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Amygdala network dysfunction in late-life depression phenotypes: Relationships with symptom dimensions

Wenjun Li [a, b], B. Douglas Ward [b], Chunming Xie [b], Jennifer L. Jones [c], Piero G. Antuono [c], Shi-Jiang Li [a, b], Joseph S. Goveas [a, *]

[a] Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA
[b] Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA
[c] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

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ABSTRACT

The amygdala, a crucial hub of the emotional processing neural system, has been implicated in late-life depression (LLD) pathophysiology. However, the overlapping and diverging amygdala network function abnormalities underlying two clinical LLD phenotypes (i.e., LLD alone and LLD with mild cognitive impairment [LLD-MCI]) are unknown. The aim of this study is to investigate the amygdala functional connectivity (FC) differences between LLD alone, LLD-MCI and healthy controls, and to examine the relationships between amygdala network dysfunction and symptom dimensions. A resting-state functional connectivity magnetic resonance imaging study was conducted to probe amygdala FC in a total of 63 elderly participants (LLD [n = 22], LLD-MCI [n = 15], and age- and gender-equated healthy older adults [n = 26]) using a seed-based voxelwise R-fcMRI approach. LLD-only adults showed increased FC in the posterior default mode and vermis, and diminished connections in the fronto-parietal, salience and temporal areas, relative to controls. The LLD-MCI participants showed diminished FC in the default mode, cognitive control, salience and visual regions, whereas increased FC was limited to lateral parietal cortex compared with healthy controls. The LLD-MCI group also showed diminished FC in the occipital and posterior default mode areas, relative to the LLD-only group. Distinct amygdala FC abnormalities that explain depressive and anxiety symptom severity, and executive functioning were identified. The amygdala FC impairments may distinguish LLD phenotypes. These functional network abnormalities may also explain the heterogeneity seen in the LLD clinical presentations.

1. Introduction

Late-life major depression (LLD) presents with considerable cognitive symptom heterogeneity; while some have intact cognitive functioning, others with greater illness severity demonstrate impairments in memory, information processing speed and executive function performances (Butters et al., 2004). In addition, depression often coexists with mild cognitive impairment (MCI) in the elderly (Bhalla et al., 2009). The complex bidirectional and reciprocal relationships between depressive and cognitive symptomatology in late life suggests that distinct, as well as overlapping, neurophysiologic features might underlie two common phenotypic presentations of LLD (i.e., LLD with and without comorbid MCI).

Despite age-related decline in many cognitive domains, emotional processing function is well preserved and sometimes enhanced in healthy older adults (Charles, 2010). The improvements in emotional processing with age are supported by the 'cognitive control' hypothesis of healthy aging. This theoretical construct postulates that the positivity effect seen in older adults is a result of executive control brain regions exerting greater regulation on limbic areas that process negative emotional stimuli (Mather, 2012; Mather and Knight, 2005). The amygdala, a medial temporal lobe (MTL) brain region and a crucial hub of the emotional processing neural system, plays a vital role in

* Corresponding author. Medical College of Wisconsin, Department of Psychiatry and Behavioral Medicine, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA.
E-mail addresses: wli@mcw.edu (W. Li), ward@mcw.edu (B.D. Ward), cxie@mcw.edu (C. Xie), jljones@mcw.edu (J.L. Jones), pantuono@mcw.edu (P.G. Antuono), sjli@mcw.edu (S.-J. Li), jgoveas@mcw.edu (J.S. Goveas).

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processing threats and triggering various responses to emotionally valenced stimuli. The amygdala is closely interconnected with important brain regions that subserve multidomain cognitive functions, and is central to diverse cognitive–emotional interactions (Pessoa, 2008). In line with the cognitive control hypothesis, extensive observations of dampened amygdala and posterior cortical regional reactivity, and enhanced frontal activation in response to emotionally laden stimuli, have been reported in older adults compared with their younger counterparts (Gunning-Dixon et al., 2003; St Jacques et al., 2009; Tessitore et al., 2005). Emotional processing dysregulation is considered a core feature of major depression, including LLD. Although accumulating studies implicate the amygdala in LLD pathophysiology (Burke et al., 2011), the amygdala network function abnormalities in LLD were not previously investigated.

Task-based functional magnetic resonance imaging (T-fMRI) studies have provided unique insights into the role of fronto-limbic circuitry underlying emotional and cognitive changes associated with LLD (Aizenstein et al., 2005, 2009; Wang et al., 2008; Wang et al., 2012). Using various emotional and cognitive paradigms, prior studies have reported frontal hypoactivity (Aizenstein et al., 2005, 2009) and increased limbic activation in some (Aizenstein et al., 2005) but not all (Naismith et al., 2010) LLD studies. Although T-fMRI studies provide unique information as to how specific brain regions respond during a particular task, they offer little information into how functionally related structures serve as interconnected nodes of a dynamic brain network. Moreover, this imaging modality is prone to task-related motion artifacts and false-negative findings because of compromised performance during demanding stimuli in older depressed adults with varying cognitive function levels.

Resting-state functional connectivity MRI (R-fcMRI) is a task-free imaging method increasingly utilized to probe brain network dysfunction in neuropsychiatric disorders, including LLD (Li et al., 2014; Tadayonnejad and Ajilore, 2014). The R-fcMRI technique measures temporal interregional correlations of spontaneous low-frequency blood oxygenation level-dependent fluctuations between functionally connected but spatially separated brain regions at rest (Biswal et al., 1995). Abnormal functional connectivity (FC) in the default mode, executive control and reward processing brain networks has been previously reported in LLD compared with normal older individuals (Alexopoulos et al., 2012, 2013; Wu et al., 2011). Recently, more pronounced FC vulnerabilities in the hippocampal memory networks were demonstrated in patients with LLD and MCI comorbidity compared with older adults with either disorders occurring alone (Xie et al., 2013). A lone study focusing on the amygdala also examined main and interactive relationships between depressive symptoms and memory performance in elderly subjects (Xie et al., 2012a); however, amygdala FC abnormalities in different phenotypic presentations of LLD have not yet been examined.

This study's primary objective was to investigate the amygdala FC in individuals with LLD alone, LLD comorbid with MCI and age- and gender-equated healthy elderly. Based on the evidence from previously published functional activation and R-fcMRI aging studies using healthy and LLD participants, we hypothesized that the LLD-only group would show diminished amygdala FC with executive control nodes and increased FC with posterior default mode network regions. We also hypothesized that the comorbid group would show globally diminished amygdala FC in similar brain regions that were associated with poorer cognitive performance in older adults, as evidenced in a previous study. Secondarily, we examined the amygdala FC differences that explained the variance in depressive symptom severity and multidomain cognitive performance within each group.

2. Methods

2.1. Participants

A total of 63 participants aged 60 or older participated in this cross-sectional study. The participant groups included cognitive normal healthy controls (CN: n = 26), late-life depression (LLD: n = 22), and LLD with mild cognitive impairment (LLD-MCI: n = 15). All patients diagnosed as having LLD and/or MCI were recruited from the Medical College of Wisconsin (MCW) Geriatric Psychiatry and Memory Disorders Clinics. Control subjects were recruited from the community through local advertisements. All participants provided written informed consent according to MCW Institutional Review Board-approved protocols.

Study participants received detailed clinical and neuropsychiatric assessments, as described previously. The core neuropsychological battery administered to all participants included the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Mattis Dementia Rating Scale-2 (MDRS-2) (age- and education-corrected MOANS-scaled score of ≥5) (Lucas et al., 1998), education-adjusted Logical Memory II Delayed paragraph recall (LMII-DR) subscale from the Wechsler Memory Scale-Revised (Wechsler, 1987), Physical Self Maintenance Scale/Instrumental Activities of Daily Living (PSMS/IADL) (Lawton and Brody, 1969), 30-item Yesavage Geriatric Depression Scale (GDS) (Yesavage et al., 1982), Diagnostic assessment for Axis 1 disorders, including the depression module from the Structured Clinical Interview for DSM IV (SCID) (First et al., 2002), and Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959). All participants scored ≤4 on the modified Hachinski Ischemic Scale (HIS). Clinical assessment findings were reviewed during the weekly consensus conferences attended by neurologists, neuropsychologists and a geriatric psychiatrist. Age of onset of first episode of major depression was obtained from all depressed participants.

Inclusion criteria:

(1) LLD included a GDS score of 10 or above, MMSE ≥ 24, PSMS ≤ 6 and IADL ≤ 9, score above the education-adjusted cutoff on the LMII-DR (Delayed recall score > 8 for 16 or more years of education or score > 4 for 8–15 years of education), and SCID depression module positive for major depression. Because clinically significant anxiety often coexists with LLD, we did not exclude patients with HAM-A scores ≥17, if the study psychiatrist determined that the primary diagnosis was a depressive disorder.

(2) LLD-MCI: All subjects who met the MCI criteria (amnestic MCI: n = 13; nonamnestic MCI: n = 2), scored 10 or above on the GDS and were SCID depression module positive for major depression were included in this group. To be included in this group, participants had to meet the MCI criteria prior to being diagnosed with the current depressive episode. One amnestic MCI subject who scored 9 on the GDS and met the SCID criteria for dysthymic disorder was included in this group. One subject in this group also had an HAM-A score ≥17.

MCI was operationally defined according to the established criteria (Winblad et al., 2004): subjective report of cognitive decline, objective cognitive impairment that includes scoring 1.5 SD below on memory and/or nonmemory measures (see below), intact activities of daily living (ADLs) and relatively preserved instrumental ADLs (IADLs) and no dementia. Participants met the clinical diagnosis of amnestic MCI or nonamnestic MCI, MMSE score ≥24, age- and education-corrected MOANS-scaled score of ≥5, and score in the normal range on the PSMS and IADL scales. (a) Amnestic MCI: