Review

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Brain Structural Connectivity in Late-Life Major Depressive Disorder

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ABSTRACT

Disrupted brain connectivity might explain both the pathogenesis and consequences of late-life major depressive disorder (LLD). However, it remains difficult to ascertain whether and how specific circuits are affected. We reviewed literature regarding brain connectivity in LLD, and we specifically focused on the role of structural pathology. LLD is associated with greater levels of cerebrovascular disease, and greater levels of cerebrovascular disease are associated with both depression development and treatment nonresponsiveness. Cerebrovascular disease is most often measured as white matter hyperintensity (WMH) burden, and histopathology studies suggest that WMHs reflect myelin damage and fluid accumulation (among other underlying pathology). WMHs appear as confluent caps around the ventricles (periventricular), as well as isolated lesions in the deep white matter. The underlying tissue damage and implications for brain connectivity may differ by WMH location or severity. WMHs are associated with lower white matter microstructural integrity (measured with diffusion tensor imaging) and altered brain function (measured with functional magnetic resonance imaging). LLD is also associated with lower white matter microstructural integrity and gray matter volume, which may also alter the network properties and function of the brain. Damage to brain structure (reflected by WMH, reduced white-matter microstructural integrity, and atrophy) may affect brain function and is therefore a likely pathophysiological mechanism of LLD. Additional research is needed to fully characterize the developmental course and pathology underlying these imaging markers and to understand how structural damage explains the various clinical manifestations of LLD.

Keywords: Aging, Connectivity, Depression, Diffusion tensor imaging, Functional MRI, Structural MRI

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Depression is a brain disease associated with altered reward processing, heightened response to emotional stimuli, and altered brain structure spanning multiple regions (1,2). While early neuroimaging research focused on localizing these characteristics to specific brain regions, recent conceptual frameworks emphasize the need to understand mental disease as a result of complex, interconnected networks (3). In recent years, neuroimaging methods for analyzing brain connectivity have grown in popularity (4). This research supports the idea that depression may be a disconnection syndrome; for example, recent diffusion tensor imaging (DTI) research found that depression was associated with reduced intrafrontal and frontal-subcortical white matter microstructural integrity (5).

Disrupted brain connectivity might explain both the pathogenesis and consequences of depression. The role of altered brain connectivity in depression is particularly important among older adults. Depression is associated with excess disability (6), and in late-life major depressive disorder (LLD), this risk may be potentiated by age-associated changes to brain structure (7–9). Indeed, LLD increases risk for dementia (10,11) and mortality (12); among patients with LLD, the severity of brain structural pathology predicts mortality risk (13). Given these consequences and the fact that the global population is rapidly aging (14), researchers and mental health practitioners should understand and work to advance current knowledge regarding how brain connectivity is altered in LLD.

Research conceptualizing LLD as a disconnection syndrome dates back, at least, to the vascular depression hypothesis (15,16). The vascular depression hypothesis, which remains of central importance to understanding brain connectivity in LLD, states that "cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes" (15). This review provides background information on the vascular depression hypothesis and then reviews current research regarding how brain connectivity is disrupted in LLD. We discuss research on structural connectivity in LLD, how variability in brain structure relates to brain function, and whether depression is characterized by local or diffuse connectivity disruption.

THE VASCULAR DEPRESSION HYPOTHESIS

Early research found that white matter hyperintensities (WMHs) (identified on T2-weighted or T2-weighted fluid attenuated inversion recovery magnetic resonance imaging) are more common among older adults with depression (17–20).

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Other early research found that greater age is associated with more hyperintensities and that hyperintensities are related to worse treatment outcomes (21). Compared with nonvascular depression, vascular depression is associated with greater levels of cognitive impairment and disability (22).

Research today continues to provide evidence for and refine the initial formulation of the vascular depression hypothesis, which includes prominent roles of both WMHs and neuropsychological dysfunction. A recent systematic review confirmed that, indeed, compared with healthy control subjects, WMHs are more common among patients with LLD (23). Further, one large clinical study (n = 217) found that WMH severity and performance on several cognitive tests predicted depression severity over a course of pharmacotherapy treatment for LLD (24); this study also found that clinical vascular factors were correlated with both neuropsychological and imaging-related vascular measures. The internal validity of vascular depression is supported by research demonstrating that deep white matter hyperintensities (when compared with neuropsychological and clinical measures) were best at distinguishing vascular and nonvascular subgroups in two independent samples of LLD patients (25).

Importantly, recent longitudinal research now demonstrates that WMH progression (increases in WMH burden over time) predicts worse depression outcomes among older adults in both community settings (26) and clinical settings (27,28). In individuals with depression, WMH progression has been linked with the development of dementia (29). These findings clearly support the clinical relevance of the vascular depression hypothesis and suggest that cerebrovascular disease (as indicated by WMHs) is involved in the pathogenesis, persistence, and consequences of LLD. These observations provide strong motivation to further investigate the pathophysiological nature of WMHs and how they disrupt brain connectivity in depression.

THE PATHOPHYSIOLOGY AND DEVELOPMENT OF WMH

Postmortem studies are a rich source of information regarding the pathophysiology of magnetic resonance identified WMHs. Early research found that WMHs indicate gliosis and demyelination (30); however, the pathology of WMHs has been long recognized to vary by lesion type (31). More recently, astrogliosis and oligodendrocyte loss were observed in periventricular but not subcortical WMHs, whereas regardless of location, small vessel loss, myelin damage, and vacuolation (allowing for fluid accumulation) contributed to white matter degradation in WMHs (32); these findings suggest that the pathophysiology of periventricular and subcortical WMHs may differ and that myelin damage may occur in the absence of (or perhaps before) oligodendrocyte loss.

A recent postmortem study of confirmed dementia cases found that WMH pathology was consistent with microinfarcts, except in juxtacortical lesions, which were enlarged perivascular spaces (33). Other research suggests that ischemic disease, rather than small-vessel disease, has a prominent role in WMH pathophysiology (34). These pathophysiological studies provide strong evidence that WMHs broadly reflect the impact of cerebrovascular disease and related processes on the brain. Note that postmortem studies are limited by selection bias (e.g., overrepresentation of end-stage disease). Given that WMH pathology and etiology are likely heterogeneous or at least multifactorial with variability by stage or severity, there is a need for in vivo studies of WMH etiology.

Several cross-sectional imaging studies have investigated the clinical correlates of WMHs. High blood pressure (35,36) and arterial stiffness (37,38) are among the best-recognized correlates of white matter pathology. In a study of hypertensive patients with controlled blood pressure, estimated glomerular filtration rate was associated with WMH burden (39). Other factors related to vascular disease, for example, inflammatory cytokines (40), may also be related to brain structural pathology. Inflammatory cytokine levels correlate with WMHs (41–43). One study among older adults with depression found that peripheral markers of immune-inflammatory control, lipid metabolism, clotting process, and vascular reactivity (among others) correlated with WMHs (44). Brain-derived neurotrophic factor and vascular endothelial growth factor are related to future vascular brain injury among older adults (45). Elevated cortisol levels during stress may relate to white matter pathology (46). Other factors including anemia (47) and the intake of salt (48), calcium, and vitamin D (49) also correlate with WMHs.

Longitudinal imaging studies are needed to clarify which of these factors are involved in the etiology of WMHs and which of these factors are markers of prevalent structural pathology. Available longitudinal evidence has mostly focused on blood pressure and demonstrates that high blood pressure (50), and in particular high ambulatory blood pressure (51,52), predicts WMH accumulation over time. Given the clinical importance of WMHs (discussed above), there remains a need for more longitudinal research to precisely characterize the complex and likely multifactorial determinants of WMHs. Comprehensive research regarding the determinants of WMH development and progression could clarify when and how to intervene to prevent the consequences WMH on brain connectivity.

RELATIONS BETWEEN WMH AND BRAIN CONNECTIVITY

Cerebrovascular disease has long been thought to disrupt brain connectivity in depression; for example, an early study demonstrated that depressed patients with co-occurring clinical vascular disease had reduced auditory transmission at the pons (53). DTI, which measures the degree of anisotropic diffusion of water as a proxy of microstructural integrity, now provides in vivo confirmation of a relation between WMHs and white matter structure. This research has shown that WMHs are associated with reduced white matter microstructural integrity (54,55). In fact, clinical atherosclerotic disease itself is associated with reduced white matter microstructural integrity (56,57). Therefore, vascular disease and WMHs are associated with white matter structure.

These structural changes have observable relations to brain function. Multimodal imaging research has shown that "functional connectivity reflects structural connectivity" (58) [for a review, see (59)]. Several recent studies have begun characterizing how WMHs affect cerebral blood flow and brain function: regions with WMH show reduced blood