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Brain structural connectivity in late-life major depressive disorder

Stephen F. Smagula, Ph.D. and **Howard J. Aizenstein, M.D. Ph.D.**

Department of Psychiatry, Western Psychiatric Institute and Clinic of University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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 responsiveness. Cerebrovascular disease is most often measured as white matter hyperintensity (WMH) burden, and histopathology studies suggest WMH 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 MRI). LLD is also associated with lower white matter microstructural integrity and grey matter loss 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 are therefore likely pathophysiological mechanisms 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 LLD's various clinical manifestations.

Keywords

functional MRI; structural MRI; Diffusion tensor imaging; depression; connectivity; aging

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

Corresponding author: Stephen F. Smagula, 3811 O'Hare Street, Pittsburgh, PA 15213, sfs26@pitt.edu.

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regions, recent conceptual frameworks emphasize the need to understand mental disease as a result of complex, inter-connected 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 research found depression was associated with reduced intra-frontal 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 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 (WMH; identified on T2-weighted or T2-weighted fluid attenuated inversion recovery MRI) are more common among older adults with depression (17-20). Other early research found greater age is associated with more hyperintensities, and that hyperintensities are related to worse treatment outcomes (21). Compared with non-vascular 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 included prominent roles of both WMHs and neuropsychological dysfunction. A recent systematic review confirmed that, indeed, compared with healthy controls, WMHs are more common among patients with LLD (23). Further, one large clinical study (n=217) found 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 deep white matter hyperintensities (when

compared with neuropsychological and clinical measures) were best at distinguishing vascular and non-vascular sub-groups 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 (26, 27) and clinical settings (28, 29). In individuals with depression, WMH progression has been linked with the development of dementia (30). These findings clearly support the clinical relevance of the vascular depression hypothesis, and suggest 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 WMHs

Post-mortem studies are a rich source of information regarding the pathophysiology of MR identified WMHs. Early research found that WMHs indicate gliosis and demyelination (31), however the pathology of WMHs has been long recognized to vary by lesion type (32). More recently, astrogliosis and oligodendrocytes loss was observed in periventricular but not subcortical WMHs, whereas regardless of location, small vessel loss, myelin damage, and vaculoation (allowing for fluid accumulation) contributes to white matter degradation in WMHs (33); these findings suggest the pathophysiology of periventricular and subcortical WMHs may differ, and that myelin damage may occur in the absence of (or perhaps before) oligodendrocytes loss.

A recent post-mortem study of confirmed dementia cases found WMH pathology was consistent with microinfarcts, except for in juxtacortical lesion, which were enlarged perivascular spaces (34). Other research suggests ischemic, rather than small vessel disease, has a prominent role in WMH pathophysiology (35). These pathophysiological studies provide strong evidence that WMHs broadly reflect the impact of cerebrovascular disease and related processes on the brain. Note that post-mortem studies are limited by selection bias (e.g. over-representation of end-stage disease). Given that WMH pathology and etiology is 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 (36, 37) and arterial stiffness (38, 39) 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 (40). Other factors related to vascular disease, for example inflammatory cytokines (41), may also be related to brain structural pathology. Inflammatory cytokine levels correlate with WMHs (42-44). One study among older adults with depression found peripheral markers of immune-inflammatory control, lipid metabolism, clotting process and vascular reactivity (among others) correlated with WMHs (45). Brain derived neurotrophic factor and vascular endothelial growth factor are related to future vascular brain injury among older adults (46). Elevated cortisol levels during stress may relate to white matter pathology (47). Other

factors including anemia (48) and salt (49), calcium, and vitamin D (50) intake 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 (51), and in particular high ambulatory blood pressure (52, 53) predicts WMH accumulation over time. Given the clinical importance of WMH (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 in order to prevent the consequences WMH on brain connectivity (discussed below).

Relations between WMHs 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 (54). Diffusion tensor imaging (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 (55, 56). In fact, clinical atherosclerotic disease itself is associated with reduced white matter microstructural integrity (57, 58) Therefore, vascular disease and WMH are associated with white matter structure.

These structural changes have observable relations to brain function. Multi-modal imaging research has shown that “functional connectivity reflects structural connectivity” (59) (for a review, see (60)). Several recent studies have begun characterizing how WMHs affect cerebral blood flow and brain function: regions with WMH show reduced blood flow (61); periventricular and deep WMHs are associated with a decline in cerebral blood flow over a period of about 4 years (62). While these studies demonstrate a prospective association between WMH and future blood flow in the brain, it will also be important for future research to evaluate how reduced cerebral blood flow may impact white matter health over time (63) (consistent with the potential ischemic pathophysiology of WMH discussed above).

In LLD, prevalent WMHs are associated with altered functional MRI signal (64), including abnormal default-mode network connectivity (65) and more pronounced functional activation in response to an affective-reactivity task (66). White matter microstructural integrity (expressed as fractional anisotropy measured with DTI) also relates to resting state functional connectivity among older adults with depression (67). Altogether, WMHs are related to altered white matter microstructural integrity, and both WMHs and white matter microstructural integrity relate to brain function.

The relevance of WMH extent and localization

Some research has examined the spatial distribution of WMHs related to depression. WMHs are more common/extensive among older adults with depression, and increases in WMH severity may result in more of the brain being affected. For example, in older adults without depression, WMHs may be limited to bilateral parietal-temporal regions, whereas older adults with depression tend to have WMHs extending into frontal regions (68, 69). Compared with non-depressed control participants, depression is associated with greater WMHs in several tracts relevant to cognitive and affective functions (70). More extensive WMHs observed in depressed patients may reflect more severe/advanced stage cerebrovascular disease, or alternatively, an amplified impact of cerebrovascular disease on brain health due to other reasons (e.g. stress related neurotoxicity affecting cell bodies (71)).

WMHs localized to specific tracts (e.g. those involved in social, cognitive, and affective processing) may be particularly clinically and mechanistically relevant. For example, some studies have found that periventricular WMHs predict cognitive decline over time, whereas sub-cortical WMHs do not (72, 73). In a meta-analysis, deep but not periventricular WMH correlated with depression (74). However interpreting these findings requires considering other evidence which demonstrates that periventricular, deep brain, and overall WMH are all highly correlated, and that an arbitrary, categorical distinction between periventricular and deep brain WMHs is not empirically supported (75); this study suggests WMHs extended smoothly out from the ventricles as a function of increasing overall burden. Consistent with these observations, a recent population-based study demonstrated that depression was associated with WMH accumulation around the ventricles (76), and another recent study found the ratio of WMH to non-WMH tissue differed between depressed patients and controls only in the upper cingulum (77).

These findings suggest WMHs tend to accumulate and affect tracts near ventricles. Nevertheless, the localization of WMHs may still have great clinical and mechanistic relevance. The impact of WMH localization on depression and its consequences might depend on differences in the underlying pathology that WMHs indicate (see above, e.g. whether oligodendrocyte loss occurs). Alternatively, differences in localization may simply reflect the overall the reach/severity with which WMHs affect key white matter tracts. In either case, it appears that a critical level of damage to a tract, or set of tracts, may affect brain networks and confer LLD. However, there remains a need to investigate how the spatial patterns WMH accumulation and their underlying pathology (e.g. using high-field imaging) relate to the incidence and manifestations of LLD.

Tract specific and whole-brain white matter microstructural integrity in LLD

A recent meta-analysis found, compared with healthy control participants, patients with LLD had lower fractional anisotropy (FA) across multiple regions and that the largest effects were observed in the frontal lobe, uncinate fasciculus, and cingulum (78). Voxel-based research similarly suggests LLD is associated with lower FA across multiple white matter tracts including those implicated in cognitive and affective processing (76, 79). Network

based analysis of DTI data suggests LLD is associated with reduced connectivity of temporal regions (80). Altogether, these findings support a conceptualization of LLD as a disease of reduced structural brain connectivity. It does not appear variability in the microstructural integrity of a single tract is a completely accurate predictor of LLD, instead, evidence suggests LLD involves altered structural network properties and white matter damage in key regions important to cognitive and affective processing. To date, there remains a need for research to elucidate how variability in white matter structures and structural network properties impact functional connectivity patterns, and in particular, how these connectivity changes precipitate the emergence of LLD's specific clinical manifestations (e.g. altered reward processing or low mood). If specific structural changes can be linked to both alterations in functional circuitry and the specific manifestations of LLD, this might suggest that these particular circuits are generally relevant to mood and clinical depression (e.g. potentially in the absence of overt, pronounced structural pathology, as in depression among younger adults).

Grey matter structure and network organization

LLD has been associated with smaller grey matter volume across numerous brain regions (81). One study found depression was associated with lower levels of grey matter volume across multiple regions, but most significantly in the insula and anterior cingulate cortex (76). Cortical thickness may also differ between LLD patients and controls; for example, lower cortical thickness has been noted among LLD patients in right frontal, parietal, and temporal brain regions (82). However, other studies have failed to find differences in grey matter volume between depressed patients and healthy controls (79), and the regions implicated across studies are not always consistent.

A recent meta-analysis utilizing data from region of interest studies found that LLD patients (compared with healthy controls) had lower grey matter volume in the hippocampus, orbitofrontal cortex, putamen, and thalamus (83). A subsequent meta-analysis argued that a voxel-based approach provides a more comprehensive strategy to identify the grey matter correlates of depression that is not biased by the need to pre-specify regions of interest (84); this study found, compared with healthy controls, LLD patients had lower grey matter volume in the hippocampus, parahippocampus, lentiform nucleus, amygdala, medial frontal gyrus, and right subcallosal gyrus, but had significantly larger right lingual gyrus volumes. Discrepancies between the results of these studies may reflect differences in the analytic approach (e.g. region of interest vs. voxel-based approaches) or sampling characteristics (e.g. including clinical and physical health characteristics of the LLD or control group).

Nevertheless, current research generally agrees that LLD is associated with widespread loss of grey matter that may be more pronounced in regions important for cognitive and emotional processing. A recent application of network-based analysis techniques suggests LLD is associated with different regional (85) and global grey matter network properties (86). These findings suggest grey matter changes are relevant to understanding how brain connectivity is altered in LLD. However, the current multi-modal evidence-base is limited, and there remains a need to further investigate how grey matter alterations (potentially

together with white matter changes) relate to structural network properties, brain function, and the incidence of depression.

Conclusions and future directions

The enduring impact of the vascular depression hypothesis on the field speaks to the very powerful relationships between cerebrovascular disease, brain structure, and depression among older adults. Several studies suggest the etiology of WMHs involves vascular disease factors including blood pressure, vascular stiffness, and immunological markers (36-39, 42-45). Longitudinal evidence from a variety of settings demonstrates that WMH, and their accrual, predicts future depression (26-29). Multi-modal imaging research has confirmed that WMHs are associated with worse white matter microstructural integrity (55-57). Further, brain structural pathology is associated with altered brain function in LLD (64-66). This literature supports a conceptualization of LLD as a disconnection syndrome (Figure), wherein several physical health factors precede pathological changes to brain structural connectivity, which affects brain function, and leads to the clinical manifestations of LLD.

Despite these exciting advancements connecting levels of analyses using multimodal imaging, substantial gaps in our understanding remain. In particular, there is a need for more longitudinal clinical neuroscience research to answer questions regarding the etiology, preventable risk factors, and course of brain connectivity changes in LLD. The model we present (Figure) is designed to summarize current knowledge and concepts that are plausible but mostly based on cross-sectional research. Longitudinal research is needed to determine which specific factors are markers of LLD rather than etiological factors, and also to clarify whether any specific factors are bi-directionally related over time (e.g. WMH and fractional anisotrophy, or reduced blood flow and WMH). Therefore, comprehensive prospective research is required to advance our understanding of how brain connectivity changes relate to the pathogenesis of LLD. In particular, there is a need to mechanistically understand how WMHs develop, what they mean pathologically, and how they relate to other structural pathology, altered brain function, and the specific clinical manifestations of LLD.

For example, current longitudinal research demonstrates high blood pressure predicts WMH accrual over time (51-53). However, the etiology of WMH development (as well grey matter and white matter microstructural integrity loss) is likely multi-factorial. Additional longitudinal research is needed to clarify whether several known correlates of WMH (e.g. cytokines and growth factors (42-45)) are in fact determinants of changes to brain connectivity. Multi-modal studies are needed to address whether/how the determinants of change to multiple aspects of brain structure differ, and how changes to different aspects of brain structure interrelate. In addition, most research examining relations between brain structure and function in LLD has focused on the role of WMHs (64-66). Future research is needed to investigate how multiple structural characteristics (including measures of grey matter, white matter microstructural integrity, and network properties) together affect functional connectivity.

More basically, future research is also needed to clarify what differences in stage or severity of WMH progression reflects about the underlying pathology. New advances in highfield

imaging may help clarify the pathophysiology and course of WMHs in LLD, which would also help clarify their causes and consequences. Research is needed to determine whether WMH or fractional anisotropy changes found in depression are similar across the implicated regions in terms of their underlying pathology, consequences on brain function, and clinical relevance. Future neuroimaging studies may reveal nuisances in the level or nature of apparent structural damage across tracts (or sets of tracts) that have specific implications for the functional circuitry and clinical presentation of LLD.

Because the manifestations of depression are heterogeneous, research should test whether certain structural and functional connectivity alterations relate to specific aspects of depression's clinical presentation. The original report on the vascular depression hypothesis (15) suggested, compared with non-vascular depression, patients with vascular depression had greater executive function impairment, psychomotor retardation, lack of insight, and disability. Imaging research is now poised to clarify the pathogenic mechanisms and underlying neurobiological substrates of these clinical manifestations. For example, does damage to a particular set of white matter tracts affect brain function to cause apathy, while another set of white matter and functional alterations underlies excessive sadness? Although not reviewed in the present work, research has begun characterizing the functional connectivity of mood disturbances among older adults (87-90). Future multimodal imaging studies are needed to conclusively isolate the how brain structural changes relate to functional connectivity changes of known clinical relevance. Enhancing our knowledge of the risk cascades leading to altered brain connectivity in LLD will greatly improve our ability to identify those at risk and target novel interventions to prevent LLD and its consequences.

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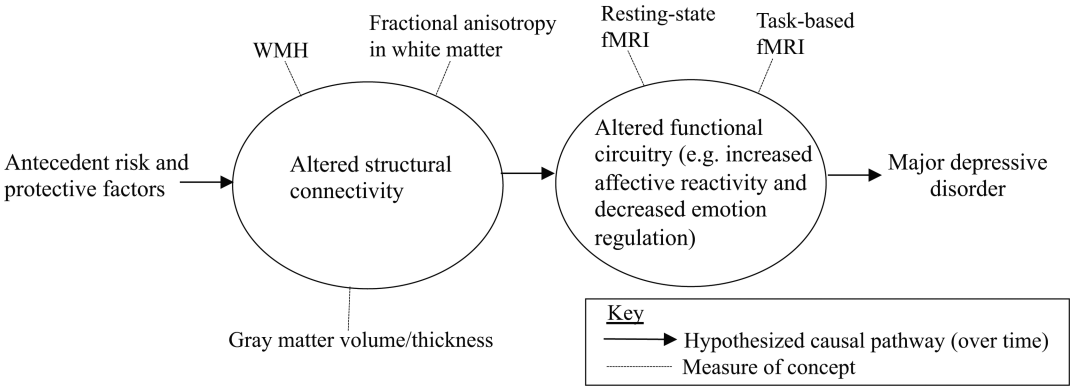

Figure. Conceptualization of late-life major depressive disorder as a disconnection syndrome

Over time, risk and protective factors potentially affect structural connectivity, which affects function circuitry, leading to major depressive disorder.