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State of the Science of Neural Systems in Late-Life Depression: Impact on Clinical Presentation and Treatment Outcome

Kevin J. Manning, Ph.D. and **David C. Steffens, M.D., M.H.S.**

Department of Psychiatry, University of Connecticut School of Medicine

Abstract

Major depression in older adults, or late-life depression (LLD), is a common and debilitating psychiatric disorder that increases the risk of morbidity and mortality. Whereas the detrimental consequences associated with LLD highlight the importance of facilitating timely diagnosis and treatment, older adults with LLD are often inadequately or unsuccessfully treated. The latest treatment developments suggest that interventions targeting executive dysfunction and neuroticism, constructs associated with poor response to antidepressants in older adults, are successful in treating depression in LLD. Specific behavioral interventions (computerized cognitive training, mindfulness meditation, and aerobic exercise) appear to improve depressive symptoms and ameliorate executive dysfunction and neuroticism. Yet, we do not fully understand the mechanisms by which these treatments may work. The current paper reviews recent research on neural network changes underlying executive dysfunction and neuroticism in LLD and their association with clinical outcomes (e.g., treatment response, cognitive functioning).

Keywords

neuroticism; executive functioning; geriatric depression; cognitive training; mindfulness

Introduction

Major depression in older adults, or late-life depression (LLD), is a common and debilitating psychiatric disorder. Four percent of older women and three percent of older men have a current diagnosis of LLD[1], and LLD increases the risk of dementia[2], disability[3], and mortality[4]. The detrimental consequences associated with LLD highlight the importance of facilitating timely diagnosis and adequate treatment. Yet, over 50% of patients fail to respond to initial pharmacological treatment, and remission from depression is achieved in only 1/3 of older patients treated with an antidepressant or cognitive behavioral therapy (CBT)[5]. Therefore, it is imperative to develop novel treatments for depression that can either augment pharmacotherapy or be used independently in older adults with LLD. Barriers to

Corresponding Author: Kevin J. Manning, Ph.D., University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030, 860-679-2272, manning@uchc.edu.

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psychiatric care in older adults also highlight the importance of developing interventions that are accessible to interdisciplinary team-based care providers[6–8].

Depression-related treatment development requires the identification of modifiable constructs relevant to the pathophysiology of LLD. Converging neuropsychological and neuroimaging evidence indicates the cognitive process of executive functioning and the personality trait of neuroticism each individually and independently predispose and perpetuate mood disturbance and cognitive decline in older adults[9–12]. Older adults with executive dysfunction and neuroticism are commonly treatment-resistant to standard antidepressants[13, 14]. Yet, increasing evidence suggests executive dysfunction and constructs associated with neuroticism respond to behavioral interventions in older adults[15–17]. Thus, neuroanatomical substrates of executive dysfunction and neuroticism may be useful treatment targets in LLD. Executive functioning is a term used to refer to processes that regulate higher order cognition, emotional wellbeing, and reward processing[18]. Executive functions enable individuals to evaluate risks and rewards, engage in decision-making and planning, regulate emotional responding and inhibit inappropriate choices[18]. Neuroticism is defined as a tendency toward emotional reactivity[19]. Individuals high in neuroticism are predisposed to experience psychological distress and negative mood states and are described as anxious, apprehensive, and prone to experience worry, sadness, loneliness, and dejection[19].

The latest treatment developments suggest that behavioral interventions targeting neuroanatomical substrates of executive dysfunction and neuroticism are successful in ameliorating these behaviors and treating depression in LLD. The purpose of this paper is to review recent research on neural network changes underlying executive dysfunction and neuroticism in LLD and their association with clinical outcomes (e.g., treatment response, cognitive functioning). We begin by initially describing the relevant neural networks in LLD. We then provide an overview of treatments that seek to improve depression by targeting executive dysfunction and neuroticism and associated neurobiological substrates. We focus on the interventions of cognitive training, mindfulness meditation, and aerobic exercise as 1) current evidence indicates these treatments bring about clinical improvement and engender neuroplasticity, or the brain’s ability to change structurally and functionally as a result of external stimulation and 2) cognitive training, mindfulness meditation, and aerobic exercise can all be implemented in an interdisciplinary care setting. Finally, we end with a brief discussion of screening implications within primary care practices as a means to enhance early identification, prevention, and treatment of LLD.

Major Neural Networks Relevant to LLD

Neuroimaging has helped clarify the neuroanatomical substrates associated with LLD. Connectivity analyses from functional magnetic resonance imaging (fMRI) have been especially helpful. Functional connectivity is based on the observation that spontaneous blood oxygen dependent (BOLD) signal fluctuations among interconnected brain regions tend to be temporally correlated. It is thought that functional connectivity during rest (where subjects are instructed to lie still with their eyes closed) or when subjects complete experimental tasks reflects important inter-relationships among brain structures with related

functions. Converging evidence has identified three prominent functional networks in geriatric depression and other psychiatric illnesses[11, 20, 21]. These are a: 1) a Cognitive Control Network (CCN), mediated by connections between the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate, and posterior parietal connections, and involved in complex cognitive processing and emotional regulation; 2) a Default Mode Network (DMN), mediated by medial prefrontal cortex (mPFC)-posterior cingulate connections, and normally inhibited during complex cognitive processing and active during internal mentation, and a 3) Salience Network (SN), with the right anterior insula as the primary hub, that assess the significance of external stimuli and, together with amygdala activity, assigns emotional and motivational value to that stimuli.

Understanding abnormalities within and between functional networks can further elucidate potential treatment targets in LLD. Broadly speaking, prominent symptoms of LLD are associated with decreased activity in the CCN (executive dysfunction) and hyperactivity in the SN and DMN (emotional arousal, rumination, apathy, negativity bias)[11, 21]. Recently, Karim et al.[22] investigated whether antidepressants resulted in functional connectivity changes to CCN, DMN, and SN in 33 adults with LLD. Thirty-nine percent of the sample did not experience depression remission at three months. Compared to non-remitters, those who achieved remission experienced significant changes in the CCN and DMN over the course of treatment. Specifically, remitters experienced increased connectivity between the CCN-posterior cingulate of the DMN and decreased connectivity between the CCN-middle temporal gyrus of the DMN. Group differences in remitters and non-remitters were also observed in the SN and other aspects of the CCN-DMN. Considering that decreased activity in the CCN and over-activity in SN-DMN are associated with executive dysfunction and negative thinking/rumination[11, 23], respectively, interventions that enhance the efficiency and processing of the CCN and SN-DMN may be especially useful in the treatment of LLD.

Underlying Network Dysfunction

Executive Dysfunction

Behavioral signs of executive dysfunction are common in LLD. Estimates suggest 30–40% of non-demented older adults with major depression exhibit signs of executive dysfunction on cognitive examination[24]. Depressed older adults often perform poorly on tests of verbal fluency (participants are required to generate as many words as possible that begin with a certain letter or belong to a category), the Wisconsin Card Sorting Test (a measure of novel problem solving, cognitive flexibility, and working memory), the Tower of London (a test of planning) and the Stroop Color–Word Interference (a test of response inhibition)[25]. Performance on these tests correlates with structural and functional abnormalities in cognitive control regions, namely the dorsolateral prefrontal cortex (DLPFC), the dorsal and rostral regions of the anterior cingulate, and parietal association regions[10, 11].

Weakness in Cognitive Control Network (CCN) regions is associated with poor treatment response in LLD. It is well established that worse performance on behavioral measures requiring response inhibition, sustained attention, and cognitive flexibility, as well as greater subjective complaints of perceived weaknesses in these domains, are predictive of poor antidepressant treatment response in older adults with major depression[26–28]. More recently,

functional connectivity analyses have been used to shed light on the neuroanatomical substrates linking behavioral evidence of cognitive control dysfunction to poor treatment responses. For example, Alexopoulos et al. [11] found that 16 older adults with non-psychotic unipolar depression exhibited decreased functional connectivity between the left DLPFC and dorsal anterior cingulate and the left DLPFC and bilateral inferior parietal cortices when compared to non-depressed healthy older adults. Decreased CCN connectivity at baseline also correlated with behavioral measures of executive functioning and distinguished older depressed adults who remitted following 12 weeks of antidepressant treatment from those who did not. Furthermore, compared to remitters, non-remitters demonstrated decreased functional connectivity at baseline between the bilateral DLPFC, dorsal anterior cingulate, and inferior parietal cortices[11]. Similar findings have been found with CBT as the treatment modality. Gallagher-Thompson et al. [29] found that increased activity in the DLPFC and other CCN regions during an executive functioning test (Wisconsin Card Sorting Test) completed in the scanner predicted a better CBT response in 45 older adults with major depression.

Neuroticism

Elevated neuroticism is common in LLD. Data from two large cohorts, the Neurocognitive Outcomes of Depression in the Elderly[30] and the Neurobiology of Late-Life Depression[31] studies, indicate high neuroticism self-reported on personality questionnaires is present in about 45% of older adults with LLD. It has long been established that neuroticism increases the vulnerability to develop clinical anxiety and major depressive disorders[32], [33]. The presence of neuroticism also perpetuates major depression in older adults and is detrimental to the cognitive functioning of this cohort[34]. While controlling for depression severity, high neuroticism was associated with both poor depression response and global cognitive decline over 10 years in older adults with LLD[9]. Clinically, neuroticism is measured with questionnaires like the NEO-Personality Inventory[19], a measure used to assess the “big five” personality traits (neuroticism, extraversion, openness, conscientiousness, agreeableness). Related proxies of neuroticism include responses on questionnaires measuring stress resilience or rumination and emotional categorization tests, also referred to as a negative self-referential processing task, where individuals read a list of negative and positive words and endorse whether or not those words apply to them[35].

Neuroticism is associated with structural and functional abnormalities in brain regions related to emotional processing and emotional regulation. While controlling for depression and anxiety symptoms, Carballedo et al.[36] found that high neuroticism in 45 middle aged adults was associated with decreased resting state functional connectivity between the Cognitive Control Network (CCN) and Salience Network (SN), and increased functional connectivity between regions of medial PFC (mPFC). The mPFC is a prominent hub of the Default Mode Network (DMN) critical to social cognition, self-reference, and emotional evaluation[12]. Increased resting state functional connectivity in the mPFC and amygdala is also correlated with neuroticism in LLD[12]. Evidence suggests similar networks are engaged when functional connectivity analyses are correlated with proxies of neuroticism like negative self-referential processing. That is, a larger endorsement of negative words during negative self-referential processing is associated with increased connectivity between the

CCN (DLPFC) and mPFC in depressed younger adults[37] and non-depressed adults high in neuroticism[38], implying the need for the CCN to "over-regulate" or compensate for hyperactive "bottom-up" negative arousal associated with self-criticism. Treatments that strengthen "top-down" CCN functioning and alleviate "bottom-up" arousal may be especially useful in treating clinical symptoms of LLD, considering older adults with LLD have greater CCN dysfunction compared to both age-matched controls and younger depressed subjects[39].

Current Perspectives on Select Behavioral Interventions in LLD

We review here the recent literature on the interventions of computerized cognitive training, mindfulness meditation training, and aerobic exercise as they relate to the treatment of LLD. Wherever possible, we emphasize research showing that these treatments are effective in hard to treat LLD patients who exhibit executive dysfunction or elevated neuroticism. Two converging lines of research support the premise that these treatments result in clinical change in LLD by targeting the Cognitive Control Network (CCN), Default Mode Network (DMN), and Salience Network (SN). First, clinical studies suggest cognitive training, mindfulness meditation, and aerobic exercise improve depression symptoms and executive dysfunction or neuroticism in LLD [17, 40, 41]. A second line of research indicates these treatments in non-clinical samples (e.g., healthy middle aged adults, convenience college samples) actually change brain functioning[42–44].

Computerized Cognitive Training

Computerized cognitive training (CCT) is a behavioral intervention that uses repetitive learning to improve cognition or socio-emotional functioning and presumably engender neuroplasticity[45]. The goal of CCT is to enhance cognitive or socio-emotional learning and reorganize underlying brain systems, thereby affecting clinical change[46]. CCT is an established method to improve cognitive functioning in older healthy adults[47, 48] and more recent studies have investigated the underpinnings of this treatment. Cao and colleagues[49, 50] followed older adults who underwent 24 hours of CCT targeting memory, problem-solving, and visuospatial abilities, and who also completed neuroimaging at baseline and one year later. Compared to a control group, CCT increased the integrity of white matter in brain regions associated with the CCN, increased resting state functional connectivity within the CCN, and decreased resting state functional connectivity between the CCN and DMN. Moreover, increased connectivity within the CCN correlated with improved cognitive functioning. Elsewhere, in a sample of 36 healthy younger adults who underwent two MRIs one week apart, five hours of CCT targeting executive functioning was associated with reduced amygdala activity during the presentation of negative pictures[51]. Exploratory evidence from this study further indicated that CCT improved resting state connectivity between the amygdala (the hub of the SN) and inferior frontal gyrus (part of the CCN).

Early evidence is promising in linking (non-computerized) cognitive training to structural brain changes. Preliminary evidence in 11 older adults with mild cognitive impairment (MCI) also suggested that (non-computerized) memory training showed a trend towards increased gray matter volume in the mPFC over three months, whereas MCI participants who underwent yoga training did not experience any change in volume over that same time

frame[52]. Elsewhere, changes in white matter integrity measured with diffusion tensor imaging were reported between older healthy adults who underwent 8 weeks of non-computerized memory training and a control group[53]. Integrity of the uncinate fasciculus, a white matter pathway connecting the prefrontal cortex with limbic regions, decreased in the control group and slightly increased in the treatment group[53]. Notably, older adults with LLD exhibit decreased structural integrity of the uncinate fasciculus compared to non-depressed age-matched peers, and decreased integrity is correlated with executive dysfunction and depression symptoms[54]. Together, this evidence suggests CCT in healthy adults without psychiatric illness is associated with functional brain changes to the CCN, DMN, and SN, and structural changes to brain regions correlated with self-referential processing and emotion regulation

Executive dysfunction and depression symptoms improve following CCT in LLD. Morimoto et al.[40] developed a CCT program designed to target the executive functions of response inhibition, cognitive flexibility, and sustained attention. The authors tested the intervention in older adults with LLD who had failed at least one trial of antidepressant. Findings revealed that 30 CCT hours completed over one month resulted in a greater decrease in depression compared to treatment with escitalopram over three months. Treatment with CCT, but not escitalopram, also improved cognitive flexibility and results indicated worse cognitive flexibility at baseline was associated with larger improvements in depression in those who received CCT[15]. Elsewhere, Anguera et al.[16] found that both CCT targeting executive functioning and problem-solving therapy improved depression in LLD, yet only CCT improved performance on objective measures of executive functioning. Notably, Anguera and colleagues also found that CCT, but not psychotherapy, improved negative self-referential processing in LLD. Patients who underwent CCT endorsed less negative words as describing themselves post-treatment when compared to patients who underwent problem-solving therapy. Thus, while yet untested, it is plausible that CCT may improve neuroticism in older adults, consistent with evidence that CCT targeting executive functioning decreases rumination[55] and increases self-reported stress-related resilience[56] in samples of college students.

Mindfulness Meditation Training

Mindfulness meditation training (MMT) involves exercising focused attention and practicing emotional regulation through nonjudgmental awareness. Nonjudgmental awareness involves the cognitive reappraisal of emotion-laden thoughts and -perspective taking. The MMT trainee aims to view wandering thoughts in a non-evaluative manner; that is, as simply thoughts, and not inherent to any sense of self. It is increasingly apparent that MMT activates the CCN and DMN. Creswell and colleagues[44] conducted pre- and post-intervention resting state functional connectivity analyses on 35 well-educated middle aged adults who were randomly assigned to either to three days of MMT or relaxation activities (e.g., walking, stretching). Participants reported modest elevations in work-related stress but were otherwise apparently free of cognitive impairment and psychiatric distress. Compared to relaxation activities, MMT increased resting state connectivity between the CCN (DLPFC) and DMN (PCC), neural system changes commonly associated with increases in sustained attention and emotional regulation. Elsewhere, using a sample of 15 cognitively

normal and psychiatrically healthy middle aged adults, Zeidan et al.[57] provided evidence that four 20 minute sessions of MMT resulted in decreased anxiety symptoms and greater activation in DMN and SN regions, namely the mPFC, anterior cingulate, and anterior insula. These findings are consistent with a recent meta-analysis of 300 meditation practitioners pointing to an association between MMT and structural brain regions in regions of the prefrontal cortex, insula, and mPFC[58].

MMT improves cognitive dysfunction and psychopathology in older adults. Lenze and colleagues[17],[48] have recently used MMT in older adults with memory complaints. The authors initially demonstrated the treatment efficacy of MMT in 34 older adults, 73% of whom met criteria for a diagnosis of generalized anxiety disorder or a depressive disorder (i.e., both LLD and minor depressive symptoms)[17]. MMT resulted in six-month improvements in worry severity and executive functioning and memory. In a recent randomized controlled trial of 103 older adults with various psychopathologies, including LLD, MMT compared to a health-education control condition resulted in greater improvement in memory and scores on measures of worry and depression[59]. Further, in a study of 138 adults who previously met criteria for major depression and had an average age of 50 years, eight weekly sessions of MMT (with encouragement to practice mindfulness meditation daily at home) improved NEO-PI-R neuroticism levels at 15 months[60]; moreover, the association between MMT and neuroticism remained significant when accounting for change in depression severity and antidepressant usage.

Aerobic Exercise

It is established that aerobic exercise has effects on overall brain health[61], [62]. It is also becoming increasingly clear that exercise may alleviate depressive symptoms in LLD. Using exercise as a treatment for depression is a natural extension of the seminal “vascular depression hypothesis,” whereby cerebrovascular disease is understood to predispose and perpetuate depression and executive dysfunction in older adults[63], [64], as well as result in decreased physical mobility[65]. Thus, aerobic exercise, by modifying vascular risk factors and enacting neuroplasticity, may prevent or even ameliorate cerebrovascular disease and associated decreased blood flow, and subsequently enhance mood and improve cognitive functioning.

Exercise in older adults improves brain functioning in regions involved in executive functioning and emotional arousal. Compared to a wait-list control group (n=12), older non-depressed adults (n=12) who completed a six week daily 30 minute session of physical exercise using a Nintendo Wi (consisting of aerobic, balance training, weight lifting, and yoga) experienced a significant increase in gray matter volume in the DLPFC and posterior cingulate (PCC)/precuneus cortex, as well as increased functional connectivity between the striatum and regions involved in the CCN and DMN[66]. Elsewhere, preliminary findings from a small study of eight psychiatric healthy and eight depressed middle aged adults who underwent an eight week aerobic exercise intervention revealed a significant decrease in depression in the patient group and decreased activity in the posterior insula and mPFC[67].

Aerobic exercise is effective in reducing mild depressive symptoms in older adults. A meta-analysis of 41 randomized controlled trials of aerobic and nonaerobic exercise interventions

in adults aged 60 or older found that both aerobic and non-aerobic exercise were associated with significantly lower depression severity and this effect was most pronounced in studies requiring a diagnosis of major depression[41]. Aerobic exercise was also as effective as antidepressant treatment in reducing depression and improving cardiovascular risk factors in adults (average age 50) with mild major depressive disorder[68]. Twelve weeks of aerobic exercise was likewise judged to be as equally effective compared to psychotherapy in reducing depression symptoms in LLD[69]. Moreover, compared to psychotherapy, aerobic exercise led to improved physical fitness and enhanced quality of life reporting.

Conclusions and Recommendations

Increasing evidence suggests behavioral interventions can enact clinical change in LLD by targeting the Cognitive Control Network (CCN), Default Mode Network (DMN), and Salience Network (SN). Computerized cognitive training, mindfulness meditation, and aerobic exercise not only improve depression symptoms, but also appear to ameliorate executive dysfunction and neuroticism, constructs associated with poor response to antidepressants in older adults. Moreover, evidence from non-clinical samples suggest these treatments change underlying brain functioning. Additional research is needed, however, to bridge the gap between clinical studies, consisting of largely behavioral outcomes, and imaging studies with healthy samples. Future studies with large clinical samples are needed to demonstrate that post-treatment symptom improvement in LLD is directly related to changes in the CCN, DMN, and SN. Positive findings of mediation between treatment (e.g., computerized cognitive training), target (e.g., increased CCN connectivity), and symptoms (e.g., reduction in depression) would strongly support intervention use in LLD. However, consistent with the recent NIMH clinical trial funding initiative (https://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/index.shtml), failure to establish mediation would also be a valuable finding and lead to further scientific exploration. For example, the identification of new treatment targets would be necessary should cognitive training change clinical symptoms, but not result in (currently hypothetical) changes to functional connectivity. Alternatively, should functional connectivity changes occur in the absence of clinical improvement, modifications to treatment duration and intensity might be required.

While this research progresses, we believe the current body of evidence can be applied toward two clinical recommendations. First, brief assessments of neuroticism, depression, and executive functioning could be routinely provided to older patients in the waiting rooms of primary care offices or administered by nursing staff as part of a clinical encounter. In the presence of LLD, elevations in neuroticism and executive dysfunction would help alert clinicians to older adults at risk for poor antidepressant response (and potential cognitive decline). Second, clinicians treating depressed older adults may wish to consider recommending cognitive training, mindfulness meditation, or aerobic exercise (or a combination of all three; see [70] for an example of combination treatment) as an easy-to-implement augmentation to standard pharmacotherapy treatment.

In summary, understanding abnormalities within and between the cognitive control, default mode, and salience network has helped elucidate the neuroanatomical substrates of executive

dysfunction and neuroticism in LLD and the association between these constructs and treatment response. Ongoing research using functional connectivity holds promise: 1) in unlocking the pathophysiology of depression, 2) identifying neural patterns that might successfully predict treatment response and illness course in LLD, and 3) help inform individualized decisions surrounding beneficial treatments. While there is much progress to be made, this research provides an exciting opportunity for interdisciplinary collaboration between clinicians and neuroscientists involved in geriatric mental health.

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Table 1

Recommendations for Translating Current Neuroscience of Late-Life Depression Into Clinical Practice.

Recommendation	
Define Neural Circuits Associated with Interventions and Treatment Response.	Consistent with the current NIMH Strategic Priority 1.1 and clinical trial funding initiative, we must improve understanding of the function of the brain in both health and neuropsychiatric illness in order to develop effective treatments.
Use Established Assessments in Clinical Practice.	Brief assessments of neuroticism, depression, and executive functioning are proven to be associated with poor outcomes in older adults and should be routinely provided to older adults in order to assess for risk of depression, poor depression treatment response, and cognitive decline.
Recommend Additional Interventions.	Stimulation and stress relief in the form of cognitive training, aerobic exercise, and mindfulness meditation are easy-to-implement augmentations to standard pharmacotherapy that can enhance clinical improvement.