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Brain-based Mechanisms of Late-Life Depression: Implications for Novel Interventions

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Abstract

Late-life depression (LLD) is a particularly debilitating illness. Older adults suffering from depression commonly experience poor outcomes in response to antidepressant treatments, medical comorbidities, and declines in daily functioning. This review aims to further our understanding of the brain network dysfunctions underlying LLD that contribute to disrupted cognitive and affective processes and corresponding clinical manifestations. We provide an overview of a network model of LLD that integrates the salience network, the default mode network (DMN) and the executive control network (ECN). We discuss the brain-based structural and functional mechanisms of LLD with an emphasis on their link to clinical subtypes that often fail to respond to available treatments. Understanding the brain networks that underlie these disrupted processes can inform the development of targeted interventions for LLD. We propose behavioral, cognitive, or computational approaches to identifying novel, personalized interventions that may more effectively target the key cognitive and affective symptoms of LLD.

Keywords

Aging; Depression; Functional Connectivity; White Matter; Apathy; Executive Function

1. Introduction

Depression is the leading cause of disability worldwide.[1,2] Late-life depression (LLD) is particularly prone to poor outcomes, including failure to remit despite adequate treatments with antidepressant medications and/or psychotherapy, exacerbation of medical comorbidities, and diminished daily functioning.[3,4] One promising approach to improving the efficacy of interventions for LLD is to elucidate the functional and structural neuroanatomy corresponding to clinical subtypes of depression that are common in LLD and respond poorly to standard antidepressant approaches. A better understanding of the brain

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Declaration of interests

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network dysfunctions underlying LLD can inform the development of targeted interventions for these poor responders.

In this review, we present the results of studies that have examined the brain-based mechanisms of LLD with an emphasis on some of the common clinical subtypes – namely, depression with executive dysfunction, negative cognitive bias, and apathy – that frequently do not remit with antidepressant medications. We focus primarily on functional and structural neuroimaging studies that include detailed behavioral and/or cognitive assessments and/or take advantage of recent advances in MRI sequences or computational approaches. Next, we present two examples of how neuroimaging can inform novel treatment approaches - physical exercise interventions and cognitive training - that may optimize functioning of networks underlying these common clinical syndromes in LLD.

2. Network Model of Late-Life Depression

Our conceptualization of LLD is based on the premise that major depression in older adults is dependent both on disrupted intrinsic functional and structural connectivity *within* key networks – the salience network, the default mode network (DMN), and the executive control network (ECN) – as well as large-scale interactions *between* these brain networks. In this model (Figure 1), the salience network (dorsal anterior cingulate cortex (dACC) and anterior insula), the DMN, (medial PFC, posterior cingulate cortex, and precuneus), and the ECN (dACC, dorsolateral prefrontal cortex (DLPFC), and posterior parietal cortices) are involved in implementing attentional and regulatory processes that are core to both the implicit cognitive and affective biases common in LLD and to the maladaptive cognitive strategies implicated in the abnormal experience and regulation of emotional responses in depression.

2.1. Salience Network

The salience network is critical for prioritizing stimuli.[5–7]Salience is the process by which attention is directed towards or away from stimuli; more salient stimuli capture attention.[8–10] and stimuli with affective meaning (valence) have greater salience.[11] In addition the salience network works in concert with the ECN to allocate attentional resources to accomplish goal-directed behaviors while ignoring goal-irrelevant information.[5,6] In aging, the salience network, particularly the insula, shows decreased intrinsic connectivity as well as decreased connectivity with other networks and with the locus coeruleus.[12–14] For individuals suffering from depression, the salience network is biased toward selectively attending to negative stimuli. This bias toward negative information is related to the reduced extrinsic functional connectivity between the salience network and the ECN, along with increased functional connectivity of the DMN.[13,15,16]

2.2. Default Mode Network (DMN)

The DMN plays a key role in the individual's understanding of their place in the world.[17] Self-referential thinking, or making sense of one's place in the internal and external environment, is necessary for effective daily functioning,[18]including social aspects of daily functioning that are commonly impaired in LLD. The ability to reflect on past experiences

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and apply them to current and future experiences also depends on the DMN and facilitates goal-directed behaviors [19,20]. In normal aging, intrinsic functional connectivity of the DMN appears to be decreased in older adults relative to in young adults.[21] In individuals suffering from depression, biases in processing stimuli (e.g., interpreting neutral stimuli as negative, assigning greater salience to negative internal states and external stimuli) contribute to negative representations of the past and future, as well as negative self-referential thoughts, guilty rumination, depressive ideation and reduced well-being.[22–25]

2.3. Executive Control Network (ECN)

The ECN supports the flexible maintenance of goal-directed behaviors in the face of changing internal and environmental demands.[26,27] More specifically, control processes are "managed" by the ECN, a regulatory system that modulates the operation of other cognitive and emotional systems to enable the individual to function efficiently. This network is comprised of the dACC as well as the DLPFC and posterior parietal regions.[26] The dACC contributes to control processes by detecting conditions that signal the demand for increased cognitive control, which contributes to the engagement of the DLPFC. Parietal regions work in concert with the dACC and DLPFC to engage cognitive resources in response to the changing. Both intrinsic and extrinsic connectivity of the ECN is quite susceptible to disruption in aging,[28] which may contribute to the comorbid cognitive symptoms and poor mood outcomes often observed in LLD. Thus, disruption of the ECN likely contributes to both the cognitive and affective symptoms of LLD.

2.4. Pathophysiology of LLD

Multiple etiologic mechanisms contribute to network disturbances and lead to the clinical expression of LLD. Genetic variation, age- and disease-related processes have been implicated in the pathogenesis of LLD; including vascular disease, abnormal neurotrophin levels, transcriptomic variation, and dysregulation in endocrinologic and immunologic systems.[29] In particular, cerebrovascular comorbidities, including small vessel ischemic changes, are common in LLD.[30,31] Cardiovascular risk factors (e.g., diabetes, hypertension, atherosclerosis, hyperlipidemia) increase risk of LLD onset. Further, vascular changes including endothelial dysfunction and increased intima media thickness are more pronounced among depressed older adults.[32–34] Such vascular pathology compromises cerebral blood flow by reducing blood flow velocities and decreasing vasomotor reactivity, with LLD participants showing perfusion deficits in frontal, temporal, and subcortical areas.[31,35,36] Additional pathogenic pathways include abnormalities in inflammatory signaling, which exacerbates vascular burden[31] and promotes excitotoxicity and oxidative damage.[30] Disruptions in neural homeostasis and accelerated cellular aging,[29] perhaps indexed by telomere length,[37] may also contribute to the development and course of LLD.

3. The Relationship of White Matter Abnormalities to Network Disturbances in LLD

White matter abnormalities are common in aging and pronounced in LLD. They may contribute to the clinical manifestation of depression by disrupting connections among key regions regulating mood and cognitive processes. LLD is associated with greater severity

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of microvascular lesions, including white matter hyperintensities (WMH), a radiologic hallmark of small vessel disease.[38] Greater WMH burden predicts incidence of depression in older adulthood, persistence of symptoms, and non-remission following antidepressant treatment.[39–42] Along with global burden, LLD is associated with greater severity of WMH in specific white matter tracts including the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus.[43–45] By providing dense structural connections between key nodes of the salience network, the DMN and the ECN, these fiber bundles support executive functions, salience detection, and self-referential thinking.

LLD is also characterized by compromised microstructural integrity in normal-appearing white matter, as assessed by diffusion-tensor imaging.[46–51] Relative to controls, reduced white matter integrity among depressed older adults is observed across a distributed set of cerebral networks,[46,51] though lower integrity of the uncinate fasciculus, cingulum, and frontal association fibers is most consistently reported.[52,53]

Compromised white matter tracts within the salience network, the DMN and the ECN may contribute to functional network abnormalities and mediate the expression of depression symptomatology. WMH in non-depressed older adults have been associated with decreased structural connectivity of white matter tracts,[54] and alterations in functional activation and resting state connectivity.[55] In depressed older adults, WMH severity predicted greater activation of the anterior cingulate during an affective-reactivity task (i.e., presentation of fearful faces), suggesting an association between WMH and heighted sensitivity of the dACC to negative stimuli.[56] Greater WMH burden in LLD has also been liked to altered connectivity within the DMN,[57] suppressed activation of the DLPFC during a cognitive control task, and reduced connectivity of the DLPFC with task-relevant brain regions including the middle frontal gyrus and supramarginal gyrus.[58] Moreover, when compared to healthy controls, depressed older adults exhibit reductions in functional as well as structural connectivity between the PCC/precuneus and the dACC of the ECN, which, in turn, predicts poorer executive function and working memory performance.[59] These data collectively suggest that white matter abnormalities in LLD are associated with alterations in neural recruitment and connectivity in networks that subserve cognitive and emotional processing. In addition, as outlined below, microvascular lesions and disruptions in microstructural integrity may predispose to specific clinical phenotypes of LLD and predict response to antidepressant treatment.

4. Network-Level Disruptions Contribute to Clinical Manifestations of LLD

4.1. Depression with Executive Dysfunction

Executive dysfunction, which is present in approximately 40% of older individuals with LLD,[60] appears to reflect inefficient functioning within the ECN,[28,61–64] as well as the ECN's interactions with the salience network and the DMN. These network-level dysfunctions give rise to behavioral manifestations of executive dysfunction that are common in patients with LLD and executive dysfunction, or depression-executive dysfunction (DED) syndrome. These behavioral disruptions include difficulty inhibiting attention towards task-irrelevant stimuli and a diminished ability to accomplish goal directed actions.[60] Further, DED syndrome is characterized by disability, declines in quality of life,

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and poor antidepressant response.[65–67]Longitudinal study of intact aging adults suggests that declines in executive function and decreased white matter integrity both attenuate the often observed age-related increase in positive mood and may contribute to difficulties with emotion regulation that make older adults susceptible to depression[68]. Further, in those who do suffer from LLD, impairments in executive functions often persist even after remission of depression.[69] Thus, as with other LLD subtypes, understanding specific patterns of abnormal network interactions in DED can help to inform novel treatment approaches.

Converging evidence shows reduced functional connectivity between the dACC and spatially distal brain regions in LLD. For example, Respino et al.[28] observed that resting state functional connectivity is decreased between a seed in the dACC and posterior regions of the bilateral precuneus, consistent with other observations of decreased connectivity among the salience network and the posterior ECN and DMN in aging.[70–72] This decoupling between the precuneus and the dorsal ACC is particularly important due to the putative role of the precuneus in executive functions supported by the DMN that are often disrupted in LLD, including self-referential thinking,[73] task-switching, working memory, and cognitive flexibility.[74]

Relying on a novel approach for the analyses of resting state fMRI data termed regional homogeneity, which leverages the synchronization of the fMRI time series to provide a measure of local network connectivity, Respino et al.[28] reported greater regional homogeneity of the dACC in depressed older adults relative to age-matched healthy controls. Further, within the subjects with LLD, greater regional homogeneity of the dACC was associated with better cognitive flexibility and working memory. The observed link between dACC regional homogeneity and executive functions in LLD highlights the role of the dACC as an important hub that supports efficient connectivity among networks central to LLD, whereas disrupted connectivity with this region may contribute to the expression of LLD with executive dysfunction.[75,76]

There is a relationship between measures of connectivity at the structural level, particularly increased WMH, and executive dysfunction in LLD both cross-sectionally[77,78] and longitudinally.[79] In a prospective study of 64 older adults, a dose-response relationship between WMH and cognition was detected. Specifically, greater baseline WMH severity was associated with greater memory and executive function deficits in those with LLD, but not in controls.[79] Recent studies have also investigated the impact of WMH in older adults on connectivity at the network level, investigating how network disruptions contribute to poor executive functions. Among non-depressed older adults, WMH are associated with altered functional connectivity in the ECN[80] and in the DMN.[81]

In LLD, WMH may preferentially affect specific white matter fibers tracts, such as the superior longitudinal fasciculus and the uncinate.[44] WMH in these fiber tracts are tied to executive dysfunction[44] and disrupted reward learning.[82] Further, decreased structural connectivity of the anterior and posterior cingulate, middle frontal cortex, supramarginal gyrus, and thalamus is associated with poorer executive function, as measured by performance on a task requiring set-shifting and cognitive inhibition,[63] supporting a relationship between WMH and regionally-specific structural alterations in connectivity.

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Thus strategically located microvascular lesions and corresponding disruptions in structural connectivity may predict the nature and intensity of cognitive symptoms and contribute to a profile of executive deficits in LLD.

4.2. Negative Cognitive Bias

Preferential processing of negative stimuli in depression reflects a discounting of positive, rewarding information,[83,84] giving rise to depressive ideation, sadness, and anhedonia.[85,86] Individuals with LLD display a range of mood-congruent negative processing biases, illustrated by slower reaction times and less accuracy on tasks using positively-valenced stimuli, a heightened sensitivity to negative feedback, and a tendency to interpret ambiguous stimuli (e.g., neutral faces) as negative compared to healthy controls. These biases are believed to contribute directly to depression, where individuals have a persistently negative view of oneself, the world, and the future.[87] Moreover, these abnormalities in processing of emotional information predict recurrence of mood episodes.[88] Affective processing in MDD[89] is characterized by deficits in attentional disengagement from negatively-valenced stimuli and impaired cognitive control when processing negative information.[90]

In individuals suffering from depression, negative cognitive biases in processing of both internal and external stimuli contribute to negative self-referential thoughts.[91–95] Negative self-referential thoughts produce a range of cognitive (guilt, rumination, and self-criticism) and affective (e.g., feelings of worthlessness and sadness) symptoms of depression[22–25] and are associated with resistance to traditional antidepressant treatments.[96,97] Alterations in network connectivity both within and between the salience network, the DMN, and the ECN have been tied to negative cognitive biases, including negative self-referential thinking. For example, negative self-referential thinking in depression is associated with abnormal task-based activation of the anterior nodes of the DMN.[98–100] Dominance of the DMN relative to the “task-positive” network engaged during executive control is associated with symptoms of rumination during the depressed state.[101] Moreover, following treatment with antidepressant medication, normalization of hyperconnectivity has been observed in the posterior, but not anterior DMN.[102]

In addition to the role of abnormalities in functional connectivity, abnormal white matter integrity in the salience network and the DMN of older depressed adults interferes with the shifting of attention away from negative thoughts about one’s self.[103,104] Further, aging related white matter microstructural abnormalities in the dACC and in the uncinate are associated with residual negative self-referential thinking following treatment with an SSRI.[105] These findings suggest that disrupted connections among the salience network, the DMN and the ECN may interfere with the maintenance of one’s self-representation, leading to persistent negative self-referential thoughts.[106–108]

4.3. Apathy

One-third to one-half of LLD patients suffer from apathy[109] a persistent and disabling disorder of motivation characterized by reduced goal-directed behavior, emotional blunting, and cognitive disturbances.[110,111] Apathy of LLD predicts chronicity of depression, compromised quality of life, and high caregiver burden.[86,112–116] Remission rates

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with pharmacotherapy are especially low in LLD with prominent apathy;[117] in some cases, selective serotonin reuptake inhibitors (SSRIs) even may result in worsening of apathy.[118–121]

Behavioral and cognitive disturbances in apathy of LLD include impairments in the generation and execution of strategies that guide goal-directed behavior, attentional set-shifting, and working memory.[10,121,122] Abnormalities in brain networks subserving these processes, including the salience network and the ECN, and their reciprocal interactions with reward structures (e.g., nucleus accumbens) may underlie apathy of LLD. Through dense reciprocal connections, the SN interacts with structures of the reward network to signal anticipatory reward and intrinsic motivation, key processes that trigger goal-directed action[123] that are disrupted in apathy.[10] Structural abnormalities in the salience network are common biological substrates of apathy.[124,125] Apathetic, depressed older adults exhibit focal atrophy in the dACC of the salience network,[126,127] and our group has shown that structural abnormalities in frontolimbic white matter and the insula of the salience network predict persistence of apathetic states in LLD.[128] Impaired integration of signals among these networks has also been associated with the presence of apathy in LLD.[129] Depressed older adults with apathy exhibit diminished intrinsic connectivity of the salience network and alterations in functional connectivity between the salience network and key nodes of the ECN and anterior portion of the DMN.[130,131]

In addition to the functions noted earlier, the ECN serves to translate intention into action,[132] by supporting planning, action generation, and selective and sustained attention[132,133] processes that are commonly disrupted in apathy.[10] Not surprisingly, then, compromise of the ECN, and its large-scale network connections, may contribute to the development of apathy in LLD. Relative to non-apathetic depressed older adults, depressed older adults with comorbid apathy demonstrate altered connectivity between structures of the ECN and the salience network (e.g., insula).[128] Moreover, the ECN interacts with structures of the reward network to guide reward-based decision making. Reduced rsFC between regions of the ECN and the reward network is associated with slowed decision speed and greater effort sensitivity,[134] factors that contribute to reduced action initiation in apathy.[135] In addition, depressed adults with comorbid apathy exhibit microstructural abnormalities in fiber bundles connecting hub nodes within these networks, which may hinder the integration of reward-related signals.[126] Taken together, these studies indicate that a core set of brain networks (salience, DMN, ECN) interact to support different phases of motivated behavior, and the apathy syndrome may arise in LLD from disturbances in connectivity among these key circuits. In other words, apathy within the context of depression (emotional indifference, unwillingness to exert effort to perform goal-directed behaviors) may be a result, at least in part, of disruption in the networks important for salience detection and goal-directed behavior.

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5. The Use of Computational Models to Understand Specific Behavioral and Network Disturbances in LLD

There is a high degree of variability in network-level changes and associated maladaptive behaviors and cognitive processes that arise due to the combined effects of aging and depression. As a result, there are multiple potential combinations of motivational and mood disturbances that contribute to poor course of illness and treatment response in LLD, reflecting underlying network pathology. Understanding these individual differences at the network level can inform targeted, personalized interventions. In the following section we review how specific network changes may point at such focused treatment strategies.

5.1. Computational Approaches to Identifying Networks Implicated in LLD

Computational modeling approaches provide precise, quantifiable parameters of maladaptive behaviors in aging and MDD, particularly deficits emerging from negative cognitive biases, including associative learning and value representation.[136–140] These models may be applied to address the combined effects of aging and depressive symptomatology on resulting motivational and mood disturbances that are common in LLD. Thus far, computational models in LLD have been particularly useful in accounting for changes in goal-directed behaviors, decision-making, and motivation in depressed older adults.[141,142] For example, Dombrovski et al.[143] used a reinforcement learning modeling approach and observed that depressed older adults with a history of suicide attempts were less likely to effectively use positive vs. negative feedback to learn stimulus-response contingencies. These findings suggest that deficits in experiential learning and optimal choice selection may contribute to depressive symptoms and suicidality in a subgroup of older adults who possess an inability to consider alternative options in the context of a negative view of the world.

A promising application of computational approaches in the study of late-life mood disorders is to select and optimize model parameters corresponding to behavioral performance (e.g., learning rate, prediction error) to understand individual differences in the disrupted cognitive processes of LLD. The application of individualized modeling approaches can enhance our understanding of individual developmental trajectories in aging and depression, disrupted networks and behaviors that may be risk factors for psychopathology late in life, and personalized treatment targets in individuals with late-life depression.

These modeling approaches have been applied to characterize behavioral and network disruptions that correspond to specific clinical symptom profiles of depression, which may be used to identify more effective personalized treatments for depression. Reinforcement learning models of the pursuit of positive, rewarding outcomes of behavior have been widely shown to demonstrate deficits in motivation and effort expenditure that give rise to motivational disturbances in depression, including apathy and anhedonia.[139,144,145] The patterns of behaviors identified by these reinforcement learning models are associated with reduced activation in response to regions of the salience network (dACC and anterior insula) and prefrontal regions of the ECN (e.g., DLPFC).[146,147]

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Computational modeling has been less widely explored in older adults with depression, but may be useful for identifying individual differences in the clinical manifestations of LLD at the network level to identify individuals who are at high risk for relapse following treatment[148] and would benefit from treatments that target motivational disturbances, such as the interventions utilizing cognitive remediation or physical activity described below.

5.2. Advanced Modeling of White Matter Abnormalities and LLD Pathogenesis

Modern quantitative techniques have the potential to characterize the pathophysiology of white matter abnormalities in LLD and assess their impact on cognitive and affective circuitry. Graph-theoretical approaches can be applied to diffusion imaging to model the network topology of white matter tracts.[149] By quantifying multiple properties of the structural connectome, including estimates of network efficiency and integration, these metrics may provide greater insight into the morphologic substrates of brain network dysfunction in LLD. In a sample of adults with small vessel disease, those with comorbid depression showed impaired edge connections in select subnetworks including corticolimbic fibers, commissural fibers, and frontoparietal pathways, compared to controls.[150] Similarly, depressed older adults with comorbid cognitive weaknesses showed greater disruptions in network properties (lower connective strength) within corticostriatal and ECN systems compared to cognitively intact depressed older adults,[151] highlighting select structural network characteristics associated with the presentation of cognitive deficits in LLD.

Modern DTI-derived parameters have also been established to probe microstructural properties with greater sensitivity and specificity. For instance, peak-width of skeletonized mean diffusivity (PSMD) is a novel, DTI-derived metric of small vessel disease that provides a global estimate of diffuse white matter dysfunction. A recent study found that a PSMD outperformed conventional SVD (WMH) and diffusion markers in predicting cognitive performance and dysregulation of executive function behaviors in participants with LLD.[152] Another DTI-derived metric, free water diffusion, models extracellular abnormalities in the white matter compartment, and has recently been applied to interrogate diffusion properties in schizophrenia and Alzheimer's disease, though it has not yet been evaluated in LLD. Finally, dynamic contrast-enhanced MRI is a novel technique for quantifying blood-brain barrier permeability in vivo.[153,154] While this approach has not yet been used in LLD, it may be leveraged to characterize the contribution of blood brain barrier dysfunction to structural and functional network abnormalities in LLD. Applying these modern approaches to identify pathophysiologic processes contributing to white matter abnormalities in LLD may reveal novel mechanistic pathways for targeted intervention.

5.3. The Use of Statistical Classifiers to Identify Subtypes of Depression

A particular application of computational approaches to further our understanding of depression and treatment response focuses on identification of brain-based subtypes of psychiatric disorders. Neuroimaging-based computational approaches have been developed to guide personalized approaches to targeted treatment selection, relying on individual-level predictions to determine whether a given treatment is likely to succeed. A recent computational development in quantifying individual differences for personalized treatments is based on the classification of subtypes of depression based on unbiased computational

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methods with the goal of identifying statistical classifiers that can be applied at the level of the individual.van Waarde et al.[155] used resting state fMRI and trained a support vector machine (SVM) classifier on individual patients' pre-treatment scans to predict the outcome of ECT in individuals suffering from TRD.

A study by Drysdale et al.[156] used a canonical correlation and hierarchical clustering approach to identify subtypes of depression based on unique combinations of network-level resting-state functional connectivity and clinical symptoms of MDD. With this approach, they identified distinct biotypes of depression that varied in degree of anhedonia and anxiety (i.e., the clinical features most highly associated with observed patterns of functional connectivity in the depressed sample). Further, the biotypes differed in their response to treatment with TMS, suggesting that connectivity-based biotype classification may be an indicator of potential for treatment response and provide actionable information about the optimal treatment option at the individual level. In another study, Dunlop et al.[157] used baseline resting state functional connectivity (RSFC) between the subcallosal cingulate cortex and other brain areas to predict differential outcome to cognitive behavioral therapy or pharmacotherapy in individuals with MDD. They found that RSFC patterns differentially predicted response to the two treatments, with negative summed RSFC associated with remission after pharmacotherapy and positive summed connectivity associated with remission after psychotherapy.

These studies all highlight the application of rigorous computational approaches to facilitate precision psychiatry by classifying complex patterns of neural, behavioral, and clinical features of depression. By targeting specific deficits, this may increase the likelihood of symptomatic response.[158,159] These computational approaches may also be extended to treatment prediction in late-life depression, with preliminary evidence for modeling approaches that may account for age-related changes in network connectivity and cognition that contribute to accelerated brain aging and negative cognitive biases in LLD.[160]

6. Neuroscience-Informed Interventions for LLD

As we have noted, many individuals treated with antidepressant medications or psychotherapy do not achieve adequate response, even after multiple treatment trials.[3,4,161]Even when standard treatments improve mood symptoms, some individuals, especially older adults, are left with persistent executive dysfunction,[65,97,162,163] negative self-referential thinking or persistent motivational disturbances that are associated with disability,[65,97,163] and increased risk of depression recurrence.[30,65,69,97,163] Clearly, additional treatment strategies are needed to improve outcomes among these patients. In particular, nonpharmacological interventions targeting putative network mechanisms of LLD, some of which, may harness neural plasticity in the aging brain, offer promising treatment alternatives.

6.1. Physical Activity Interventions

Physical activity is a promising therapeutic strategy for LLD, demonstrating a capacity to target symptoms with poor treatment response rates and provoke connectivity changes in distinct neural networks. Structured physical activity training significantly reduces

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depressive symptoms in mid- and late-life,[164,165] yielding effect sizes moderate to large in magnitude. When paired with antidepressant medication, physical activity may also maximize treatment outcomes. In a large-scale RCT of 121 depressed older adults, 81% of participants achieved remission following 24 weeks of sertraline combined with aerobic exercise training, compared to 45% in the sertraline-only condition.[166,167]

Physical activity may also attenuate symptoms of LLD inadequately addressed by traditional antidepressants, including executive dysfunction, apathy, and disability. Physical activity effectively improves cognitive performance in older adulthood, producing the greatest gains in executive function,[168,169] the domain most impacted in LLD. In older adults with major depression, medication combined with aerobic exercise training produced significantly greater improvements in general cognition, visuospatial/executive functions, and disability than medication alone.[170] Apathy symptoms are reduced following physical activity training in nursing home residents[171] and individuals with schizophrenia,[172] and future studies are needed to characterize its therapeutic potential for the treatment of apathy in LLD. Taken together, physical activity is a low-cost and accessible strategy to reduce geriatric depression with the potential to attenuate the most treatment-resistant symptoms of LLD.

Physical activity may generate improvements in mood and cognitive function by selectively remediating neural circuits disrupted in LLD. In community-dwelling older adults, 24 weeks of aerobic exercise training altered resting state connectivity within the DMN,[173] as well as inter-network connectivity between key nodes of the DMN and the ECN.[174] In a recent RCT, 12 months of moderate-intensity walking increased connectivity in the salience and dorsal attention networks.[175] Exercise-induced changes in DMN connectivity have been shown to mediate the relationship between exercise and improvements in executive functioning.[176] Along with modulating functional network dynamics, physical activity produces volumetric increases in the prefrontal cortex and hippocampus,[177–179] key structures that exhibit morphologic changes in LLD[180] and have been linked to poor antidepressant treatment response rates.[181,182] Physical activity stimulates several cellular processes that may have restorative or neuroprotective effects on neural network abnormalities in LLD, leading to improved mood and improvement in cognitive function. Physical activity promotes neurogenesis, upregulates neurotrophic factors, and suppresses pro-inflammatory signaling and oxidative damage[183] – directly targeting cellular and molecular pathways implicated in depression pathogenesis.

Vascular health is also improved by physical activity, which increases cerebral blood flow and angiogenesis[184] and thus may be a particularly promising treatment for depressed older adults with pronounced vascular pathology. Future trials selectively targeting distinct symptom dimensions or profiles will advance our understanding of the clinical phenotypes of LLD that may benefit most from physical activity.

6.2. Cognitive Remediation for LLD

Network dysfunction in aging and depression can be targeted using cognitive interventions that are designed to improve functions in the networks implicated in LLD through repetitive stimulation. For example, we conducted a proof-of-concept randomized clinical trial of a video game-like intervention designed to target the ECN by improving age-related

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deficits in multitasking. Individuals over the age of 60 with a current major depressive episode were randomized to problem solving therapy (PST) adapted to treat depression with executive dysfunction or the digital multitasking intervention. The two intervention groups showed a similar improvement in depression, whereas those randomized to the video game-like condition demonstrated significant improvements in working memory and sustained attention.[185] Further, relative to subjects completing PST, subjects completing the multitasking intervention showed greater improvement in self-referential thinking.

Cognitive training may alleviate both depression and executive dysfunction by targeting engagement of the ECN, as well as the salience network and the DMN. A cognitive intervention designed to improve reasoning and problem-solving in older adults found increased cerebral blood flow in regions of the ECN post-training.[186]Though few studies have examined the underlying neural mechanisms tied to improved mood symptoms in LLD. [187,188], a group-based metacognitive intervention for older adults targeting executive functioning strategies was associated with increased resting state functional connectivity within the ECN, as well as increased anticorrelation between the ECN and DMN.[189] Further, in a recent single-arm study of middle-aged and older adults with LLD, four weeks of a digital cognitive control intervention effectively engaged the ECN (increased ECN connectivity), and generated improvements in mood, executive function performance, and self-reported dysexecutive behaviors.[190] These results suggest that the engagement of the ECN through repeated cognitive stimulation may be a central mechanism for rescuing dysfunctional brain networks that contributes to both the mood and executive dysfunction in many suffering from depression.

Cognitive training in LLD with apathy has been less widely studied. However, in patients suffering from schizophrenia, targeted cognitive training reduced negative symptoms, including motivational disturbances, and improved associated cognitive and functional deficits.[191] Thus, a similar approach that selectively targets cognitive processes and neural networks disrupted in apathy of LLD may prove to be efficacious. In older adults with major depression, four weeks of a novel mobile DCT program improved working memory and sustained attention, key processes disrupted in apathy.[190] Moreover, in the cognitive training study referenced above, training-related changes in functional connectivity of the ECN and DMN were associated with reduced apathy post-intervention.[190] These data provide the first evidence that selective cognitive training of attentional and cognitive control deficits may rescue neural circuits disrupted in apathy and contribute to mood and cognitive improvements.

7. Conclusions

While standard approaches to LLD treatment are efficacious in alleviating the mood symptoms of many suffering from LLD, many individuals are left with residual cognitive symptoms and are prone to relapse. Understanding networks that contribute to common clinical subtypes of LLD can inform the development and application of alternative treatment approaches by optimizing the functioning of aspects of the aging brain. Two such approaches that demonstrate preliminary evidence of efficacy, at least in a subset of older individuals with depression, are digital cognitive training and physical

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exercise interventions. While we are not advocating that these types of interventions replace traditional antidepressant treatments for LLD, these may be reasonable alternatives for depressed older adults who either don't respond well or can't tolerate traditional antidepressants. Further, given the difficulty many older adults have in accessing expert care for depression using neuroscience to inform and test interventions that are not only efficacious but scalable may prove to be quite beneficial.

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Highlights

- Brain aging may contribute to poor antidepressant response of late-life depression.
- Disrupted brain networks contribute to common subtypes of late-life depression.
- Novel interventions may rescue brain networks central to late-life depression.

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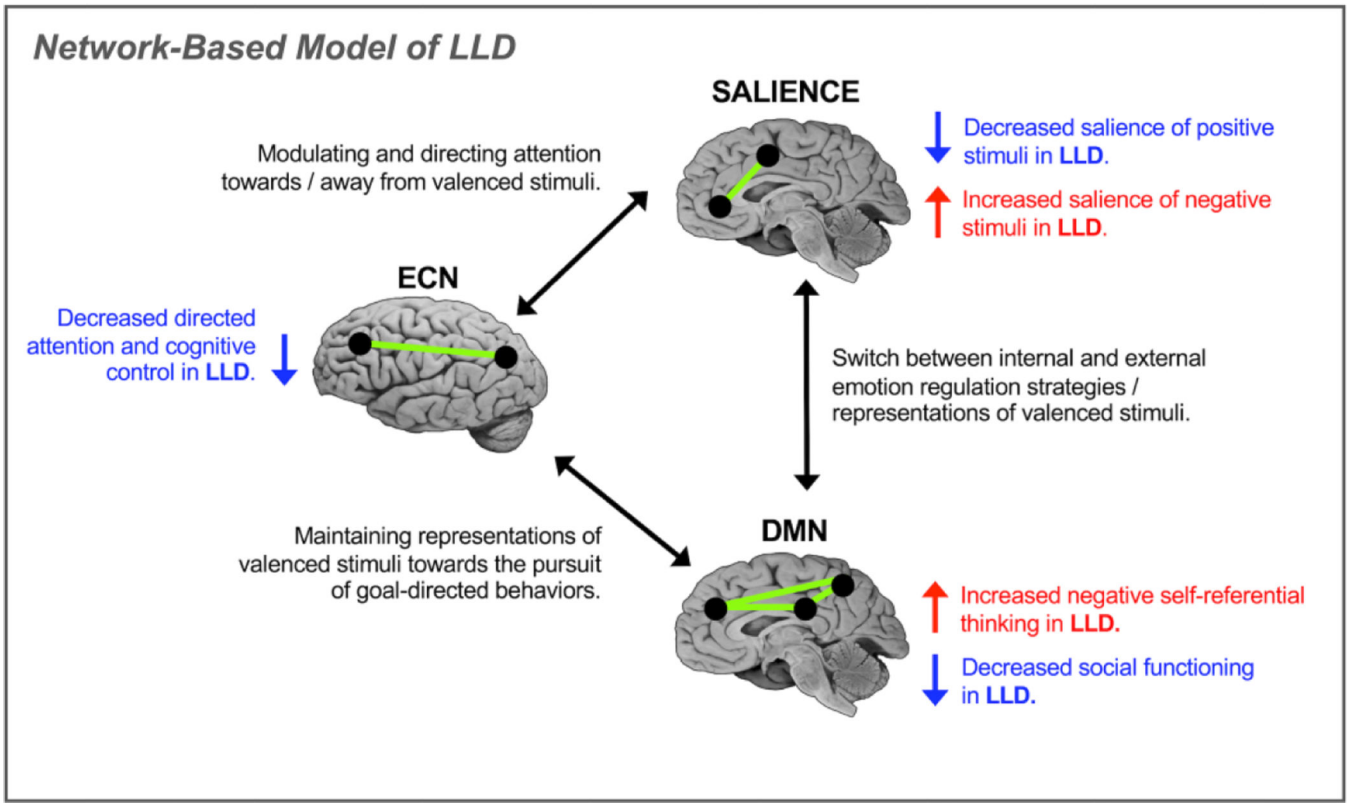

Figure 1:

Proposed network model of late-life depression (LLD). The model accounts for intrinsic connectivity within and extrinsic connectivity between the salience network, the default mode network (DMN) and the executive control network (ECN). Network-level disruptions in connectivity give rise to disrupted cognitive processes of LLD related to disrupted pursuits of goal-directed behaviors and maladaptive representations of affectively valenced stimuli.