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Amygdala Network Dysfunction in Late-Life Depression Phenotypes: Relationships with Symptom Dimensions

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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

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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.

Keywords

Depression; mild cognitive impairment; amygdala; functional connectivity; MRI; depressive symptoms; elderly; late-life; symptom dimensions

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 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; Aizenstein *et al.*, 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; Aizenstein *et al.*, 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; Alexopoulos *et al.*, 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.

METHODS

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: In meeting the criteria for objective cognitive impairment, participants had to score below the education-adjusted cutoff on the LMII-DR (i.e., ≤ 8 for 16 or more years of education, and ≤ 4 for 8–15 years

of education), and score 1.5 SD below the mean on one or more subscales (one of the impairments had to be memory) of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Immediate Memory, Visuospatial Ability, Language, Attention, Delayed Memory) (Randolph, 1998). One amnestic MCI subject did not complete the RBANS. (b) Nonamnestic MCI: For meeting the criteria for objective cognitive impairment, participants had to score within normal limits on the LMII-DR and 1.5 SD below the mean on one or more nonmemory subscales of the RBANS.

3. **CN**: The eligibility criteria were similar to those used for the LLD cohort, *except* these subjects could not meet criteria for any Axis 1 disorders or be on psychoactive medications. *Exclusion criteria* included past or current history of concurrent Axis 1 psychiatric disorders, such as psychotic or bipolar disorders; alcohol or substance abuse/dependence during the past five years; active suicidality; MMSE scores < 24; history of neurological disease, including Parkinson's disease, dementia, multiple sclerosis, seizures, or stroke; head injury with loss of consciousness; MRI contraindications and unstable chronic medical conditions.

MRI Data Acquisition

All MRI scans were acquired using a GE 3T whole-body scanner (GE, Waukesha, Wisconsin, USA) with a standard transmit-receive quadrature head coil. These included an 8-min task free R-fcMRI scan using a single-shot gradient echo-echo planar (EPI) imaging and a 6-min high-resolution three-dimensional spoiled gradient-recalled echo (SPGR) pulse sequences. All participants were instructed to close their eyes and relax during the scans. The R-fcMRI imaging parameters were: TE = 25 ms, TR = 2000 ms, flip angle (FA) = 90°, number of slices = 36, slice thickness = 4 mm, matrix size = 64 × 64, and field of view (FOV) = 240 × 240 mm. The SPGR axial images were acquired for anatomical reference with parameters: TE = 3.2 ms, TR = 8.2 ms, TI = 450 ms, FA = 12°, number of slices = 150, slice thickness = 1 mm, matrix size = 256 × 192, and FOV = 240 × 240 mm^2.

MRI Data Processing

R-fcMRI data preprocessing was performed using AFNI software (http://afni.nimh.nih.gov/afni), FSL software (http://fsl.fmrib.ox.ac.uk/) and MATLAB programs (The MathWorks Inc., Natick, Mass.), as described previously (Li *et al.*, 2014; Xie *et al.*, 2012a; Xie *et al.*, 2013). Briefly, outlier points in the time series were removed followed by volume registration, estimation of the motion parameters, and detrending using linear least squares. Participants who had images with translational motion > 2mm or rotational 2° were re scanned to minimize motion artifacts. Next, nuisance signals, such as from physiological noise (cardiac and respiratory), white matter (WM), cerebrospinal fluid (CSF), and six rigid-body motion vectors were regressed out from each time series. The only difference was that global signal regression was not performed because of concerns that this procedure may artificially introduce anti-correlated FC results (Murphy *et al.*, 2009). Finally, a band-pass filter (0.015Hz to 0.1Hz) was applied to obtain only the low-frequency fluctuations portion of the data.

Structural MRI data was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using VBM8 toolbox in Statistical Parametric Mapping (SPM) software (http://www.fil.ion.ucl.ac.uk/spm).

Amygdala Functional Connectivity

The seed-based R-fcMRI method was used to examine the whole-brain voxelwise resting-state FC of the amygdala. The bilateral amygdala seed region of interest (ROI) was manually traced on the axial slices with reference to the sagittal and coronal slices of the high-resolution SPGR images, as described previously (see supplement for details) (Honeycutt *et al.*, 1998; Xie *et al.*, 2012a).

The high-resolution amygdala tracing ($0.98 \times 0.98 \times 1$ mm^3) was then downsampled to match the resolution of the R-fcMRI data ($3.75 \times 3.75 \times 4$ mm^3). Only voxels in the R-fcMRI that were at least 70% occupied by the traced amygdala voxels in the structural images were included in the amygdala seed ROI in the further analyses to accommodate the resolution difference. Pearson product-moment correlation was used to obtain a whole-brain amygdala functional connectivity (AFC) map for each participant by cross-correlating between the mean time course of the amygdala seed and the time courses of all voxels within the entire brain. Next, the correlation coefficient (cc) maps were subjected to Fisher's z-transformation to obtain an approximately normally distributed m = 0.5*ln{(1+cc)/(1-cc)}. Finally, each individual AFC map was spatially transformed to the Montreal Neurological Institute (MNI) space, followed by smoothing of the image, using a 6-mm Gaussian kernel.

Statistical Analysis

Demographic information (age and education), except gender (using χ^2-tested), and neuropsychological measurements were compared among the three participant groups, using analysis of variance (SPSS 18.0; SPSS Inc., Chicago, Ill.). Post-hoc Fisher's Least Significant Difference Test examined the sources of the differences between the means of the three groups.

One-sample *t*-tests were used to obtain the AFC patterns in each participant group separately. Analysis of covariance (ANCOVA) was used to examine the differences in voxelwise AFC among the three participant groups, while controlling for age, gender, education and voxelwise whole-brain GM volume (GMV). Post-hoc *t*-tests revealed sources of between-group differences within the ANCOVA results. We adopted a built-in AFNI program (3dClustSim), a type of Monte Carlo simulation method, to correct for the multiple comparisons (voxelwise $p < 0.05$, $\alpha < 0.05$, and cluster size > 3960 mm^3).

Stepwise linear regression was used to investigate the relationships between neuropsychological measures (GDS, LMII-DR, HAM-A and MDRS-2 Initiation/Perseveration [Init/Pers] scores, respectively) as dependent variables and the set of regressors, including age, gender, education, GMV, and mean AFC of brain regions (10 ROIs determined by ANCOVA), as independent variables. The regression analyses were conducted separately in each participant group. The forward selection approach was used to determine the subset of regressors that significantly contributed to the linear model by

individually adding the most statistically significant regressors until no further regressor met the p-value entrance criterion. The statistical threshold for a regressor to be added to the model was set at $p < 0.05$. We used this approach to reduce the number of regressors included in the linear model, because the smaller sample sizes, particularly for the LLD-MCI group (N = 15), limited the degrees of freedom available to determine the best model fit.

RESULTS

Demographic and Neuropsychiatric Characteristics

No significant ($p > 0.05$) differences were found in age, gender, and education among the three groups. Age of depression onset did not significantly differ between the two LLD groups (p= 0.225). The neuropsychiatric characteristics are summarized in Table 1.

Voxelwise Whole-Brain Amygdala Functional Connectivity

(1) Within group AFC pattern—The within group AFC network patterns for CN, LLD, and LLD-MCI groups are shown in Figure S1. The positive AFC was found in the middle temporal gyrus (MTG), middle and inferior occipital gyrus (MOG and IOG), fusiform gyrus (FFG), superior parietal lobe (SPL), inferior frontal gyrus (IFG), insula, caudate, anterior and posterior cingulate gyrus (ACC and PCC), parahippocampal gyrus (PHG), and hippocampus. The negative AFC was found in the dorsolateral prefrontal gyrus (DLPFC), lateral inferior parietal lobe (Lat. IPL), thalamus, and retrosplenial cortex.

(2) ANCOVA and post-hoc differences—The ANCOVA showed brain regions with altered AFC in the depressed groups compared with the CN group ($p < 0.05$, cluster size > 3960 mm^3) (Figure 1 and Table 2). Post-hoc t-tests revealed sources of between-group differences (Figure 2).

a) LLD versus CN: Relative to CN subjects, LLD subjects showed significantly *diminished* AFC in the right SPL, IFG, middle frontal (MFG), precentral (PreCG) and inferior temporal gyri (ITG), and temporal pole (TP). The left Lat. IPL and right PCC and the cerebellar vermis showed *increased* AFC in the LLD group (Figure 2, top).

b) LLD-MCI versus CN: The largest AFC difference was observed between LLD-MCI and CN groups. Compared with the CN, the LLD-MCI group showed *decreased* AFC in the bilateral IOG and MOG, FFG, SPL, PreCG; right IFG and MFG; and left TP, PHG, hippocampus, MTG, and cuneus. Only the left Lat. IPL showed *increased* AFC in the LLD-MCI compared with the CN group (Figure 2, middle).

c) LLD-MCI versus LLD: *Decreased* AFC in IOG, MOG and FFG bilaterally; and cuneus, TP, and MTG on the left were seen in LLD-MCI compared with LLD group (Figure 2, bottom).

Stepwise Linear Regression

In the *LLD* group (Figure 3A), GDS (R^2 = 0.26, p = 0.0159) and HAM-A (R^2 = 0.21, p = 0.0327) correlated with the mean AFC in the left MTG. In the *LLD-MCI* group (Figure 3B), GDS (R^2 = 0.68, p = 0.0048) correlated with the mean AFC in right IOG/MOG/FFG, PCC, and left TP/PHG/hippocampus clusters. The DRS-2 Init/Pers (R^2 = 0.78, p = 0.0001) correlated with the mean AFC in the left TP/PHG/hippocampus, and right vermis clusters. LMII-DR (R^2 = 0.16, p = 0.0397) and DRS-2 Init/Pers (R^2 = 0.15, p = 0.0479) correlated with education and GMV in the *CN*, respectively (Figure S2).

DISCUSSION

The primary finding was that diminished amygdala functional connectivity with the fronto-parietal regions and increased connections in the posterior default mode areas and cerebellar vermis distinguished cognitively intact LLD patients from normal older individuals. The LLD-MCI subjects showed dampening in the enhanced amygdala-posterior DMN connectivity. Furthermore, globally decreased functional connections with other regions subserving emotional processing and cognitive functions were seen in individuals with comorbidity. In the secondary analysis, specific amygdala FC abnormalities that explain variations in the severity of depressive and anxiety symptoms, and executive function performance, were observed in the depressed groups. Our findings support the amygdala network function role and highlight the impairments in its functional interconnections with other emotional processing and intrinsic resting-state network hubs in differentiating common clinical presentations of LLD.

Amygdala Functional Connectivity Abnormalities in LLD

The amygdala FC pattern identified in healthy older adults includes brain regions that are commonly activated to emotional processing task paradigms in functional MRI studies of young and elderly subjects (Fusar-Poli *et al.*, 2009; Gunning-Dixon *et al.*, 2003; Tessitore *et al.*, 2005). In using R-fcMRI, we were able to provide novel evidence supporting the role of the amygdala as a crucial emotional processing network hub in older adults.

Our findings demonstrated decreased FC between the amygdala and cognitive control regions in patients with LLD. DLPFC hypoactivity during cognitive control tasks was consistently observed in younger and older patients with depression (Aizenstein *et al.*, 2005; Siegle *et al.*, 2007). Diminished cognitive control network function was also reported in older depressed adults (Alexopoulos *et al.*, 2012). The cognitive control neural system enables efficient information processing to flexibly adapt to changing environmental and personal demands, and is critical for carrying out attention-dependent executive function tasks. These brain areas also downregulate emotional responses to negatively valenced stimuli, thereby leading to positivity effect in the elderly (Mather, 2012). In this regard, dampened functional connections between the amygdala and cognitive control brain resources observed here may underlie executive dysfunction and/or impaired downregulation of emotional processing in LLD. Our LLD-only participants had relatively preserved executive function performance (i.e., normal DRS-2 Init/Pers scores). We postulate that abnormal amygdala-cognitive control connectivity is associated with

executive dysfunction in LLD patients and should be examined in future studies. LLD patients showed increased amygdala connectivity primarily in the posterior DMN regions. Stimulus-induced heightened activity and a failure to downregulate activity within the DMN are reported in major depression (Sheline *et al.*, 2009). Interestingly, a phenomenon of "double dissociation," i.e., increased DMN and diminished cognitive control FC, has been previously reported in LLD compared with normal older adults (Alexopoulos *et al.*, 2012; Smith *et al.*, 2009). The DMN consists of multiple interacting subnetworks that are engaged when performing divergent cognitive and behavioral functions (Buckner *et al.*, 2008). Abnormal amygdala FC in specific DMN nodes, therefore, may lead to different symptom dimensions in those with LLD. For instance, the increased amygdala FC with distinct DMN regions may be associated with abnormal self-referential thought processes and increased negative rumination, greater depressive and anxiety symptoms (e.g., MTG, as observed in this study), memory encoding and retrieval functions, and navigating social events (Buckner *et al.*, 2008).

A substantial body of literature provides evidence of the involvement of the cerebellum in emotion and cognitive functions and is linked to major depression pathophysiology (Schmahmann, 2010)(Schmahmann *et al.*, 2007). Aberrant cerebellar-cerebral connectivity was also associated with affective and cognitive dysfunction in geriatric depression in a prior investigation (Alalade *et al.*, 2011). The increased amygdala-vermis connectivity observed here further highlights the region's importance in the neurobiological underpinnings of LLD.

Amygdala Network Dysfunction in LLD-MCI

Consistent with the LLD-only group findings, those with coexisting LLD and MCI also exhibited diminished amygdala FC in the fronto-parietal areas compared with healthy elderly. This suggests that the disrupted downregulation of negative affect by the cognitive control neural system is also present in individuals with LLD-MCI comorbidity.

By contrast, amygdalar connections with the posterior default mode clusters showed somewhat divergent abnormalities compared to those observed in the LLD-only group. The amygdala-IPL connectivity remained enhanced, which was likely a result of diminished cognitive control associated with syndromal depression. Decreases in FC between the amygdala and posterior default mode nodes, as well as the visual cortices, were seen in those with coexisting LLD and MCI, relative to other groups. We recently demonstrated that decreased amygdala FC in certain default mode (i.e., PCC, MTG) and visual cortices (i.e., MOG) were associated with poorer memory scores in older adults. The interactive effects of depressive symptoms and memory performance on the amygdala network function also were seen in the PCC and temporal lobe regions in older nondepressed adults (Xie *et al.*, 2012a). Longitudinal amygdalar FC declines in these regions also correlated with episodic memory changes over time in nondepressed MCI subjects (Yao *et al.*, 2014). We did not find abnormal amygdala functional connections in DMN and visual cortices to be related to memory performance in the comorbid group; rather, amygdala FC abnormalities were associated with depressive symptoms (e.g., in the MTL and visual cortices) and executive function scores (e.g., in the MTL and vermis) in this study. These novel findings suggest

that the amygdala FC abnormalities with specific DMN nodes, visual cortices, and the vermis may explain different behavioral dimensions commonly encountered in those with comorbidity.

Possible Pathophysiological Mechanisms

Our findings of diminished functional connections between the amygdala and fronto-parietal regions and enhanced connectivity with the posterior DMN and vermis lend support to the disrupted cognitive control model of LLD. The impaired abilities of the executive control brain areas in regulating emotions may be a result of ischemic damage to the fronto-limbic white matter tracts in older adults with depression. A few studies have examined the relationships between white matter compromise and brain network dysfunction in LLD, but the results are inconsistent (Aizenstein *et al.*, 2011; Steffens *et al.*, 2011). Thus, the role of WM tract compromise in explaining amygdala network dysfunction in LLD requires additional clarification. Our preliminary results in the comorbid group point to the possibility that multiple mechanisms may underlie network dysfunction when LLD emerges in individuals with MCI. While some findings in the comorbid group might still be explained by the disrupted cognitive control hypothesis of LLD, different mechanisms might be driving the diminished amygdala function with other default mode nodes and visual cortices. A possible additional mechanism in those with comorbidity could be neurodegeneration. While our results remain significant even after controlling for GMV, regional amygdala atrophy might still be driving our findings. Greater MTL atrophy is associated with the coexistence of LLD and MCI compared with either disease occurring alone (Xie *et al.*, 2012b). Since age of depression onset has been associated with reduced MTL volume in LLD, we performed exploratory analysis, but did not find any associations between the age of onset and amygdala FC differences in either depression groups.

Limitations

The modest sample size in the comorbid group is an important limitation. The majority of our LLD participants (in both groups) were taking antidepressants. Therefore, we are unable to distinguish medication effects from those associated with the disease itself. Also, we have made interpretations based on these cross-sectional data. Therefore, we are unable to comment on causal relationships. Other variables related to depression that might influence functional connectivity and behavioral measures (such as duration of current depressive episode, past medication trials and antidepressant treatment response history) were not considered in this study. Spurious correlations in R-fcMRI data may continue to persist even after monitoring for head motion in real time and performing motion regression. An independent component analysis-denoising procedure may serve as an alternate method to improve overall FC measurements (Griffanti *et al.*, 2014). Effective connectivity methods (Friston *et al.*, 2013) may provide additional insight into the directionality of FC between the amygdala and other emotional processing and intrinsic network brain regions. Finally, multiple comparison corrections were not conducted for stepwise linear regression analyses. Regardless, the findings in the LLD-MCI group remain significant (Figure 3B) even if a Bonferroni correction procedure is applied ($p=0.0125$, i.e., correcting for separate regression analyses for four behaviors).

Conclusion

We demonstrate that distinct and overlapping abnormalities exist in the amygdala network function in LLD patients with and without MCI. The amygdala network function abnormalities might differentially contribute to the emergence and persistence of mood, anxiety, neurovegetative and cognitive symptoms in LLD phenotypes. Future research using comprehensive neuropsychological and behavioral evaluations coupled with multimodal neuroimaging approaches is essential to determine amygdala network function and structure in different LLD phenotypes, and to evaluate the underlying mechanisms that contribute to network dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Diminished amygdala functional connectivity with the fronto-parietal regions and increased connections in the posterior default mode areas and cerebellar vermis distinguished cognitively intact late-life depression (LLD) patients from normal older individuals.
- The LLD with mild cognitive impairment (LLD-MCI) subjects showed dampening in the enhanced amygdala-posterior default mode network connectivity.
- Globally decreased functional connections with other regions subserving emotional processing function were seen in those with comorbidity, relative to the other groups.
- Specific amygdala functional connectivity abnormalities that explain variations in the severity of depressive and anxiety symptoms, and executive function performance were observed in the depressed groups.
- Our findings support the amygdala network function role and highlight the impairments in its functional interconnections with other emotional processing and intrinsic resting-state network hubs in differentiating common clinical presentations of LLD.

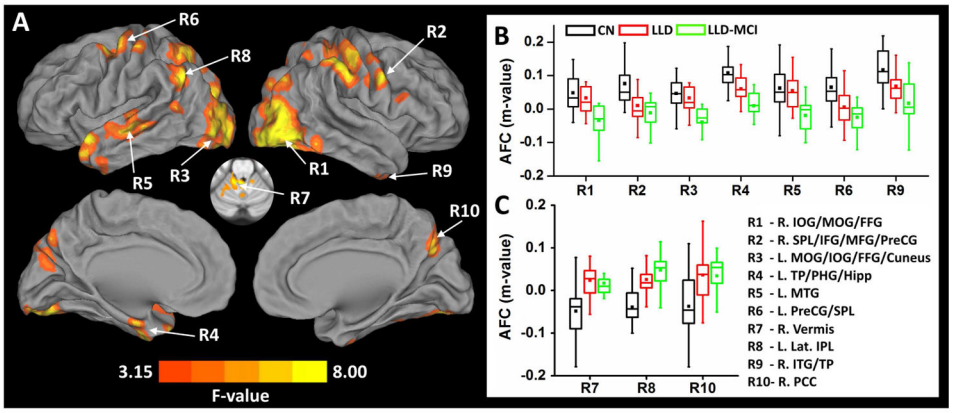

Figure 1.

Analysis of covariance (A) illustrates the brain regions with significantly altered Amygdala Functional Connectivity (AFC) in LLD and LLD-MCI patients, when compared between the patient groups and CN group ($p < 0.05$ and cluster size > 3960 mm^3). Boxplots (B) and (C) indicate the data distribution in individual groups with decreased AFC and increased AFC in the patient groups compared with CN group, respectively. In the boxplots, the band inside the box indicates the median point, the bottom and top box indicate 25% and 75% respectively, and the whiskers indicate 1.5 standard deviation of the data. The mean is displayed as colored squares within each boxplots.

Abbreviations – IOG: inferior occipital gyrus, MOG: middle occipital gyrus, FFG: fusiform gyrus, SPL: superior parietal lobule, IFG: inferior frontal gyrus, MFG, middle frontal gyrus, PreCG: precentral gyrus, TP: temporal pole, PHG: parahippocampal gyrus, Hipp: hippocampus, MTG: middle temporal gyrus, Lat. IPL: lateral inferior parietal lobule, ITG: inferior temporal gyrus, PCC: posterior cingulate gyrus, CN: cognitively normal healthy controls, LLD: late-life depression, LLD-MCI: late-life depression with mild cognitive impairment.

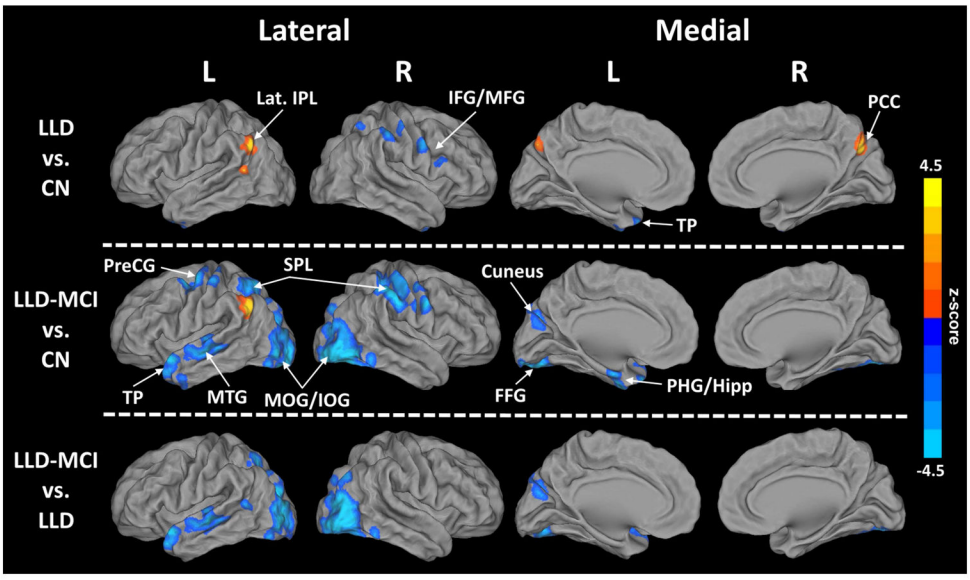

Figure 2.

Post-hoc t-tests depict the sources of analysis of covariance results ($p < 0.05$ and cluster size > 3960 mm^3). Warm colors indicate an increased Amygdala Functional Connectivity (AFC) and cool colors indicate a decreased AFC.

Abbreviations – IOG: inferior occipital gyrus, MOG: middle occipital gyrus, FFG: fusiform gyrus, SPL: superior parietal lobule, IFG: inferior frontal gyrus, MFG, middle frontal gyrus, PreCG: precentral gyrus, TP: temporal pole, PHG: parahippocampal gyrus, Hipp: hippocampus, MTG: middle temporal gyrus, Lat. IPL: lateral inferior parietal lobule, ITG: inferior temporal gyrus, PCC: posterior cingulate gyrus, CN: cognitively normal healthy controls, LLD: late-life depression, LLD-MCI: late-life depression with mild cognitive impairment, L/R: left/right.

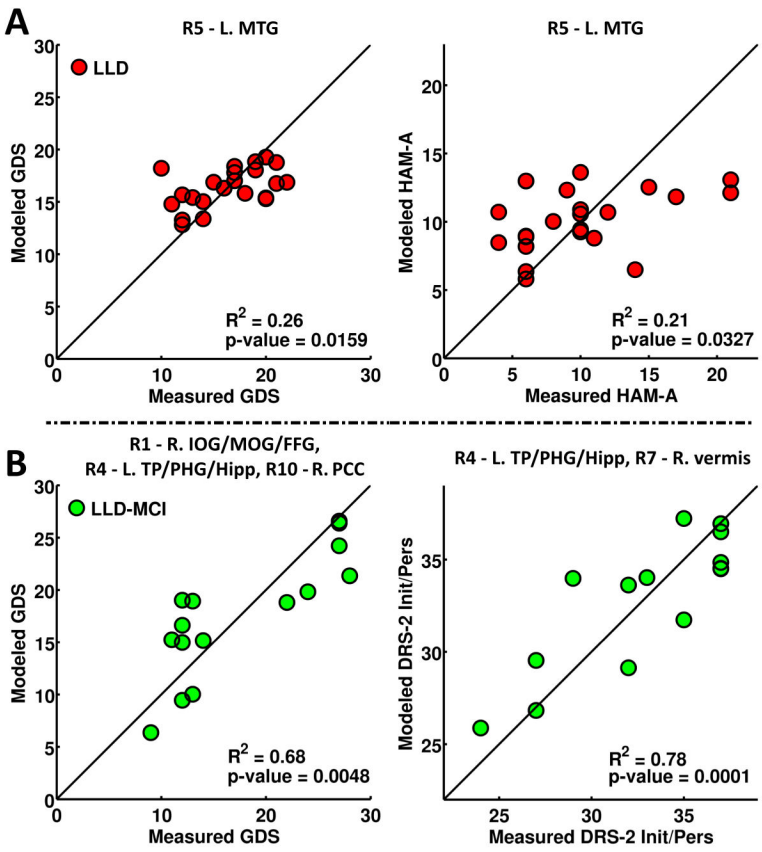

Figure 3.

Stepwise linear regression examining factors correlated with behavioral measures within the LLD and LLD-MCI groups. Modeled behaviors are based only on the significant regressor (listed on top of each plot) through forward selection. The regressors tested include age, gender, education, GMV, and the mean AFC values from the ten brain regions that showed differences.

Abbreviations – IOG: inferior occipital gyrus, MOG: middle occipital gyrus, FFG: fusiform gyrus, TP: temporal pole, PHG: parahippocampal gyrus, Hipp: hippocampus, MTG: middle temporal gyrus, PCC: posterior cingulate gyrus, GMV: gray matter volume, LLD: late-life depression, LLD-MCI: late-life depression with mild cognitive impairment, L/R: left/right.

Table 1

Demographics and Neuropsychological Characteristics

	CN (n = 26) Mean ± SD	LLD (n = 22) Mean ± SD	LLD-MCI (n = 15) Mean ± SD	p-value
Age	71.19 ± 6.95	68.14 ± 5.79	71.73 ± 7.00	0.177
Gender (F/M)	15/11	18/4	8/7	0.123
Education	15.54 ± 2.49	14.91 ± 2.74	13.93 ± 2.96	0.193
Age of depression onset	N/A	32.95 ± 14.93	41.33 ± 22.86	0.225
Neuropsychiatric measurements				
GDS	1.96 ± 2.05	16.36 ± 3.67	17.53 ± 7.23	**<0.001**^{a,b}
MMSE	28.77 ± 1.39	28.27 ± 1.20	26.80 ± 1.82	**<0.001**^{b,c}
HAM-A	1.17 ± 1.17	10.09 ± 4.93	9.33 ± 4.03	**<0.001**^{a,b†}
Recall Scores				
Immediate	14.85 ± 3.59	14.18 ± 3.80	7.60 ± 4.03	**<0.001**^{b,c}
Delayed	12.96 ± 3.17	12.50 ± 3.95	4.47 ± 4.49	**<0.001**^{b,c}
DRS-2 raw scores				
Attention	36.46 ± 0.51	36.41 ± 0.59	36.07 ± 1.10	0.217
Init/Pers	36.42 ± 1.17	36.36 ± 1.92	32.07 ± 5.12	**<0.001**^{b,c}
Construct	5.96 ± 0.20	5.95 ± 0.21	5.87 ± 0.52	0.601
Conceptual	37.65 ± 1.35	36.73 ± 3.51	35.47 ± 3.02	**0.049**^{b}
Memory	23.81 ± 1.10	24.00 ± 1.15	20.33 ± 3.68	**<0.001**^{b,c}
Total	140.35 ± 2.43	139.95 ± 3.11	130.13 ± 6.47	**<0.001**^{b,c}
Current antidepressants (%)				
No antidepressant	N/A	2 (9.1)	2 (13.3)	
SSRI monotherapy	N/A	3 (13.6)	3 (20.0)	
SNRI monotherapy	N/A	5 (22.7)	3 (20.0)	
Other	N/A	3 (13.6)	1 (6.7)	
Combination treatment	N/A	9 (40.9)	6 (40.0)	
Current cognitive enhancers (%)				
No cognitive enhancer	N/A	N/A	11 (73.3)	
ChEI monotherapy	N/A	N/A	2 (13.3)	
Memantine monotherapy	N/A	N/A	2 (13.3)	
Combination treatment	N/A	N/A	N/A	

Notes - ANOVA showed significant differences in GDS, MMSE, HAM-A, Recall scores (immediate and delayed), and DRS-2 raw scores (except for Attention, Construct, and Conceptual).

$^{a–f}$Post-hoc analyses revealed the source of ANOVA (a: LLD vs CN, b: LLD-MCI vs CN, c: LLD-MCI vs LLD).

†Two CN subjects did not have HAM-A scores, the Mean and SD are based on the remaining 24 subjects.

Abbreviations: CN, cognitively normal healthy controls; LLD, late-life depression; LLD-MCI, late-life depression with mild cognitive impairment; SD, standard deviation; F/M, female/male; GDS, geriatric depression scale; MMSE, mini-mental state examination; HAM-A, Hamilton anxiety; DRS-2, dementia rating scale-2; Init/Pers, Initiation/Preservation

Table 2

Amygdala Functional Connectivity (AFC) ANCOVA Results

	Regions	Side	Cluster size (mm^3)	Coordinates (LPI)			Post-hoc z-score			
				X	Y	Z	F-value	LLD vs CN	LLD-MCI vs CN	LLD-MCI vs LLD
R1	IOG	R	26856	−34	85	−7	10.97		−4.06	−3.34
	MOG			−32	85	10	8.06		−2.97	−3.48
	FFG			−36	69	−13	10.75		−4.06	−2.99
R2	SPL	R	26712	−56	25	48	12.33	−2.66	−4.27	
	IFG			−54	−14	22	5.81	−3.19	−2.59	
	MFG			−54	−28	24	7.67	−3.64	−2.58	
	PreCG			−54	0	32	8.12	−2.52	−3.33	
R3	MOG	L	21792	27	85	14	9.51		−3.18	−3.86
	IOG			43	83	−3	8.36		−3.57	−2.84
	FFG			31	73	−15	7.57		−3.63	−2.77
	Cuneus			15	73	20	5.81		−3.06	−2.66
R4	TP	L	7208	51	−10	−13	11.05		−3.92	−3.87
	PHG/Hipp			17	9	−25	6.44		−2.96	
R5	MTG	L	6024	55	19	−5	6.89		−3.23	−3.24
R6	PreCG	L	5208	39	7	56	6.89		−2.83	
	SPL			45	21	52	4.65		−2.54	
R7	Vermis	R	4728	−14	45	−25	7.28	3.39		
R8	Lat. IPL	L	4329	53	49	42	8.16	2.41	3.39	
R9	ITG/TP	R	4200	−34	−2	43	8.17	−2.57		
R10	PCC	R	4016	−10	63	30	5.89	2.7		

Abbreviations – IOG: inferior occipital gyrus, MOG: middle occipital gyrus, FFG: fusiform gyrus, SPL: superior parietal lobule, IFG: inferior frontal gyrus, MFG, middle frontal gyrus, PreCG: precentral gyrus, TP: temporal pole, PHG: parahippocampal gyrus, Hipp: hippocampus, MTG: middle temporal gyrus, Lat. IPL: lateral inferior parietal lobule, ITG: inferior temporal gyrus, PCC: posterior cingulate gyrus, CN: cognitively normal healthy controls, LLD: late-life depression, LLD-MCI: late-life depression with mild cognitive impairment, L/R: left/right.