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The segregated connectome of late-life depression: a combined cortical thickness and structural covariance analysis

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ABSTRACT

Late-life depression (LLD) has been associated with both generalized and focal neuroanatomical changes including gray matter atrophy and white matter abnormalities. However, previous literature has not been consistent and, in particular, its impact on the topology organization of brain networks remains to be established. In this multimodal study, we first examined cortical thickness, and applied graph theory to investigate structural covariance networks in LLD. Thirty-three subjects with LLD and 25 controls underwent T1-weighted, fluid-attenuated inversion recovery and clinical assessments. Freesurfer was used to perform vertex-wise comparisons of cortical thickness, whereas the Graph Analysis Toolbox (GAT) was implemented to construct and analyze the structural covariance networks. LLD showed a trend of lower thickness in the left insular region ($p < 0.001$ uncorrected). In addition, the structural network of LLD was characterized by greater segregation, particularly showing higher transitivity (i.e., measure of clustering) and modularity (i.e., tendency for a network to be organized into subnetworks). It was also less robust against random failure and targeted attacks. Despite relative cortical preservation, the topology of the LLD network showed significant changes particularly in segregation. These findings demonstrate the potential for graph theoretical approaches to complement conventional structural imaging analyses and provide novel insights into the heterogeneous etiology and pathogenesis of LLD.

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1. Introduction

Late-life depression (LLD), often defined as depression in people over the age of 60, is common, and often associated with cognitive decline and future risk of dementia, increased disability, and mortality (Naismith et al., 2012). Estimates of the prevalence of clinically relevant depressive symptoms in older adults typically range from 10% to 15% and rates of major depression from 1% to 5%. Several diverse etiological factors have been proposed, including structural abnormalities due to vascular (Thomas et al., 2001) and neurodegenerative factors (Tsopelas et al., 2011), hypothalamo-pituitary-adrenal axis dysfunction and dysregulation of neurotransmitters such as serotonin (Meltzer et al., 1998).

Previous imaging studies have revealed a varied assortment of structural and functional abnormalities: localized gray matter atrophy in frontal cortex (Ballmaier et al., 2004) and subcortical structures (Colloby et al., 2011), increased distribution of white matter hyperintensities (WMHs) (Herrmann et al., 2008), microstructural deficits in white matter pathways (Sexton et al., 2012), and altered functional connectivity between subcortical regions (Kenny et al., 2010). However, the prevailing neuroimaging literature in LLD is still inconclusive. A meta-analysis of magnetic resonance imaging (MRI) studies in LLD only found weak evidence of hippocampal atrophy (7 of 15 studies) (Sexton et al., 2013), whereas others have not demonstrated any significant differences in gray matter (Colloby et al., 2011; Koolschijn et al., 2010) or WMH (Colloby et al., 2011). A previous hypothesis-driven comparison of frontal lobar cortical thickness in this sample also did not show any significant differences compared with healthy controls (Colloby et al., 2011). These disparate findings could simply reflect the heterogeneity and the complex interaction of various factors in the pathophysiology of LLD, which might in turn obscure subtle disease-related alterations in the interaction patterns existing in large-scale networks of brain regions. In this regard, a multivariate technique might better explain the reported variability in neuroanatomical findings across studies compared with the conventional approach examining localized differences in discrete regions between groups.

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Table 1
Description of network measures investigated in this study

Small worldness is a measure of how much a network is locally interconnected compared against a random network while retaining efficient global connectivity between distant brain regions. Thus, its main attributes are a higher clustering coefficient but a similar characteristic path length compared with that of a random network.			
Integration		Segregation	
Characteristic path length	The shortest path length is the smallest number of connections to get from one node to another. The characteristic path length is the average of the shortest path length between all the pairs of nodes in the network. It is the most commonly used measure of network integration.	Clustering coefficient	The clustering coefficient of a node is a measure of the number of edges that exist between its nearest neighbors. The clustering coefficient of a network is thus the average of clustering coefficients across the nodes.
Global efficiency	The global efficiency is the average of the inverse shortest path length in the network.	Transitivity	Often used as an alternative to clustering coefficient, transitivity reflects the likelihood for a network to have interconnected nodes that are adjacent to one another, and is normalized by the whole network. It is also more robust compared to clustering coefficient, as it is not influenced by nodes with small number of connections (Newman, 2003).
		Modularity	The extent to which a network is characterized by densely interconnected nodes with relatively few connections between nodes in different modules ("cliques"). It is a reflection of the natural segregation within a network.
		Local efficiency	The local efficiency refers to the global efficiency of the subgraph (i.e., fully connected network not connected to the main graph) formed by the adjacent neighbors of the node.

In recent years, graph theoretical concepts have been increasingly applied to study the organizational principles of the brain by modeling it as a large-scale network with interconnected nodes and edges (Bullmore and Sporns, 2009). This framework rests on the fundamental premise that the maintenance or disintegration of complex systems is shaped by the interactions among their constituent elements. Bearing similarities to real-world scenarios such as the social network (i.e., 6 degrees of separation) and the cascading hyperlinks of the Internet, the human brain also possesses an inherent architecture known as the "small-world phenomenon" (Hagmann et al., 2008; Sporns et al., 2005). The small-world topology, with its short path lengths and high clustering (see Table 1 for a brief description of each network measure) supports efficient segregation and distribution of information processing with minimal cost (Bullmore and Sporns, 2009) and confers resilience against pathological damage (Achard et al., 2006). Conversely, deviations from small worldness toward randomization (shorter path lengths and lower clustering) or regularization (longer path lengths and higher clustering) have been found in the networks associated with neurodegenerative and psychiatric diseases, such as Alzheimer's disease (He et al., 2008), schizophrenia (Bassett et al., 2008), and major depressive disorder (Singh et al., 2013). The structural covariance method, referring to the coordinated variations in gray matter morphology (e.g., cortical thickness or volume), is increasingly used to infer structural connectivity between regions and construct large-scale brain networks (Alexander-Bloch et al., 2013). A key assumption underlying this methodology is that morphological correlations are related to some degree of axonal connectivity between brain regions with shared trophic, genetic, and neurodevelopmental influences (Alexander-Bloch et al., 2013). Although altered structural covariance networks have been found in a variety of brain diseases, it remains challenging to interpret disease-related changes in networks as we presently lack a clear understanding of the cellular and molecular mechanisms that drive the emergence of large-scale covariance across networks. Nevertheless, structural covariance networks derived from cortical thickness correlations have shown substantial agreement with white matter connections (Gong et al., 2012) and functional connectivity (Kelly et al., 2012).

To date, there have been very few studies assessing large-scale networks in LLD, yielding inconclusive evidence (See Table 2 for a literature summary). A recent diffusion tensor imaging (DTI) study of white matter connections identified longer path length and impaired global efficiency in LLD compared with controls (Bai et al., 2012). Using inter-regional correlations of gray matter volumes, another study in LLD also reported higher clustering in addition to longer path length (Ajilore et al., 2014), although no network differences were revealed by the same group in a subsequent analysis of white matter network on the same sample (Charlton et al., 2014). Preserved network organization in LLD has been reported in other studies using gray matter volumes (Lim et al., 2013) and functional data (Bohr et al., 2013). Furthermore, no study has performed a combined analysis of regional cortical thickness and network properties in the same sample, which will allow us to directly investigate the macro-level impact of cortical atrophy beyond the potentially affected regions.

The aims of this multimodal study are 3-fold: (1) we extended our previous frontal lobe study on this sample by employing a whole-brain vertex-wise approach to compare cortical thickness between LLD and controls; (2) from the regional thickness measures across the whole brain, we constructed a structural covariance network from the inter-regional correlations of cortical thickness to investigate global and regional properties of the LLD network; and (3) last, we investigated the resilience of both networks against random failures and targeted attacks. We hypothesized that LLD would be characterized by lower regional cortical thickness as well as aberrations in small worldness reflecting a shift toward a regularization of the network.

2. Method

2.1. Participants and clinical assessment

Subjects above the age of 60 years presenting to local psychiatry services with a history of a major depressive episode (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] criteria), current or previous were recruited. Specifically, the LLD group composed of participants who were still depressed ($n = 16$) as well as others who had remitted ($n = 17$). Healthy individuals were recruited via an advertisement placed in the local Elders Council magazine inviting participation to the study and all came from the same geographical area as the participants with depression. All participants and controls underwent the same set of assessments and structured interviews, although the controls did not do the

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