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Intrinsic inter-network brain dysfunction correlates with symptom dimensions in late-life depression

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ABSTRACT

Prior studies have demonstrated dysfunctions within the core neurocognitive networks (the executive control [ECN], default mode [DMN] and salience [SN] networks) in late-life depression (LLD). Whether inter-network dysfunctional connectivity is present in LLD, and if such disruptions are associated with core symptom dimensions is unknown. A cross-sectional resting-state functional connectivity magnetic resonance imaging investigation was conducted of LLD (n = 39) and age- and gender-equated healthy comparison (HC) (n = 29) participants. Dual regression independent component analysis approach was used to identify components that represented the ECN, DMN and SN. The intrinsic inter-network connectivity was compared between LLD and HC participants and the relationship of inter-network connectivity abnormalities with dimensional measures was examined. Relative to HC participants, LLD subjects showed decreased inter-network connectivity between the bilateral ECN and default mode subcortical (thalamus, basal ganglia and ventral striatum) networks, and the left ECN and SN insula component; and increased inter-network connections between the left ECN and posterior DMN and salience (dorsal anterior cingulate) network components. Distinct inter-network connectivity abnormalities correlated with depression and anxiety severity, and executive dysfunction in LLD participants. LLD subjects also showed pronounced intra-network connectivity differences within the ECN, whereas fewer but significant DMN and SN disruptions were also detected. Investigating the intrinsic inter-network functional connectivity could provide a mechanistic framework to better understand the neural basis that underlies core symptom dimensions in LLD. Inter-network connectivity measures have the potential to be neuroimaging biomarkers of symptom dimensions comprising LLD, and may assist in developing symptom-specific treatment algorithms.

1. Introduction

Late-life depression (LLD) is a recurrent, clinically heterogeneous syndrome that currently is defined by specific psychiatric symptom dimensions, as well as multidomain cognitive dysfunction. LLD is associated with delayed treatment response, leaving many to suffer from persistent emotional distress, poor medical and functional outcomes, cognitive decline, increased suicide rates, and premature mortality (Naismith et al., 2012). Substantial literature suggests that poor treatment outcomes in the depressed elderly are associated with greater symptom severity and cognitive impairment, specifically persistent executive function and episodic memory impairments (Alexopoulos et al., 2005; Andreescu et al., 2007; Gildengers et al., 2005; Sheline et al., 2010a). However, current knowledge regarding the neural substrates of categorically defined LLD provides a limited perspective on the neurobiological mechanisms underlying multiple symptom dimensions comprising this disorder. Regardless, the aberrant frontal-subcortical neural circuitry, which is thought to be driven by underlying cerebrovascular ischemia and neurodegenerative processes, may contribute to

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clinical features of poor treatment response in LLD (Aizenstein et al., 2014; Taylor et al., 2013). Frontal, striatal, and limbic regional abnormalities could simultaneously impair function in multiple brain networks and explain the considerable variability seen in the clinical manifestation of LLD.

Converging evidence supports brain network dysfunction as a model of the potential neural mechanisms involved in the pathogenesis of LLD's clinical heterogeneity (Li et al., 2015; Tadayonnejad and Ajilore, 2014). The three core neurocognitive networks, the executive control (ECN), default mode (DMN), and salience (SN) neuronal systems are considered relevant contributors to the abnormal behaviors and impaired cognitive processes observed in depression (Mulders et al., 2015). Signs of executive dysfunction frequently accompany LLD (Taylor et al., 2013), and the ECN plays a critical role in such functions, including working memory, cognitive control, judgment, and decision-making in the context of goal-directed behaviors. Using seed-based resting-state functional connectivity magnetic resonance imaging (R-fcMRI) technique, diminished functional connectivity (Fc) within the ECN is observed in LLD and is predictive of poor treatment response, persistent depressive symptoms and executive dysfunction (Alexopoulos et al., 2012). LLD is also associated with enhanced DMN Fc in symptomatic (Alexopoulos et al., 2012; Eyre et al., 2016) but not remitted (Sexton et al., 2012) patients. Intrinsic ECN and DMN Fc changes differ based on antidepressant response, and could serve as early markers of treatment response variability in LLD (Karim et al., 2016). The DMN regions primarily mediate episodic and autobiographical memory, self-monitoring, and related social cognitive functions (Buckner et al., 2008). These same DMN areas also play an important role in emotional regulation and are linked to impaired self-referential processing, negativity bias, and increased rumination during depressive episodes (Sheline et al., 2009). Finally, the SN is sensitive to salient environmental events and is involved in interoceptive awareness and emotional experiences (Menon and Uddin, 2010). Disrupted SN connectivity has been detected in major depression, and may be reflective of disease severity and increased somatization (Manoliu et al., 2013; Paulus and Stein, 2006). These investigations focus on intra-network Fc disruptions in LLD, but there is a dearth of R-fcMRI studies that examine the interactions between the aforementioned functional networks in LLD. The ECN, DMN, and SN are densely interconnected and, therefore, dysfunction in any one of these networks may also disrupt other functional systems resulting in the clinical heterogeneity seen in LLD.

To further understand the brain network abnormalities underlying the clinical heterogeneity of LLD, it is imperative to examine how network dysfunction relates to the different symptom dimensions comprising LLD. It is plausible that the neurobiological mechanisms underlying symptom dimensions may not cleanly map to the neural correlates of the categorically defined LLD diagnosis. Such an approach brings the field of LLD research one step closer to the goals of the Research Domain Criteria (RDoC) project, a National Institute of Mental Health initiative that aims to develop novel ways to classify psychiatric syndromes based on neurobiological measures and behavioral dimensions.

By applying the dual regression independent component analysis (ICA) approach on R-fcMRI data, we first aimed to determine the inter-network Fc between ECN, DMN, and SN in individuals with LLD. The ICA method extracts low frequency signal fluctuations at rest and from a single data-driven analysis allows simultaneous estimation of multiple spatially independent intrinsic networks that correspond to those established by task-based functional MRI studies (Beckmann et al., 2005; Biswal et al., 2010; Smith, S.M. et al., 2009). Secondly, we examined the association of inter-network Fc abnormalities with specific symptom dimensions that are commonly encountered in persons with LLD (i.e., depressive and anxiety symptoms, executive functioning and episodic memory). We hypothesized that intrinsic ECN connectivity abnormalities with sub-networks of the DMN and SN would differentiate LLD from nondepressed cognitively healthy comparison (HC) subjects. We further postulated that the observed inter-network Fc abnormalities would correlate with depression and anxiety severity and greater executive dysfunction in LLD. Finally, we performed a voxelwise ICA analysis in the ECN, DMN, and SN to examine intra-network Fc differences in the regions implicated in emotional regulation that distinguish LLD from HC subjects.

2. Methods and materials

2.1. Participants

We enrolled 68 participants aged 60 years and older into the current study. The participant groups included patients with LLD ($n = 39$) and age- and gender-equated HC ($n = 29$) participants. All LLD subjects were recruited from the Medical College of Wisconsin (MCW) Geriatric Psychiatry and Memory Disorders Clinics. The HC subjects were recruited from the community using advertisements. The MCW Institutional Review Board approved this study, and written informed consent was obtained.

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) (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 Disorders (SCID) (First et al., 2002); modified Hachinski Ischemic Scale (HIS); and Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959). The neuropsychiatric and functional scales were chosen based on their ability to characterize cognitive functioning and depression severity in prior LLD studies (Butters et al., 2004).

2.2. Inclusion/exclusion criteria

All participants met the following criteria: MMSE score >24, age- and education-corrected Mayo Clinic's Older American Normative Studies (MOANS)-scaled score of $\geq$5 on MDRS-2, no dementia diagnosis, and HIS < 4.

LLD: Specific inclusion criteria for the LLD patients included a GDS score $\geq$10 and SCID depression module positive for major depression. The objective of this study was to investigate the neurobiological correlates of multi-domain symptoms that mimic a clinically representative sample of LLD patients. Therefore, we did not exclude participants with significant anxiety or mild cognitive impairment as long as the primary diagnosis was LLD, which is consistent with previous studies (Butters et al., 2004; Mulsant et al., 2001).

HC: The eligibility criteria were similar, except these participants had to be cognitively normal and could not be on psychoactive medications or meet lifetime criteria for any psychiatric disorders.

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; a history of neurological disease, including Parkinson's disease, dementia, multiple sclerosis, seizures, or stroke; head injury with loss of consciousness; MRI contraindications; and