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Research report

Abnormal functional connectivity of the default mode network in remitted late-onset depression

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ABSTRACT

Background: The functional neural network model has been a major method used to investigate mechanisms of neuropsychopathy. There is considerable evidence that late-onset depression (LOD) is the prodrome, or the early clinical manifestation, of Alzheimer's disease (AD). The default mode network (DMN) is one of the neural networks that can be used to explore the complex relationships between depressive symptoms, episodic memory deficits and other cognitive impairments. To date, no study has directly linked the DMN to LOD while focusing on episodic memory and the influence of apolipoprotein E4 (APOE4), a major genetic risk factor for AD in LOD patients.

Methods: In total, 33 remitted LOD (rLOD) patients and 33 elderly controls underwent fMRI scanning using low-frequency BOLD signal imaging during the resting state and during an episodic memory task. Furthermore, function-based functional connectivities (FCs) in the region of interesting (ROI) (posterior cingulate cortex (PCC) of the DMN) were analysed to explore interactions between disease states, task states and genetic risk factors (APOE4).

Results: Compared to healthy control subjects (HC), the FCs between the PCC and the right medial temporal lobe of the rLOD patients were significantly stronger during rest ($p < 0.005$) and significantly weaker ($p < 0.05$) during performance of the task. The mode of change from rest to task performance in the HC was in contrast to the mode of change in the rLOD patients. The FCs of the rLOD patients without APOE4 were significantly increased ($p < 0.05$) in the resting state, but the rLOD patients who carried APOE4 showed a trend toward decreased FCs.

Limitations: The sample size was small. While the study was cross-sectional, we did not differentiate between the various types of antidepressants the patients used, which may have had different effects on cognitive function, especially on episodic memory.

Conclusion: Our results suggested that rLOD might be the prodrome, or the early clinical manifestation, of AD and that rLOD patients with APOE4 showed an increased risk for episodic memory decline and AD.

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1. Introduction

Impairments in a wide range of cognitive domains are associated with late-onset depression (LOD) (Butters et al., 2004; Herrmann et al., 2007) and persist despite improvements in depressive symptoms (Bhalla et al., 2006; Steffens et al., 2004). Episodic memory refers to the ability to retain, recall, and encode information related to personal events and experiences that occur at specific times and places (Budson and Price, 2005). The impairment of episodic memory is dominant in Alzheimer's disease (AD) and is a prodrome of AD (Kidd, 2008). Recently, it was reported that impairments in episodic memory were present in both early onset depression (EOD) and LOD (Herrmann et al., 2007); however, compared with recurrent EOD, LOD results in more severe impairments in the memory domains (Delaloye et al., 2008; Dillon et al., 2009) and tends to develop into dementia. Additional evidence has suggested that compared to EOD, LOD shows a greater reduction in pyramidal neurons (Khundakar et al., 2009; Rajkowska et al., 2005), more severe atrophy of hippocampal volume (Hickie et al., 2005; Lloyd et al., 2004; Steffens et al., 2000), and higher levels of plasma amyloid beta-42 (Blasko et al., 2010), which may be pathologies or biomarkers of AD and amnestic mild cognitive impairment (aMCI). In addition, AD with depression leads to increased hippocampal plaques

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and tangles and more rapid cognitive decline than AD without depression (Rapp et al., 2006). A number of factors may contribute to LOD being the prodrome, or early clinical manifestation, of AD.

Advances in the development of MRI techniques and network analyses have made it possible to investigate the neurocircuits underlying the complex relationship between depressive symptoms and episodic memory deficits in rLOD patients. Preliminary studies on the relationship between the influences of two behaviours on a large-scale neural network level have been performed. Our group has found that both remitted geriatric depression patients and aMCI patients had global, abnormal topology of their white matter structure (Bai et al., 2012, 2009b, 2009c; Yuan et al., 2007), which is the basis of the functional connectivity (FC) network. Accompanying the structural network abnormalities, abnormal subregions in the amygdala-based functional connectivity network of aMCI patients with depression overlapped with areas of the memory network (Xie et al., 2012) further it was confirmed by the hippocampal FC network (Goveas et al., 2011). These findings suggest that there may be a common basis for abnormal neural networks in rLOD and aMCI patients, with minor differences.

The default mode network (DMN) is a prominent, large-scale brain network that includes the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), medial temporal lobes (MTL), dorsolateral prefrontal cortex (dlPFC) and inferior parietal lobe (IPL) (Greicius et al., 2003; Zhang et al., 2010). The DMN appears to mediate internally generated thought processes and is typically inhibited during fMRI tasks that require subjects to attend to cognitively demanding and external stimuli (Mevel et al., 2011), such as memory tasks (Spreng and Grady, 2010). The disruption of functional connectivity within the DMN has been widely reported in mental disorders, such as schizophrenia, autism spectrum disorder, attention deficit/hyperactivity disorder and major depression (MD) (Broyd et al., 2009). However, some findings suggest that the DMN is correlated with emotional processing in MD. It has been reported that during emotional processing several subregions of the DMN in MD patients showed a significant reduction in negative blood oxygenation level-dependent (BOLD) responses, which were correlated with severity of depression and feelings of hopelessness (Grimm et al., 2009). A resting-state FC study demonstrated a significant increase in subgenual cingulate and thalamic functional connectivity that was disproportionately driven by activity in the subgenual cingulate (Greicius et al., 2007) and deficits in DMN connectivity between the PCC and the caudate, which may be an early manifestation of the MD (Bluhm et al., 2009). Accordingly, it is possible that the DMN may be the primary neural network for studying the complex relationships among depressive symptoms, episodic memory deficits and other emotional or cognitive abnormalities. It is regrettable that no study has focussed on the DMN in rLOD, a special type of depression.

The APOE4 allele is a major genetic risk factor for late-onset AD (Strittmatter et al., 1993). This allele is associated with an increased risk for and the aggravation (cognitive decline) of AD (Williams et al., 2010). Furthermore, APOE4 acts in a dose-dependent manner; having a greater number of APOE alleles confers a substantially greater risk for AD and predicts a younger age of onset (Corder et al., 1993). More severe impairments were obvious and included Aβ depositions, neurofibrillary tangles (Tiraboschi et al., 2004) and structural atrophy shown by MRI (Juottonen et al., 1998). In addition, APOE4 has been reported to be associated with lower cognitive function than other alleles (Schmidt et al., 1996; Tervo et al., 2004), increases in fMRI activity, particularly in the association cortex (compensatory mechanism) (Bookheimer et al., 2000), and abnormal neural networks in normal elderly patients (Hafkemeijer et al., 2012). However, the relationship of APOE4 with disease progress has not been consistent in cases of LOD and rLOD. It was reported that patients with LOD and APOE4 displayed cognitive impairments (Krishnan et al., 1996), and additional studies suggested that elderly depressed patients with cognitive impairment were at risk for developing AD through an APOE4-independent pathway, while those with psychotic features were at risk for developing AD through an APOE4-dependent pathway (Zubenko et al., 1996). However, neither LLD accompanying cognitive impairment nor late age of onset was associated with an increased APOE4 allele frequency (Butters et al., 2003). Therefore, the relationships between APOE status, cognitive function and alterations in the neural networks of rLOD patients are of great interest.

In this study, we tested the hypothesis that there are altered resting-state and episodic memory functional connectivities that are correlated with memory deficits in rLOD patients. We studied the relationship between APOE status, cognitive function and alterations in the neural networks of rLOD patients. This study will contribute to our understanding of the role of the PCC in the pathophysiology of rLOD and the relationship between LOD and AD.

2. Materials and methods

2.1. Materials

All participants met the following inclusion criteria: (1) Hamilton Depression Rating scale (HDRS) scores lower than 7 and Mini-Mental State Examination (MMSE) scores higher than 24; (2) no reported history of psychiatric diseases, including substance abuse or dependence; (3) absence of primary neurological illness, including dementia or stroke; (4) absence of medical illness impairing cognitive function, such as diabetes; and (5) absence of any white matter changes observed in a T2-weighted MRI, such as infarction or other vascular lesions. All rLOD patients (1) were assessed with a semi-structured interview that was included in the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version (First et al., 1997), by two trained senior psychiatrists (Y. Yuan and J. You), and it was confirmed that the patients had previously met the DSM-IV criteria for MD and had been in remission for more than 6 months before enrolment; (2) had no reported history of receiving electroconvulsive therapy (ECT); (3) had no reported history of psychiatric disease, such as depression, anxiety or schizophrenia; (4) had their first depressive episode after the age of 60; and (5) had a disease course that was shorter than 5 years and a medication-free period of longer than 3 months prior to the assessment. The rLOD patients in our study were recruited from the Nanjing Brain Hospital Affiliated to Nanjing Medical University and the healthy control subjects (HC) were recruited from outpatients at the hospital and from the community. The study was approved by the Research Ethics Committee of ZhongDa Hospital Affiliated to Southeast University and Nanjing Brain Hospital Affiliated to Nanjing Medical University, and signed informed consent was obtained from all participants.

2.2. Neuropsychological test

All subjects received a cognitive battery assessment that was administered in a standardised manner by two psychiatrists (Y. Yuan and J. You). The neuropsychological battery consisted of the Rey Auditory Verbal Learning Test (RAVLT), the Trail Making Test A and B, the Clock Drawing test, the Rey–Osterrieth Complex Figure Test-Delayed Recall and the Digit Span test. Table 1 contains the descriptive demographic and neuropsychological data for the two groups. Genomic DNA was extracted from 250 μl of whole blood using a DNA direct kit (Omega Bio-Tek,

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