

Cognitive functioning in late-life depression

A growing body of literature suggests a link between depression and cognitive decline.

ABSTRACT: Depression is a highly prevalent psychiatric disorder in older adults. It is associated with poor outcomes and comorbidities, including cognitive impairment that can persist following symptomatic treatment, and may be a risk factor for dementia in some individuals. The literature on cognitive functioning in late-life depression suggests that a remote history of depression and first-time late-onset depression might both increase the likelihood of persistent cognitive impairment. A conceptual model based on findings that depression is associated with both chronic elevation of adrenal glucocorticoid production and cerebrovascular disease may assist in understanding the heterogeneity in cognitive outcomes associated with late-life depression. Because depression can injure neurons and lower brain or cognitive reserve, regular assessment of cognitive functioning in older adults with mood disorders is recommended.

Late-life depression (LLD) is a heterogeneous disorder that can be broadly defined as depression in individuals age 60 and older. It is associated with several public health concerns, including increased mortality rates, physical disability, functional decline, increased health care utilization, and increased suicide rate.¹⁻³ Epidemiological data suggest that between 11% and 30% of older adults experience clinically significant depressive symptoms.^{4,5} These rates are higher in clinical settings and nursing homes.⁶ Some but not all studies have found distinctive clinically relevant features associated with depression that occurs for the first time in late-onset versus earlier-onset, recurrent depression.

Cognitive functioning in LLD

A number of studies have considered cognitive impairment in late-life depression both qualitatively and quantitatively. Studies that included a clinical diagnosis of major depression, a comprehensive assessment of cognition, and a healthy comparison group have documented deficits in episodic memory, speed of information processing, executive functioning, and visual-spatial ability.⁷ Deficits in speed

of information processing and executive functioning might be particularly pertinent. Three recent studies reported that slowed speed of information processing or working memory deficits appear to predominantly mediate the cognitive impairment associated with LLD.⁸⁻¹⁰

A further point of interest has been the difference between recurrent depression and first-time late-onset depression. Although both are associated with cognitive impairment, many studies suggest that late-onset depression might be disproportionately associated with executive dysfunction and attentional deficits^{7,11,12} rather than the more primary episodic memory deficits seen in early-onset depression.^{12,13} By contrast, a recent meta-analysis did not find increased rates of episodic memory difficulties in individuals with early-onset versus late-onset depression.⁷

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This article has been peer reviewed.

The literature to date largely supports the notion that depression is associated with cognitive impairment in some but not all older adults. Speed of information processing and executive functioning appear to be particularly important cognitive domains warranting assessment. Although there might be some clinical utility in distinguishing those with late-onset depression from those with early-onset recurrent depression, it is not clear whether this differentiation is related to specific cognitive outcomes.

LLD as a risk factor for cognitive decline

A growing body of literature suggests that depression might increase the risk of cognitive decline and dementia in some older adults following treatment response or remission of depressive symptoms. A recent study found 94% of individuals with baseline cognitive impairment remained impaired 1 year later despite having achieved remission of their depressive symptoms. Further, 23% of individuals who were initially classified as cognitively intact while depressed were subsequently classified as impaired following resolution of their depressive symptoms.¹⁴ In a subsequent study with different participants, 38% of LLD individuals were diagnosed with mild cognitive impairment (MCI) and 10% with dementia following treatment response.¹⁵ Other researchers have similarly noted that cognitive impairment persists following treatment and/or remission of depressive symptoms.^{16,17}

Two recent review articles suggest that depression in late-life is associated with an approximately 50% increased likelihood of developing dementia in general¹⁸ and Alzheimer disease (AD) in particular.¹⁹ Epidemiological studies have also highlighted this relationship. One study found that baseline

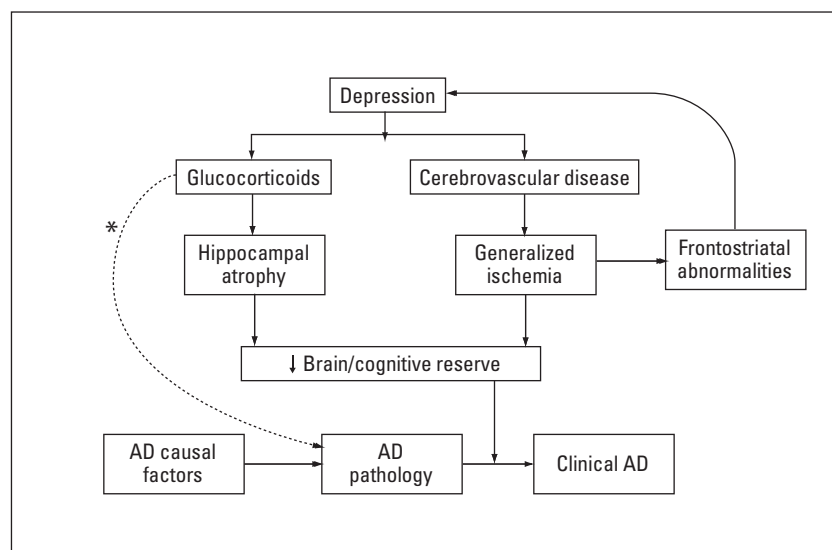


Figure 1. Proposed predominant mechanisms by which depression increases risk for AD.

*The very recently postulated direct pathway leading from hypercortisolemia (elevated glucocorticoids) to AD neuropathology is represented with a dashed line because, while evidence is growing, it has at present relatively less support than the other proposed pathways.

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depressive symptoms independently predicted a subsequent diagnosis of MCI 6 years later.²⁰ Longitudinal data from the Women's Health and Aging Study similarly found that baseline depressive symptoms predicted subsequent cognitive decline.²¹ Other studies have reported that either a remote history of depression or a number of past depressive episodes appears to increase the likelihood of later developing dementia.²² By contrast, some epidemiological studies have not found an association between depression in late life and subsequent development of dementia.^{23,24}

The heterogeneity of cognitive outcomes in LLD makes it challenging to determine the relationship between the disorder and an increased risk for cognitive impairment or future decline and dementia. A further challenge involves determining whether depression itself is a risk factor for or a symptom of prodromal dementia. Both are possibilities given the nature of LLD,

and there are likely multiple pathways linking the disorder to persistent cognitive decline and dementia.

Mechanisms that might increase risk

Mechanisms that might increase the risk depression poses for developing AD are described in **Figure 1**.²⁵ This model is based on findings that LLD is associated with both chronic elevation of adrenal glucocorticoid production and cerebrovascular disease (CVD). Together, these factors may lead to hippocampal atrophy and generalized ischemia. Generalized ischemia often has a predilection for frontostriatal regions, leading to abnormalities that could also serve to maintain or cause subsequent depressive episodes. These factors can also lower brain or cognitive reserve. When other pre-existing AD casual risk factors are present, this can hasten the progression of underlying AD pathology to clinical manifestation of AD.

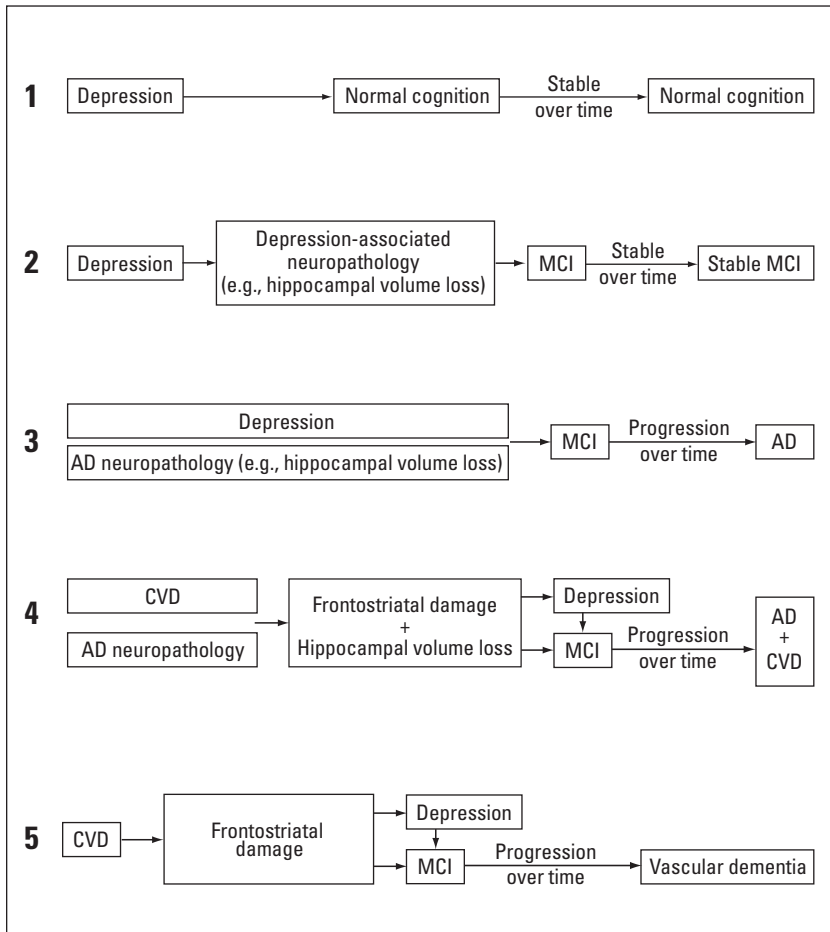


Figure 2. Pathways linking depression to five predominant cognitive outcomes.

MCI = mild cognitive impairment; AD = Alzheimer disease; CVD = cerebrovascular disease. Reproduced from *Dialogues in Clinical Neuroscience* with the permission of Les Laboratoires Servier, Neuilly-sur-Seine, France.²⁵

Brain/cognitive reserve is key in this model.²⁶ As depression further injures neurons and/or lowers reserve, earlier or more frequent (or both) expression of progressive loss and dementia may result. The variability in the rate of expression of cognitive impairment or dementia might in turn be explained by differing individual thresholds of reserve.²⁵

Since only a subset of individuals with LLD will go on to develop persistent impairment, AD, or other dementias, a number of potential pathways may account for the differing

individual cognitive outcomes shown in **Figure 2**.²⁵

These possible cognitive outcomes include normal cognition, stable MCI, AD, mixed AD and CVD, and vascular dementia. Mixed AD and CVD may be the most common outcome in individuals with late-onset depression.

An understanding of these possible pathways and the association between LLD and cognitive impairment is important as newer treatment approaches that might slow or prevent cognitive decline become available. Additionally, recommendations for

maintaining or increasing brain/cognitive reserve during aging (e.g., physical and cognitive activity, social interaction, healthy diet, decreased stress) will be particularly important for elderly depressed individuals. It is important to note that these healthy behaviors are often the very ones discontinued as a result of depressed mood.

Summary

Late-life depression is associated with functional decline and a number of other poor outcomes, including cognitive impairment. Further, impairment tends to persist in some individuals following symptomatic treatment, and some individuals are at risk for progressive cognitive decline. There are likely multiple possible pathways leading to this decline, with the lowering of brain/cognitive reserve being key. Regular assessment of cognitive functioning in older adults with mood disorders is recommended.

Competing interests

Dr Butters has received honoraria for reviewing grant applications and speaking for foundations and nonprofit scientific organizations. She has grant funding from the US National Institutes of Health, which has reimbursed her for attending scientific meetings. As a consultant for North Star Neuroscience and Fox Learning Systems, she has received remuneration for performing neuropsychological assessments.

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