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Research report

Altered resting-state functional connectivity in late-life depression: A cross-sectional study

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ABSTRACT

Background: Disrupted brain connectivity is implicated in the pathophysiology of late-life depression (LLD). There are few studies in this area using resting-state functional magnetic resonance imaging (rs-fMRI). In this pilot case-control study, we compare rs-fMRI data between age-matched depressed and non-depressed older adults.

Methods: Older participants ($\geq$ 55 years) with current major depressive disorder (MDD) were recruited to participate in an ongoing study of LLD, and were compared to the age-matched, non-depressed controls. Rs-fMRI data were collected using a 3-Tesla MRI system. In this study, a data-driven approach was chosen and an independent component analysis (ICA) was performed.

Results: Seventeen subjects with MDD were compared to 31 controls. The depressed group showed increased connectivity in three main networks compared to the controls ($p(corr) < 0.05$), including connectivity between the default mode network (DMN) and the posterior superior temporal sulcus (pSTS). Increased connectivity was also observed within the visual network in the medial, lateral and ventral regions of the occipital lobes, and within the auditory network throughout the right superior temporal cortex.

Conclusion: This data-driven, pilot study finds patterns of increased connectivity that may be unique to LLD in the DMN, as well as visual and auditory networks. The functional implications of this aberrant connectivity remains to be determined. These findings should be further explored in larger samples.

1. Introduction

The most recent global burden of disease data identified depressive disorders as a leading contributor to health burden internationally, and these data suggested that major depressive disorder (MDD) was also a contributor to burden allocated to suicide and ischemic heart disease (Ferrari et al., 2013). As the global population ages this century to unprecedented levels (UN, 2013), the rates of late-life depression (LLD) are expected to increase in parallel (Ferrari et al., 2013). This will see major impacts on our communities given the effects of LLD on cognitive, mood and somatic symptoms, as well as general functioning. Given this major burden, a deeper understanding of the neurobiology of LLD is important for the development of novel diagnostic systems and therapies.

Important markers of both structural and functional neuroplasticity in depression come from neuroimaging studies. These markers allow for an *in vivo* understanding of dysfunctional neuroplasticity processes such as reduced neurogenesis, as well as impaired synaptic plasticity and long-term potentiation (Eyre and Baune, 2012). LLD studies of neuroimaging are suggested to differ from mid-life depression in a number of ways, hence making the LLD-specific research field essential. For example, the Default Mode Network (DMN) demonstrates less functional connectivity with age (Koch et al., 2010; Tomasi and Volkow, 2012). White matter hyperintensities (WMH) are common in LLD, but rare in midlife depression (Hopkins et al., 2006). A higher burden of WMHs are associated with greater limbic activation on emotional reactivity tasks (Aizenstein et al., 2011). The differences between LLD and midlife depression may be explained by mechanistic hypotheses. Taylor et al. (2013) summarizes two key mechanistic

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constructs in LLD: the *disconnection hypothesis* and the *hypoperfusion hypothesis*. The *disconnection hypothesis* by Alexopoulos et al. (Alexopoulos, 2002) suggests ischemia and white matter pathology may disrupt neural connections among regions modulating mood and cognition. In this model, widespread cerebral WMHs cause focal damage to tracts and circuits. Such focal damage could adversely affect the tract connectivity causing 'disconnection' of brain regions. This state is believed to adversely affect the function of connected regions at rest and during cognitive tasks, and may contribute to circuitry alterations mediating symptomatology. The *hypoperfusion hypothesis* (Taylor et al., 2013) is suggested given the commonly noted vascular dysfunction in LLD and the cerebral blood flow reductions which can alter brain function and contribute to symptomatology (Broadley et al., 2002; Chen et al., 2006; Greenstein et al., 2010; Paranthaman et al., 2010; Rajagopalan et al., 2001). Regional cerebral metabolic activity is tightly correlated with cerebral blood flow, which is regulated by complex interactions between neurons, glia and vasculature (Iadecola, 2004). In late-life, vascular disease disorders such as hypertension, diabetes and atherosclerosis often lead to vascular wall hypertrophy, reduced arterial lumen diameter, arterial stiffness and endothelial cell dysfunction (Dandona et al., 2004; Touyz, 2005).

Both WMH and hypoperfusion may have consequences on brain networks that can be investigated with neuroimaging research. The most research in neuroimaging of LLD surrounds the Default Mode Network (DMN), with the other commonly studied networks including the affective/frontolimbic network, the cognitive control network (CCN) and the corticostriatal network (Alexopoulos et al., 2012, 2013; Andreescu et al., 2013; Patel et al., 2015; Tadayonnejad and Ajilore, 2014; Tadayonnejad et al., 2014; Yuen et al., 2014). The DMN is a network of regions showing synchronized activity patterns when the brain is at rest, and connectivity is decreased when the mind is engaged on the external environment (Fox and Raichle, 2007; Raichle et al., 2001). The DMN includes areas in the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the precuneus and the medial temporal lobe (MTL) (Buckner et al., 2008; Yeo et al., 2011). Evidence suggests involvement of the DMN in self-referential processing, including internal monitoring, autobiographical memory retrieval, future planning, and theory of mind (Buckner et al., 2008; Northoff and Bermpohl, 2004; Spreng et al., 2009). Dysfunction in the DMN may occur due to WMHs and hypoperfusion (Tadayonnejad et al., 2014) and may represent an imbalance between control systems involved in negative rumination and preferential internal over external attention, possibly reflecting depressive biases toward internal thoughts at the cost of engagement in the external environment (Andrews-Hanna et al., 2010; Kaiser et al., 2014). Self-referential processing dysfunction may lead to negativity bias pronounced with depression (Andrews-Hanna et al., 2010; Kaiser et al., 2014).

We are aware of 3 studies in LLD exploring the DMN specifically, 2 via seed region analysis (Alexopoulos et al., 2012; Kenny et al., 2010) and 1 by independent components analysis (ICA) (Sexton et al., 2012). ICA is a useful methodology as it provides a data-driven approach to defining resting-state networks. The only ICA study in LLD of which we are aware comes from Sexton et al. (2012), who explored a cross-sectional, multimodal neuroimaging approach to a mixture of patients with current LLD or past history of LLD. No significant differences in functional connectivity were detected between the current (or past) LLD and age-matched healthy control groups in the DMN, anterior DMN, posterior DMN, cognitive control network (CCN), or affective/frontolimbic network.

Our study is the first to apply the ICA methodology in older adults with a current major depressive episode. We used a cross-sectional analysis of high-resolution rs-fMRI data. We hypothesized that LLD would be associated with aberrant connectivity within the DMN; therefore, this network was targeted in our primary analysis. We also performed exploratory analyzes of LLD-related differences in functional connectivity in other resting-state networks to determine whether LLD is associated with broader dysfunction.

2. Methods

2.1. Participants

From November 2013 to December 2014, we recruited 17 older adults ($\geq$ 55 years) to participate in the ongoing study of geriatric depression (NCT01902004), and 31 non-depressed age-matched controls. After describing the details of the study to interested and eligible subjects, written informed consent was obtained in accordance with the procedures set by the UCLA Institutional Review Board (IRB).

2.1.1. Depressed subjects

Inclusion criteria were: (1) current episode of unipolar MDD according to DSM-5 criteria; (2) Hamilton Depression Rating Scale (HDRS-24) score $\geq$ 16; (3) Mini-Mental State Exam (MMSE) score $\geq$ 24; and (4) subjective memory complaints. Exclusion criteria were: (1) history of any other psychiatric disorders (other than unipolar MDD); (2) severe or acute unstable medical illness; (3) acute suicidal, violent behavior or history of suicide attempt within the last year; or (4) any other central nervous system diseases. Subjects were free of psychotropic medications for at least two weeks before participating in the study.

2.1.2. Non-depressed subjects

Inclusion criteria were: (1) Mini-Mental State Exam (MMSE) score $\geq$ 24; (2) subjective memory complaints; (3) no current, or history of, depression. Exclusion criteria were: (1) history of any psychiatric disorders or dementia; (2) severe or acute unstable medical illness; (3) any other central nervous system diseases; (4) no psychotropic medications use.

2.2. Clinical measures

Mood evaluation included the Hamilton Rating Scale of Depression (HDRS-24; (Hamilton, 1960)), the Hamilton Anxiety Scale (HAS; (Hamilton, 1959)). Health functioning, medical and vascular comorbidity were collected using the Stroke Risk Factor Prediction Chart (AHA, 1990); and the Cumulative Illness Rating Scale-Geriatric (CIRS-G; (Miller et al., 1992)). Stress coping /resilience was measured by the Connor–Davidson Resilience scale (CD-RISC) (Connor and Davidson, 2003).

2.3. Image acquisition

Functional resting imaging data were collected with a 3 T TIM Trio scanner (Siemens AG, Munich & Berlin, Germany). Participants' heads were positioned comfortably within a 32-channel head coil, and head motion was minimized with firm cushions. We instructed participants to close eyes and stay awake during image acquisition. Resting-state functional images were acquired for 5 minutes and 41 seconds with a multi-band gradient-echo echo-planar imaging (EPI) sequence sensitive to BOLD contrast effects. We acquired 275 contiguous EPI resting-state volumes, and the parameters for functional imaging were repetition time 1.24 seconds, echo time 38.2 ms, flip angle 65°, field of view 21.2×21.2 cm^2, acquisition matrix $118 \times 118 \times 1.8$ mm^3 iso-voxel