order of the task administration was fixed for all of the participants (i.e., stop-signal task, more-odd shifting task and keep track task). All of the participants received one 5-minute practice session for each task before the formal test to become familiar with the requirements of the task. There was a 3-minute rest period between tasks. The entire test lasted for approximately 1 hour.

2.2.1. Stop-signal task

This study adopted a version of the stop-signal task used in our previous study (Zheng et al., 2008). On the Go trial, the participants were instructed to press a button when they saw the "go" signal (a circle). The circle disappeared when the button was pressed or after 1000 millisecond had passed without a response, whichever came first. On the Stop trial, a "stop" signal (a cross) appeared shortly after the "Go" signal. The participants were instructed not to press the button on trials with a "stop" signal. The Stop trial also terminated when a button was pressed or when 1000 millisecond had elapsed because the appearance of the "go" signal. In every four