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Cognitive reserve modulates attention processes in healthy elderly and amnestic mild cognitive impairment: An event-related potential study

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HIGHLIGHTS

- Higher cognitive reserve (CR) results in better task performance via lowering neural inefficiency in elderly healthy controls (HC).
- CR differently modulates attention processes in HC and amnestic mild cognitive impairment (aMCI) patients.
- CR lowers cognitive impairment of HC and aMCI patients.

ABSTRACT

Objectives: The study aimed to investigate and compare the effect of cognitive reserve (CR) on brain activation in healthy controls (HC) and amnestic mild cognitive impairment (aMCI) patients during 0-back and 1-back tasks measured by event-related potential (ERP).
Methods: The study recorded 85 subjects (39 aMCI patients and 46 their matched controls) with a 64-channel electroencephalogram (EEG). Subjects performed 0- and 1-back tasks.
Results: Compared to HC, aMCI patients showed reduced accuracy, delayed mean correct response time (RT) and decreased P300 amplitude at central-parietal and parietal electrodes. A mediation analysis indicated that higher CR reduced neural inefficiency, which might be associated with better task performance in HC. However, no correlation was detected between CR and neural inefficiency in aMCI patients, whereas higher CR was still related to enhanced accuracy and prolonged RT in aMCI patients.
Conclusions: The present study reported that higher CR could contribute to better task performance via down-regulating neural inefficiency in HC. In addition, higher CR might modulate attention processes in aMCI via a way distinct from that in HC, and eventually result in better task performance.
Significance: The study provided evidence for that improving CR might lower cognitive impairment of healthy elderly and aMCI patients.

1. Introduction

Cognitive reserve (CR) is a concept that was proposed to explain susceptibility heterogeneities of different individuals to cognitive impairment while confronting same neural pathology (Barulli and Stern, 2013). In addition, CR might be associated with lifetime intellectual activities and some other environmental factors including Intelligence Quotient (IQ), education, occupation level and participation in leisure activities, etc. (Barulli and Stern, 2013). There is extensive epidemiological and experimental evidence to support the existence of CR: education, occupation level and participation in leisure activities have been demonstrated to be related to risk for developing dementia (Smith et al., 2010; Stern, 2012; Xu et al., 2015), cognitive impairment while aging (Barulli and Stern, 2013), and clinical changes in several other neu-

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rological and psychiatric disorders (Barnett et al., 2006; Sumowski and Leavitt, 2013; Hindle et al., 2014; Nunnari et al., 2014; Mathias and Wheaton, 2015). In addition, previous studies have demonstrated that cognitive training activities could cognitively, socially, and physically stimulate an increase of efficiency, capacity and flexibility of neural networks, and eventually contribute to prevention or delay of cognitive decline (Engvig et al., 2010, 2012; Smith et al., 2010; Sagi et al., 2012). Moreover, in a recent review for preclinical Alzheimer's disease (AD) (Dubois et al., 2016), CR is shown to be a regulable prevention factor for lowering brain Amyloid-β (Aβ) burden (neural pathology) (Liang et al., 2010; Landau et al., 2012), reducing the susceptibility of participants to neural pathology and eventually postponing disease progression to clinical AD. Thus, CR might play a crucial role in slowing down progression of AD. Mild cognitive impairment (MCI) is considered as a transitional stage between normal aging and early dementia, especially AD (Petersen et al., 1999). Multiple epidemiological, imaging and experimental evidence has demonstrated that CR modulates the relationship between neural pathology and clinical manifestation in MCI patients (Rolstad et al., 2009; Teixeira et al., 2012; Osone et al., 2015).

A hypothesis is that an adult with higher CR might have better task-related performance via more efficient task-related activation (neural reserve) and neural compensation (Stern, 2009). Neural reserve is regarded as differences between unimpaired individuals in neural efficiency of task-related brain networks that provide reserve against the impact of brain injury. Neural compensation refers to that unhealthy individuals maintain or improve cognitive performance of pathology-induced changes via the reliance on alternative brain networks (Barulli and Stern, 2013). An event-related potential (ERP) study (Speer and Soldan, 2015) and some functional magnetic resonance imaging (fMRI) studies (Kumar et al., 2008; Steffener et al., 2011) provided evidence for neural reserve and neural compensation in normal aging, respectively. ERP reflects instantly the summated excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP), primarily of pyramidal cells in the neocortex (Nunez and Srinivasan, 2006). The high temporal resolution of ERP enabled the understanding of the neural correlates of cognitive processing and functioning. Our study implemented ERP to investigate the association between CR and neural efficiency from both the magnitude of neural activation and the speed of neural processing in amnestic MCI (aMCI) patients.

The current investigation used visuospatial 0- and 1-back tasks to measure individual differences in neural efficiency. 0-back assesses pure attention to the task (a control task), while 1-back represents more paid attention. Different task difficulty is beneficial to investigate the neural effect of CR, because CR reflects modulating ability of the brain to deal with the increasing task load (Speer and Soldan, 2015). P300, a positive component that peaks between 300 and 500 ms, might be related to automatic attention processing (Polich and Corey-Bloom, 2005). Moreover, P300 amplitude was also associated with intelligence (Li, 1992; Jausovec and Jausovec, 2001; Buchmann et al., 2011) and life style (Stroth et al., 2009; Chang et al., 2013), elucidating that P300 amplitude might be associated with CR. Neural efficiency is considered as the degree to which a task-related brain network must be activated to fulfil the task. Individual differences in neural efficiency might provide neural reserve against the effect of brain changes (Barulli and Stern, 2013). According to a recent study, neural inefficiency was more stable than neural efficiency (Barulli and Stern, 2013). The study measured the correlation between CR and neural inefficiency during attention activation in healthy controls (HC) and aMCI patients, respectively.

The aim of the present study is to investigate the impact of CR on ERP changes during attention activation in HC and aMCI patients. According to the CR hypothesis, the present study hypothesized that: Both HC and aMCI patients with higher CR showed more efficient neural activity, which might be associated with better attention task performance.

2. Methods

2.1. Participants

In this investigation, a cohort of 39 aMCI patients and 46 HC were recruited through community health screening, newspaper advertisements and a memory outpatient clinic (all subjects were Chinese Han). All the participants were right-handed and between 55 and 80 years old. The present study underwent approval by the Human Participants Ethics Committee of the Affiliated ZhongDa Hospital, Southeast University. Written informed consents were obtained from all participants. In addition, each method was carried out in accordance with the approved guidelines.

2.2. Neuropsychological assessments

All participants underwent neuropsychological assessments to evaluate cognitive functions (general cognitive functions, episodic memory, executive function, information processing speed and visual spatial domains). These assessments include: Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Mattis Dementia Rating Scale-2 (MDRS-2) (Matteau et al., 2011), Clinical Dementia Rating (CDR) (Hughes et al., 1982), Auditory Verbal Learning Test-20-min Delayed Recall (AVLT-20-min-DR) (Rey, 1958), Logical Memory Test-20-min Delayed Recall (LMT-20-min-DR) (Wechsler, 1955), Rey-Osterrieth Complex Figure Test (ROCFT), Rey-Osterrieth Complex Figure Test- 20-min Delayed Recall (ROCFT-20-min-DR) (Osterrieth, 1944), Trail Making Tests A and B (TMT-A and B) (Strauss et al., 2006), Digit Span Test (DST) (Lezak, 2004), Symbol Digit Modalities Test (DSST) (Smith, 1968), Stroop Color and Word Test A, B, and C (Golden and Freshwater, 1978), Verbal Fluency Test (VFT) (Lezak, 2004), Semantic Similarity test (Wechsler, 1955) and Clock Drawing Test (Kaplan, 1983).

2.3. Inclusion criteria and exclusion criteria

All aMCI patients met the criteria (Petersen, 2004; Albert et al., 2011; Bai et al., 2011), which includes: subjective memory impairment confirmed by the subject and his informant; objective memory performance documented by an AVLT-DR score less than or equal to 1.5 Standard Deviation (SD) of age- and education-adjusted norms (cut-off of $\leq$4 correct responses on 12 items for patients with $\geq$8 years of education); MMSE score $\geq$24; CDR of 0.5; no or minimal impairment in activities of daily living; absence of dementia or insufficient dementia to meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria. In addition, controls need to have a CDR of 0, an MMSE score $\geq$26, and an AVLT-DR score >4 for subjects with 8 or more years of education. Subjects were excluded from the study if they had a history of neurological or psychiatric disorders, major medical illness, or severe visual and or hearing loss.

2.4. Proxies of cognitive reserve

All participants were assessed with the Cognitive Reserve Index questionnaire (CRIq) on their activities of daily life (Nucci et al., 2012). The questionnaire included a large number of items and aimed at summarizing all possible contributors to CR (education,