How Late-Life Depression Affects Cognition: Neural Mechanisms

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Abstract Late-life depression is a major health problem and a significant cause of dysfunction that warrants closer evaluation and study. In contrast to younger depressed patients, most depressed older adults suffer more severe variants of the disorder, including significant cognitive impairments. These cognitive changes add to the severity of symptoms and disability that older depressed patients face and likely reflect compromise of certain neural circuits, linking cognitive impairment to late-life depression. Studies examining clinical correlates, neuropsychological testing, and functional and anatomic imaging have yielded a clearer understanding of the neural mechanisms underlying cognitive deficits in late-life depression. This article discusses cognitive impairment in geriatric depression and how developing a better understanding of its neural correlates may lead to improved understanding and outcome of this specific disorder.

Keywords Depression · Geriatric · Cognition

Introduction

Depression in late life is a significant health care risk for older adults and a major cause of disability [1]. Although certain epidemiologic studies indicate that the diagnosis of major depression in community-dwelling older adults is less common than in their younger counterparts [2], select subpopulations of older adults demonstrate a much higher proportion of depression. Among older adult medical outpatients, the prevalence of depression ranges from 7% to 36%, an average of 5% higher than that of community samples [3]. Residents in nursing homes and congregate apartment residences have a 5.7% prevalence of major depression disorder and a 16.5% prevalence of minor depressive symptoms [4]. One particular issue with the diagnosis of depression in older adults is that as much as 15% of the population may have significant depressive symptomatology that does not meet formal DSM-IV-TR criteria [5] for a specific depressive syndrome [6]. Furthermore, depressed geriatric patients tend to have poorer outcome than younger depressed patients [7], which can lead to worsening medical illness and an increased risk of death [8]. Taken together, elements of depression among older adults are relatively common and present a major public health concern.

Patterns of Cognitive Impairment in Late-Life Depression

Late-life depression may be related to deficits in cognitive function, which in turn may vary according to the duration and severity of the illness. In general, depressed geriatric patients are more likely to exhibit more severe cognitive deficits than younger depressed patients [9]. In fact, significant cognitive impairment has been demonstrated in more than half of patients with late-life depression based on clinical evaluation and neuropsychological testing [10]. Cognitive impairment in late-life depression is associated with an increased severity of depressive [11–13] and anxiety symptoms [14], as well as more neurovegetative signs [15]. Furthermore, older adult patients tend to have
more residual cognitive impairments than their younger depressed counterparts, regardless of treatment [16]. One possible explanation for these differences may be that older adults with depression have less cognitive reserve, so they cannot compensate as readily for the effects of depression.

Cognitive dysfunction in depressed older adults typically consists of memory impairment, poor attention, and executive dysfunction [10, 17–20]. Lockwood et al. [19] identified three subtypes of cognitive impairment in depressed older adults. The largest group exhibits memory impairment alone, whereas other individuals exhibit executive dysfunction and memory impairment or a combination of attention and memory impairment. Those with executive dysfunction seem to be older and in other studies demonstrate more severe functional impairment [19, 21, 22], relapse [17, 22], and more residual cognitive deficits after the depression improves [16, 23]. This evidence suggests that the subgroup of individuals suffering from late-life depression with executive impairment has significant relevance in geriatric depression.

Dementia and Depression

It is likely that a significant subpopulation of depressed older adults have depression that reflects brain impairment associated with neurodegenerative processes or neural injury. Among patients with late-onset depression, a subset often develop a reversible form of dementia with significant cognitive impairment, commonly called pseudodementia, or depression with reversible dementia. These patients have a significantly increased risk of the eventual development of true dementia at rates as high as 40% over 3 years [24]. It is also well established that patients with cortical dementia, such as Alzheimer’s disease (AD), and subcortical dementia, such as Parkinson’s disease, develop depression in general at a high rate [25]. In addition, a meta-analytic and meta-regression analysis by Ownby et al. [26] showed that depression is not only a frequent “prodrome” for the development of AD, but a history of depression likely confers an increased risk for later development of AD. Clearly, depression is closely linked to Alzheimer’s dementia and subcortical dementia, and its relationship with these neurodegenerative illnesses may be bidirectional.

Vascular Disease and Depression

One of the most consistent findings in relation to geriatric depression and neurological disorders is the relationship between cerebrovascular disease and late-life depression. Patients with cardiovascular risk factors such as hypertension, diabetes, and coronary artery disease, as well as patients with cerebrovascular disease tend to have a higher risk for depression [27]. In addition, a large body of literature has documented that patients with late-life depression have an increased occurrence of white matter hyperintensities compared with healthy older adults [28–31], primarily in subcortical structures. It has been argued that underlying ischemic changes within the brain may give rise to neurotransmitter deficits or dysfunction in the frontal-striatal pathway that gives rise to depression and its associated cognitive symptoms [32]. Studies have demonstrated that strokes in the basal ganglia and left frontal regions also have led to depression and executive impairment [33, 34]. This explains why depressed individuals with primary executive impairments, such as disturbances in planning, sequencing, organization, and abstracting (as opposed to memory impairment), may have vascular pathology affecting the frontal-striatal regions. This is similar to the pattern seen in subcortical dementia such as Parkinson’s disease and Huntington’s disease, which are primarily neurodegenerative disorders of the basal ganglia and their prefrontal projections. These illnesses also typically present with depression and executive impairment [22]. Clearly, the pathogenesis of the depression syndrome (eg, vascular impairment, neurodegenerative disease) has significant implications for patterns of neuropsychological deficits.

Many attempts have been made to elucidate the mechanisms underlying the specific cognitive deficits in geriatric depression. One explanation for the observed deficits described is the compromise of underlying frontal-striatal circuits. This has been referred to as the executive control circuit [35••] and is made up of five cortical-striato-pallido-thalamo-cortical pathways, which include excitatory input and indirect inhibitory connections to the cortex. Studies have demonstrated that select cognitive deficits (eg, executive functioning) are closely related to this circuit [10]. Neuropathological studies have demonstrated abnormalities in the dorsolateral and anterior cingulated cortex in geriatric depression [36, 37]. In addition, the striatum has been associated with executive functioning and information-processing speed [10, 35••]. This mechanism may reflect an increasing prevalence of subcortical neurodegenerative and cerebrovascular disease in certain subpopulations of older adults within the disorder that disrupts executive control pathways.

Neuropsychological Deficits in Late-Life Depression

Several cognitive/neuropsychological deficits are associated with late-life depression, including impairment in executive function, attention, episodic memory, visuospatial skills, and information processing [10, 11, 18–20, 38, 39]. These cognitive processes are not orthogonal—that is, executive
dysfunction and information-processing deficits may underlie difficulties in other cognitive domains, such as learning and subsequent memory. For example, the organization of material (dependent on executive function) and the efficiency of acquisition of rapidly paced information (dependent on processing speed) may affect performance on learning tasks. Nevertheless, identifying specific cognitive targets is important in identifying and better understanding the neural substrates of behavior.

It is probable that deficits such as attention and memory are attributed to compromise of select brain networks. Elderkin-Thompson et al. [38] found that actual learning and memory deficits on the California Verbal Learning Test [40] were mediated by underlying executive dysfunction and thus may be more likely to reflect deficits in the frontal-striatal pathways. On the other hand, because depression is a risk factor for AD, memory deficits may actually reflect underlying hippocampal and entorhinal cortex deficits that frequently are early manifestations of this neurodegenerative disorder. In this case, memory impairments actually reflect medial temporal lobe disruption rather than prefrontal-subcortical pathways. It is also important to note that because white matter findings are commonly observed in late-life depression, some of these neuropsychological deficits may reflect ischemic changes that may occur in cortical and subcortical areas.

**Neuroimaging Studies**

Many studies have used structural and, more recently, functional neuroimaging to determine the specific brain regions that may be implicated in late-life depression. Typically, MRI studies have demonstrated greater reduction in gray and white matter volumes relative to comparison individuals that is consistent with small vessel vascular changes [41–43]. With regard to functional neuroimaging, greater reductions in cerebral blood flow and hypometabolism have been found in the anterior cingulate and prefrontal cortex [44–46]. It has been suggested that integrity of the anterior cingulate and its pathways is required for executive functioning, and deficits may cause dysfunction.

Recent studies have attempted to assess the biological substrates of cognitive function using functional neuroimaging. Sheline et al. [47–48] found that individuals with late-life depression have greater hyperintensities in several white matter tracts. Among depressed individuals, white matter hyperintensities in subcortical regions, specifically the right superior longitudinal fasciculus/frontooccipital fasciculus, the left superior longitudinal fasciculus (divisions 2 and 3), and the left uncinate fasciculus, correlated with executive dysfunction in the depressed older adult group. These tracts complete a pathway loop connected to the dorsolateral prefrontal cortex. Dorsolateral prefrontal cortex lesions have been well documented to be related to executive dysfunction. In addition, executive function and cognitive processing speed were associated with reductions in whole brain gray matter and white matter. Episodic memory deficits were associated with reduced whole brain white matter, whereas language deficits were associated with reduced gray matter. The authors interpret these findings to suggest that depression and cognitive deficits may be related to reduction in white matter connectivity between the insular, amygdala, and the cingular cortex.

In a more recent study, Aizenstein et al. [35–38], using functional MRI techniques, demonstrated that individuals with late-life depression show evidence of reduced activity in the prefrontal dorsolateral cortex and reduced functional connectivity between the dorsolateral prefrontal cortex and the dorsal anterior cingulate. Moreover, depressed individuals who showed improvement evidenced increased activity in the right dorsolateral prefrontal cortex.

Taken together, there is significant evidence through structural and functional imaging that depressed older adults demonstrate disruption in their prefrontal-striatal pathways and that these findings are correlated with select cognitive processes such as executive function. Alterations in functional connectivity in frontal-striatal circuits likely underlie many of the information processing, executive, and other cognitive deficits found in this disorder. However, given the increased risk of AD among those with late-life depression and the diverse white matter changes associated with vascular pathology, particularly with frontal-striatal pathways, cognitive impairments may reflect additional brain impairments. Delayed recall and an enhanced rate of forgetting is one form of memory impairment that may reflect medial temporal lobe deficits rather than frontal-striatal dysfunction.

**Treatment Implications**

A study by Alexopoulos et al. [17] indicated that the presence of executive dysfunction after successful treatment of depression was associated with an increased relapse rate. A subsequent study by Story and associates [48] found that depressed older adults with fewer cognitive deficits had better treatment outcomes than those with more severe cognitive impairments. Other studies found that the presence of memory impairment in depressed patients does not lead to poor treatment response [49, 50]. It may be of clinically significant relevance to distinguish those depressed older adults who suffer from executive dysfunction and other cognitive deficits that may be relevant in better understanding treatment resistance and susceptibility to
Research Considerations

One of the challenges confronting investigators is to delineate the causal mechanisms underlying the relationship between disruptions in neural mechanisms and both cognition and depression. Although several studies have shown associations between structural or functional changes in specific brain regions and cognition among depressed individuals or based on treatment response, questions remain as to whether identical mechanisms are responsible for affective and cognitive disturbance observed in late-life depression. For example, treatment of depression may alleviate affective symptoms but may have a negative impact on cognition through different neural mechanisms. Furthermore, several pathways may affect cognition, and they may not be limited to the frontal-striatal system. Clearly, a further elucidation of causal mechanisms using state-of-the-art functional neuroimaging technology and new psychological measures will be required to further our understanding of optimal pharmacologic treatment studies.

Conclusions

Late-life depression is a significant public health concern that merits closer attention and study. It is clear that depression in older adults is more closely related to cognitive deficits and that the nature and extent of these deficits are related to treatment outcome. Depression has been increasingly recognized as a risk factor for specific degenerative conditions, such as AD, that are closely associated with subcortical dementia and vascular disease as well. It is also clear that the cognitive deficits in late-life depression may reflect an increased likelihood of underlying brain disease that in turn may reflect a more unique set of etiologies.

The frontal-striatal pathway, particularly the connectivity between the prefrontal cortex and the striatum, seems to be a particularly promising avenue for understanding the neural mechanisms of cognitive impairment in late-life depression. It is likely, however, that additional pathways underlie different cognitive functions. Understanding the neural mechanisms underlying cognitive deficits in late-life depression will provide us with a greater understanding of the pathophysiology of these disorders and will delineate future targeted treatments for depression subtypes. These are clearly areas worthy of future research.

Disclosure
No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
• Of major importance


