Pathways linking late-life depression to persistent cognitive impairment and dementia

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Late-life depression, defined as a major depressive episode occurring in older adults (usually after the age of 60 or 65 years), is a heterogeneous mood disorder frequently associated with cognitive impairment. Late-life depression encompasses both late-onset cases as well as early-onset cases that recur or continue into later years of life. The temporal association between cognitive and depressive symptoms in elderly patients varies widely, yet increasing evidence suggests that depressive illness contributes to the development of persistent or progressive cognitive deficits in some individuals.

The neurobiologic mechanism(s) underlying this link between depression and future cognitive decline are poorly understood. The gross and microscopic neuropathology of dementia associated with depression is highly variable, and it is has become evident that mixed pathophysiologies are very common. Moreover, certain person-specific characteristics such as educational attainment and lifestyle factors may influence the timing of clinical dementia presentation, regardless of the nature and extent of pathology.

Our goals in this review are to (i) summarize evidence for the notion that prior depression increases risk of subsequent cognitive decline and dementia, especially Alzheimer’s disease (AD); (ii) outline the biological sub-

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strates proposed to mediate this association; and (iii) use the concepts of brain and cognitive reserve to integrate existing evidence into linked pathways connecting depression to AD.

**Does depression increase risk of subsequent cognitive decline and dementia?**

Clinical, case-control, and epidemiologic studies show an association between late-life depression and persistent cognitive deficits, and between history of depression and subsequent dementia, especially AD. Studies of late-life depression generally find significant cognitive impairment concurrent with affective symptoms, (eg, refs 2,3) that is mediated almost entirely by slowed information processing3-5 or working memory deficits.5 The cognitive deficits accompanying late-life depression often persist following treatment and remission of affective symptoms.5-8 One year after good treatment response for a major depressive episode, significant impairment was found in 23% of subjects who had been deemed cognitively intact while depressed.9 Two recent meta-analyses found that a history of depression approximately doubles an individual's risk of subsequent dementia in general10 and AD in particular.11 Yet, many large individual studies have found no such relationship between depression and cognitive impairment22 or subsequent dementia.12,23,24 Such findings suggest that when depressive and cognitive symptoms appear close in time they likely arise from common neuropathologic processes. Many authors emphasize the importance of determining whether depression is a true risk factor versus an early symptom occurring in the prodromal phase of dementia, particularly AD. Substantial support exists for both hypotheses, and they are not mutually exclusive. This report does not resolve this issue; rather, we review evidence for several specific pathways by which depression may be linked to subsequent cognitive decline and dementia and present two related models that accommodate and reconcile many of the seemingly disparate research findings. One model is shown in Figure 1 and presents three interacting links which affect brain and cognitive reserve thereby moderating the relationship between underlying AD neuropathology and its expression as clinical dementia. In the sections that follow we discuss the evidence for each of the pathways and links.

**Neurobiologic substrates mediating the depression-cognitive decline-dementia links**

**Glucocorticoids contribute to hippocampal atrophy and learning/episodic memory impairment**

Depression is associated with neuroendocrine changes similar to those observed in animal models of chronic stress, including abnormalities within the hypothalamic-pituitary-adrenal (HPA) axis. Most notably, depressed
subjects have been shown to exhibit increased HPA central drive with elevated corticotrophin-releasing hormone (CRH) and vasopressin production by cells of the hypothalamic paraventricular nucleus (PVN); impaired negative feedback regulation due to decreased expression of corticosteroid receptors in the hypothalamus and pituitary as well as upstream CNS regulatory centers; and adrenal hypertrophy (reviewed in ref 25). The net effect of these changes in HPA function is chronic elevation of adrenal glucocorticoid production with impaired negative feedback and abnormal homeostatic regulation. Such HPA dysregulation is clinically detectable (via dexamethasone nonsuppression or elevated 24-hour urinary cortisol) in about half of patients with major depression.25,26
HPA dysregulation may be more common among older depressed individuals, as suggested by the finding of a significant correlation between age and post-dexamethasone cortisol levels in individuals with late-life depression.27
Adrenal glucocorticoid/cortisol regulates HPA activity through both direct negative feedback at the pituitary and hypothalamus and indirect mechanisms involving higher central nervous system (CNS) centers. The human hippocampus, for example, contains large numbers of corticosteroid receptors and plays a critical role in down-regulating CRH release via a multisynaptic pathway terminating in γ-aminobutyric acid (GABA)-ergic output to the paraventricular nucleus (reviewed in ref 28). At the same time, HPA disturbances causing prolonged hypercortisolemia may promote hippocampal atrophy and functional decline, such that HPA regulation is further compromised. This interaction may underlie the observed association between hypercortisolemic disease states such as Cushing’s syndrome and depression, and both hippocampal atrophy and impairment in the verbal and spatial memory functions subserved by the hippocampus.29,30
Animal studies suggest that high-stress conditions or exogenous glucocorticoids can cause hippocampal neuronal damage31 and memory impairment.32 These changes have been observed concurrent with stress or exogenous

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**Figure 1.** Proposed predominant mechanisms by which depression increases risk for Alzheimer's dementia (AD).

*The very recently postulated direct pathway leading from hypercortisolemia or 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.*
glucocorticoid administration, and appear to progress over a lifetime of stress or glucocorticoid excess (see review in ref 33). Human studies in older adults likewise suggest that hippocampal size and function are diminished in the setting of elevated glucocorticoids, and in proportion to duration of prior hypercortisolemia. On the basis of these findings, many have hypothesized that glucocorticoids may promote hippocampal cell injury and death when chronically elevated, as in the setting of hypercortisolemia associated with major depression. Glucocorticoid-induced cellular damage may be mediated through effects on several biochemical substrates. Postulated mechanisms include decreased glucose uptake and ATP generation, elevated intracellular calcium with increased free radical production and degradative enzyme activity, and impaired uptake of glutamate from hippocampal synapses resulting in excitotoxicity. In addition, hypercortisolemia has been linked to a decrease in neurogenesis in the dentate gyrus. While the combination of cell death and decreased neurogenesis may theoretically contribute to hippocampal cell loss over time, recent evidence suggests at most a minor role for this mechanism in hypercortisolemic human subjects in the absence of co-occurring insults. Animal and human studies support the idea that glucocorticoids contribute to hippocampal atrophy and functional deficits predominantly through more subtle alterations, including reduced synapse number, atrophy of pyramidal cell dendrites, derangement of glial cells, and other changes.

Neuroimaging studies have generally shown reduced hippocampal volumes in late-life depression subjects relative to age-matched controls (See meta-analysis by Videbech and Ravnkilde), although this finding is not universal. Furthermore, many studies find a significant association between hippocampal atrophy and greater lifetime duration of depression, as assessed by number of depressive episodes, total days depressed, total days of untreated depression, duration since first depressive episode, or early-onset as opposed to late-onset depression. Although these findings differ somewhat, most studies support to some degree the notion that depression-related hypercortisolemia can compromise hippocampal structure and function, especially in the context of old age and comorbid disease. The impact of glucocorticoids on brain structures can be expected to vary not only with age and disease status, but also with individual genetic and environmentally-imparted differences influencing hippocampal volume and connectivity, HPA reactivity, and other neurobiologic factors. Besides the possibility of persistent synapal or neuron loss induced directly by prolonged hypercortisolemia, glucocorticoid-related derangement of hippocampal physiology, as described above, may increase vulnerability to damage through other pathophysiologic mechanisms. This latter effect may become clinically relevant in older persons with co-occurring neuronal insults such as accumulating AD pathology or cerebrovascular disease, promoting synapse or neuron loss through a synergistic relationship with these factors. The loss of hippocampal volume and memory function observed in some elders with late-life depression suggests the possibility that depression may be a predispositional risk factor for AD in particular. Indeed, lower hippocampal volumes independently predict subsequent AD in groups of MCI and cognitively normal elderly subjects. Likewise, deficits in verbal learning and memory, similar to those described in euthymic patients with history of major depression, also predict AD (eg, ref 53).

Biologic relationships between depression and Alzheimer’s disease

The association between depression and dementia suggested by epidemiologic data may be partially explained by one or more direct mechanistic links between late-life depression-related processes and AD-specific neuropathology (focal and diffuse cortical neuronal loss, β-amyloid plaques, and neurofibrillary tangles). Emerging evidence from neuroimaging studies, postmortem neuropathologic analyses, and animal models provides support for such links. Some structural magnetic resonance imaging (MRI) studies find that hippocampal atrophy is more strongly associated with late-onset than early-onset depression, suggesting that early AD-related pathophysiology could generate both hippocampal atrophy and depressive symptoms in some elderly persons. In addition, one of these studies failed to find a significant correlation between hippocampal volume and cortisol level among elders with depression. Furthermore, the late-life depres-
sion subjects showed persistent memory and cognitive impairment at 6-month follow-up despite effective treatment of mood symptoms and normalization of cortisol levels. All of these data are consistent with the idea that AD pathology is a major cause of hippocampal atrophy in some (but not all) individuals with late-life depression, and their depressive symptoms may represent prodromal AD.

Several recent animal and human studies suggest a possible direct pathophysiologic link between late-life depression and the neuropathologic hallmarks of AD. Postmortem studies report greater hippocampal amyloid plaque and neurofibrillary tangle pathology in AD patients with lifetime history of depression compared with those without such history, and more severe cortical neurofibrillary tangle pathology in the brains of AD subjects who suffered from comorbid depression. The hippocampal findings, combined with the observation of marked hippocampal neurofibrillary pathology early in the course of AD, provoke speculation that depression-associated hypercortisolemia may facilitate AD pathogenesis by rendering hippocampal neurons and glia vulnerable to toxic insults, as discussed in the previous section.

Neurobiologic interaction or overlap between late-life depression and AD is further suggested by the discovery of glial changes consistent with a CNS inflammatory process in both older depressed individuals and those with neurodegenerative diseases such as AD. The prolonged hypercortisolemia associated with both diseases may partially account for these findings, as glucocorticoids can induce proinflammatory changes within the CNS.

Overall, these findings provide associational evidence for a link between late-life depression and AD, yet offer little insight into whether depression history may act as a true etiologic risk factor for AD, or, conversely, whether late-life depression arises secondary to AD-related neuropathologic changes. However, two recent animal studies suggest the existence of a direct mechanistic link between hypercortisolemic depression and AD pathology. Green and colleagues found dexamethasone treatment increased β-amyloid production in a transgenic mouse model of AD, and traced this effect to increased expression of amyloid precursor protein and the β-secretase enzyme. This group also found increased tau aggregation within neuronal cell bodies and dendrites of dexamethasone-treated animals. Kang and colleagues demonstrated increased hippocampal interstitial β-amyloid levels in another mouse model of AD following acute restraint or chronic isolation stress. This finding was reproduced through direct infusion of CRH into the hippocampus, and blocked by pretreatment with CRH antagonists.

In conclusion, diverse findings from structural MRI and human or animal histopathologic studies suggest a direct relationship between late-life depression and AD-specific pathology. Reports of a cross-sectional association between later age of depression onset and hippocampal atrophy support the notion that early AD-related pathophysiology is causing depressive symptoms in these study groups and correlate with epidemiologic reports of elevated dementia risk in subjects with depression onset in the recent versus distant past (eg, refs 19, 20). Conversely, postmortem AD studies suggest an association between more severe plaque and tangle pathology and lifetime depression history preceding AD diagnosis, offering support for the idea that prior depression is a true, etiologic risk factor for AD, as suggested by other epidemiologic data (eg, ref 11). Furthermore, both stress and exogenous glucocorticoids increase β-amyloid production in rodent models of AD, consistent with a direct biologic role of human depression in AD pathogenesis. These disparate hypothesized relationships are not exclusive of one another. Given the tremendous heterogeneity of late-life depression, various dementia pathologies, and the other clinical or subclinical disease inevitably present in older individuals, depressive symptoms should be expected to bear an inconsistent relationship with cognitive decline, dementia in general, and AD specifically. Such symptoms in a given elderly individual may potentially represent either prodromal AD, or an independent process interacting with AD-related pathophysiology. As discussed in this manuscript, depression may furthermore contribute to cognitive decline and AD through glucocorticoid-related hippocampal toxicity and interrelationships with other types of pathology such as vascular disease.

Role of vascular disease in late-life depression, cognitive decline, and dementia

Substantial data exist showing an association between late-life depression and cerebrovascular changes. In separate reports, Alexopoulos and Krishnan pointed to the then-
nascent evidence that a subgroup of individuals with late-life depression showed evidence of cerebrovascular changes. Alexopoulos coined the term “vascular depression,” positing that a subgroup of individuals experience disruption of prefrontal systems that mediate both mood and executive functions, by either single vascular lesions or accumulation of lesions. The concept of vascular depression has subsequently been supported and expanded by a growing literature. Depression and vascular disease display an interesting bidirectional relationship. Depression increases risk for first-ever myocardial infarction (MI) and stroke, and has been shown to predict worse outcomes in a wide range of concurrent vascular disease states (reviewed in ref 67). Notably, clinical diagnosis of major depression confers significant relative risk for MI,88 stroke,69 and post-MI cardiac mortality.70,71 Moreover, major depression confers greater relative risk than diagnosis of dysthymia or indices of self-reported depressive symptoms, suggesting a possible dose-response relationship between severity of depressive illness and excess cardiovascular risk.87

Diverse mechanisms have been proposed to explain the link between prior depression and subsequent vascular disease.87,88,89 Depressed individuals exhibit poor treatment compliance and other behaviors such as smoking, substance abuse, and inactivity, which may cause or worsen comorbid disease. Depression is also associated with systemic physiologic derangements which may contribute to vascular pathology. As mentioned above, HPA axis dysregulation with hypercortisolism is common in depressed individuals. Elevated cortisol levels independently predict several features of the metabolic syndrome including abdominal obesity, low high-density lipoprotein (HDL) levels, and hypertriglyceridemia.74 They disrupt normal endothelial function75 and may contribute over time to the levels, and hypertriglyceridemia. They disrupt normal abdominal obesity, low high-density lipoprotein (HDL) several features of the metabolic syndrome including compliance and other behaviors such as smoking, substance abuse, and inactivity, which may cause or worsen comorbid disease. Depression is also associated with systemic physiologic derangements which may contribute to vascular pathology. As mentioned above, HPA axis dysregulation with hypercortisolism is common in depressed individuals. Elevated cortisol levels independently predict several features of the metabolic syndrome including abdominal obesity, low high-density lipoprotein (HDL) levels, and hypertriglyceridemia. They disrupt normal endothelial function75 and may contribute over time to the levels, and hypertriglyceridemia. They disrupt normal.

C-reactive-protein is directly atherogenic, and high levels of several proinflammatory cytokines have been found to predict cardiovascular events.85,86 In a reciprocal fashion, many acute and chronic vascular disease states may promote depression. MI and stroke substantially increase risk for depression during the immediate postacute period, with depressive symptoms reported in 25% to 50% of individuals (reviewed in ref 67). One study comparing cumulative 1-year incidence of major and minor depression immediately following stroke or MI found no difference between these groups.87 This finding suggests that the loss of specific neuronal populations is less important than more global postischemic vascular or inflammatory mechanisms in the pathogenesis of poststroke depression. Accordingly, depression is more frequent and severe in vascular dementia than AD,88 despite widespread neuronal loss in both dementia syndromes. Studies of individuals with chronic cardiovascular diseases show that diabetes mellitus (see meta-analysis in ref 89) and CAD,90 each approximately double risk for depression. Many but not all studies of older subjects indicate a longitudinal association between vascular disease/risk and subsequent depression. Several prospective studies in elderly subjects report that clusters of cardiovascular risk factors or pre-existing CAD independently predict incident depression, while at least one large prospective study found no relationship between an index of generalized atherosclerosis and incident depression.91 In old age, the observed association between vascular disease and depression may be attenuated by the fact that persons with severe or long-standing disease of either type incur substantial morbidity and mortality. Surviving individuals with significant vascular or depressive pathology might actually be expected to possess protective biopsychosocial factors which interrupt the positive bidirectional relationship described above.

Strong supporting evidence for the notion that vascular disease contributes to late-life depression comes from structural MRI studies showing a robust association between ischemic brain lesions and depression diagnosis or self-reported symptoms in older persons.92 Large community-based studies have demonstrated independent cross-sectional relationships between late-life depression and small basal ganglia lesions93 and white matter abnormalities visualized as hyperintense regions on T2-weighted MRI (WMHs) in deep or subcortical areas.94,95 Longitudinal studies suggest white matter changes may both predate and independently predict late-life depression.96,97
The ischemic etiology of WMHs is suggested by several lines of evidence, including post-mortem histopathologic studies in patients with late-life depression and in the general population, correlating WMHs with both evidence of cerebrovascular disease and systemic hypotensive or hypoxic disease. Ischemic damage to frontostriatal brain regions may explain the executive dysfunction, psychomotor slowing and resistance to treatment common in late-life depression. The few studies examining WMHs and cognition in late-life depression have found associations with psychomotor slowing, memory, language, and executive functioning. The relationship between WMHs and executive function may be particularly strong in individuals with late-onset depression. Taken together, these studies suggest a relationship among late-onset depression, ischemic WMHs (especially in the frontostriatal region) and executive dysfunction, raising the possibility that ischemic structural changes in the brain are a common etiologic factor of both the depression and the associated cognitive dysfunction.

The cognitive impairment related to this ischemic damage may be severe enough to culminate in a clinical diagnosis of dementia. Vascular dementia, alone or in combination with AD, occurs at high prevalence in the population (up to 44% of all dementia). In accordance with the bidirectional relationship described here, prior depression independently predicts subsequent vascular dementia (OR = 2.15) and individuals with late-life depression who develop clinical AD have high rates of cerebrovascular pathology upon postmortem examination. Indeed, prospective community-based studies report associations between baseline systemic vascular disease/risk and both higher rates of incident AD, and more rapid cognitive decline in established AD. Moreover, rapid progression of cerebrovascular disease as inferred from serial MRI predicts subsequent dementia diagnosis.

In sum, mounting evidence suggests factors associated with late-life depression may predispose to persistent cognitive impairment and dementia. Plausible moderators of this relationship include glucocorticoid-related hippocampal damage, an interaction between depression and AD neuropathology, and increased vascular disease, but the potential importance of other factors (eg, neurotransmitter and immunologic abnormalities) cannot be excluded. Moreover, in reality there appear to be abundant interactions between the three distinct links described here and depicted in Figure 1. Hypertension, for instance, is associated with diminished regional cerebral blood flow in the hippocampus and related limbic and paralimbic structures of cognitively normal older adults. Furthermore, MRI assessments of cerebrovascular disease independently predict hippocampal atrophy. Together these findings suggest ischemic and inflammatory insults related to cerebrovascular disease may affect the same neuronal populations endangered by hypercortisolemia and AD. It is conceivable that hippocampal insults related to vascular disease, hypercortisolemia depression or prodromal AD which are insufficient to cause significant cellular damage or death by themselves may produce cell death through synergistic interaction with co-occurring insults. In the context of neurodegenerative disease, cerebral ischemia may contribute to cell death outside the hippocampus, as suggested by an independent association between WMH volume and cortical grey matter atrophy in AD. Notably, plasma levels of β-amyloid predict the extent of ischemic white matter damage in MCI and AD, suggesting a reciprocal interaction between cerebrovascular and AD pathophysiology. Together these examples suggest that particular combinations of insults arising from different pathophysologies may play a crucial role in promoting cognitive decline and progressive dementia subsequent to depression, an effect related to extensive crosstalk between links and synergism of insults at the cellular level. Clearly, many factors influence the impact a particular risk or disease factor will have on expression of dementia. In the following section, we describe how the concepts of brain and cognitive reserve can be used to explain this multifactorial process and account for the highly variable clinical course, cognitive course and neuropathology associated with late-life depression.

**Brain and cognitive reserve: the final common pathway linking depression to dementia**

Brain and cognitive reserve are often used interchangeably, but in fact, have subtle but distinct differences in meaning. Nevertheless, either may account equally well for the relationship between depression and dementia. The concept of brain reserve capacity, first proposed by Satz varies across individuals such that those with greater neuronal redundancy are able to tolerate more cell loss than those with less redundancy, before manifesting clinical symptoms. The concept of redundancy refers to the notion that circuits contain more than the
minimum number of neurons needed to perform an operation. Redundancy is evident when individuals incur substantial neuronal loss before the appearance of clinical symptoms. Thus, brain reserve capacity posits that individual differences in neural redundancy translate into differences in thresholds for vulnerability to or protection from clinical symptoms after brain damage. The concept of cognitive reserve developed by Stern (eg, refs 121,122) is similar but rather than being based on differences in brain size or neuronal count, emphasizes differences in the efficiency or manner in which tasks are performed or information is processed.

Both brain reserve and cognitive reserve explain the role of risk and protective factors for cognitive impairment (including progressive decline into dementia), associated with brain damage. For example, higher educational attainment, larger head size, larger brain volume,123 social engagement,124 physical activity,125 and leisure cognitive activity126,127 may result in greater redundancy and/or efficiency and therefore reserve, thereby offering protection against exhibiting clinical symptoms of dementia. Similarly, lower levels of these protective factors may reduce neuronal or functional redundancy leading to earlier dementia symptom onset for a given level of CNS damage.

While certain mechanisms may alter an individual’s risk to develop (or change the rate of development of) AD-related pathology (eg, β-amyloid deposition), other mechanisms alter the strength of association between these biological changes and the time to develop clinical disease. We propose that depression alters an individual’s risk of cognitive dysfunction, shortening the latent period between the development of AD neuropathology and the onset of clinical dementia, thus increasing the incidence and prevalence of AD among older adults with depression.

*Proposed multiple pathways model*

We propose that the reserve threshold theory is the key explanatory mechanism behind the late-life depression/dementia association. That is, through a number of processes (several described here), depression injures neurons, thus lowering reserve such that cognitive impairment is expressed earlier and/or more frequently than it would otherwise. As depicted in Figure 1, depression is linked to vascular disease, especially in the frontostrial area. Depression also is linked to elevated glucocorticoid production, as well as amyloid deposition and neurofibrillary formation, each of which may lead to hippocampal injury. Each of these processes adds to the total brain injury burden, lowering reserve and vulnerability to express cognitive impairment.

These links and processes are not mutually exclusive; many are likely synergistic, so that they act to varying degrees across groups of individuals. This accounts for the substantial heterogeneity of the mood disorder and the presence (or absence) of a cognitive disorder and its clinical course. For example, it is possible that the diminished hippocampal volume identified in group studies could be the result of more than one underlying process. Individuals with early-onset, recurrent depression may have hippocampal volume loss due to the repeated stress associated with multiple depressive episodes. Many individuals with later-onset depression may be in the prodromal stage of AD, their hippocampi having already sustained substantial neuronal injury due to cumulative AD neuropathology.

There may be additional pathologic processes, independent of depression, which can affect cognition. For example, amyloid plaques and neurofibrillary tangles commonly accumulate in aging brains,123,128-130 and it is likely that in some cases AD pathology represents an independent, co-occurring process (ie, depression is the first manifest symptom of AD). Vascular disease accompanying AD pathology in the absence of depression, promotes cognitive decline and an earlier expression of dementia (eg, refs 111-115,131). In fact, the growing evidence that AD and cerebrovascular pathology co-occur with high frequency has led some to conclude that the strict distinction between AD and vascular dementia is artificial.131 Social isolation,124 physical inactivity,125 and lack of leisure cognitive activity126,127 may result in lowered reserve and therefore confer additional risk for exhibiting clinical symptoms of dementia. Moreover, late-life depression frequently occurs in the context of chronic medical illness, and major organ system dysfunction is frequently associated with cognitive impairment,132 acting to further lower reserve.

Thus, each of the processes mentioned above and depicted in Figure 1, independently adds to the total brain injury burden, lowers reserve, and strengthens the association between the neurodegenerative process and the clinical change in cognitive functions. We believe that this explanation underlies the relationship between late-life depression and dementia in general, and AD in par-
ticular (see Figure 1). This conceptualization de-emphasizes the importance of the distinctions between early and late-onset depression and the relative risk for AD vs vascular dementia in the context of late-life depression. The cognitive outcome of any given individual who has late-life depression depends largely on the predominance or particular mix of pathophysiology in that individual. The additive or synergistic effects of vascular disease, glucocorticoid-related brain injury, and intrinsic AD pathophysiology are reflected in the empirical findings of heterogeneous neuropathology in late-life depression and dementia. This framework, by focusing on the key concept of reserve threshold, delineates testable (and falsifiable) links between depression and subsequent dementia.

Figure 2 depicts various pathways through which the key processes outlined in Figure 1 may lead to the heterogeneous cognitive and disease outcomes reported in the literature. The pathways include (in order of figure presentation): (i) Individuals who develop depression at any point in their lives, sustain minimal or no depression-related neuropathology (eg, glucocorticoid neurotoxicity), and who have stable, normal cognitive functioning; (ii) Individuals who develop depression at any point and who experience depression-related neuropathology that results in MCI that is stable (unless they experience additional depressive episodes); (iii) Individuals who accumulate AD neuropathology over many years and who develop late-life depression (related or unrelated to AD pathology), that lowers brain reserve capacity, and results in expression of MCI earlier than otherwise would be the case, and given the underlying neuropathology, progress to AD; (iv) Individuals who accumulate AD neuropathology over many years along with co-occurring cerebrovascular disease, which damages the frontostriatal circuitry, leading to late-life depression. The total neuropathologic burden, combined with depressed mood, lowers brain reserve capacity, leads to expression of MCI (eg, memory and executive dysfunction) earlier than otherwise would be the case, and, given the underlying neuropathology, progresses to subsequent dementia.

![Figure 2. Pathways linking depression to predominant cognitive outcomes. MCI, mild cognitive impairment; AD, Alzheimer's disease; CVD, cerebrovascular disease.](image-url)
Understanding the pathways through which individuals with late-life depression develop progressive dementia in general, and AD in particular, is critical as novel treatment may prevent, forestall, or slow cognitive and/or disease progression. This work was supported in part by USPHS grants R01 MH072947, P50 AG05133, P50 MH071944, R37/R01 MH43832 and T32MH19986. We would like to thank several colleagues with whom we have discussed many of the topics discussed in this manuscript. These individuals at the University of Pittsburgh include Mary Ganguli, Ari Gildengers, Robert Nebes, Robert Sweet and Ellen Whyte, and those at other universities include Rishi Bhalla, Gwenn Smith, David Steffens, Alan Thomas, George Alexopoulos, John O’Brien, and Yvette Sheline.

AD along with co-occurring cerebrovascular disease; and (v) Individuals who develop cerebrovascular disease (with variable neuropathologic burden), that damages the frontostriatal circuitry, leading to late-life depression and MCI (eg, executive dysfunction), that will follow the course of the underlying cerebrovascular disease. Based on the weight of the findings in the published literature and consistent with our model depicted in Figure 1, we suggest that Pathway #4 (Figure 2) leading to AD with co-occurring cerebrovascular disease is the most frequently occurring pathway among individuals with late-onset depression.
REFERENCES

1. Sweet RA, Hamilton RL, Butters MA, et al. Neuropathologic correlates of late-onset major depression. Neuropsychopharmacology. 2004;29:2242-2250.
2. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004;61:587-595.
3. Sheline YI, Bartha DM, Garcia K, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biol Psychiatry. 2006;60:58-65.
4. Butters MA, Bhalla RK, Mulsant BH, et al. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: Is there a relationship? Am J Geriatr Psychiatry. 2004;12:387-394.
5. Nebes RD, Butters MA, Mulsant BH, et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychol Med. 2000;30:679-691.
6. Murphy CF, Alexopoulos GS. Longitudinal association of initiation/perseveration and severity of geriatric depression. Am J Geriatr Psychiatry. 2004;12:50-56.
7. Nebes RD, Pollock BG, Houch PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. J Psychiatr Res. 2003;37:99-108.
8. Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG. Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis. 1997;185:748-754.
9. Bhalla RK, Butters MA, Mulsant BH, et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. Am J Geriatr Psychiatry. 2006;14:419-427.
10. Jorm AF. History of depression as a risk factor for dementia: an updated review. Aust NZ J Psychiatry. 2001;35:776-781.
11. Owmby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530-538.
12. Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang CC. Depressive symptoms and cognitive decline in late life: a prospective epidemiologic study. Arch Gen Psychiatry. 2006;63:153-160.
13. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and Alzheimer’s disease: a community-based prospective study. Arch Gen Psychiatry. 1999;56:261-266.
14. Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry. 2006;63:273-279.
15. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry. 2004;75:1662-1666.
16. Speck CE, Kukull WA, Brenner DE, et al. History of depression as a risk factor for Alzheimer’s disease. Epidemiology. 1995;6:366-369.
17. Palsson S, Aervarsson O, Skoog I. Depression, cerebral atrophy, cognitive performance and incidence of dementia. Population study of 85-year-olds. Br J Psychiatry. 1999;174:249-253.
18. Geerlings DL, den HT, Koudstaal PJ, Hofman A, Breteler MM. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology. 2008;70:1258-1264.
19. Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch Neurol. 2003;60:753-759.
20. Steffens DC, Plassman BL, Helms MJ, Welsh-Bohmer KA, Saunders AM, Breitner JC. A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer’s disease. Biol Psychiatry. 1997;41:851-856.
21. Wetherell JL, Gatz M, Johansson B, Pedersen NL. History of depression and other psychiatric illness as risk factors for Alzheimer disease in a twin sample. Alzheimer Dis Assoc Discord. 1999;13:47-52.
22. Godin O, Dufouil C, Ritchie K, et al. Depressive symptoms, major depressive episode and cognition in the elderly: the three-city study. Neuroepidemiology. 2007;28:101-108.
23. Lindsay J, Lurain D, Verreault R, Hebert R, Hellwell B, Hill GB, McDowell I. Risk factors for Alzheimer’s disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002;156:445-453.
24. Mendez MF, Underwood KL, Zander BA, Mastri AR, Sung JH, Frey WH. Risk factors in Alzheimer’s disease: a clinicopathologic study. Neurology. 1992;42:770-775.
25. Checkley S. The neuroendocrinology of depression and chronic stress. Br Med Bull. 1996;52:597-617.
26. Arana GW, Mossman D. The dexamethasone suppression test and depression. Approaches to the use of a laboratory test in psychiatry. Neurol Clin. 1988;6:21-39.
27. O’Brien JT, Ames D, Schweitzer I, Colman P, Desmond P, Tress B. Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer’s disease. Br J Psychiatry. 1996;168:679-684.
28. McEwen BS. Stress and the aging hippocampus. Front Neuroendocrinol. 1999;20:49-70.
29. Starkman MN, Gebarski SS, Berent S, Scheinberg DT. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing’s syndrome. Biol Psychiatry. 1992;32:756-765.
30. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 1999;19:5034-43.
31. Cerese M, Reines A, Ferrero A, Sifonios L, Rubio M, Wikinski S. Chronic treatment with high doses of corticosterone decreases cytoskeletal proteins in the rat hippocampus. Eur J Neurosci. 2006;24:3354-3364.
32. Park CR, Zoladz PR, Conrad CD, Fleshner M, Diamond DM. Acute predator stress impairs the consolidation and retrieval of hippocampus-dependent memory in male and female rats. Learn Mem. 2008;15:271-280.
33. Kim JJ, Song EY, Kosten TA. Stress effects in the hippocampus: synaptic plasticity and memory. Stress. 2006;9:1-11.
34. Peavy GM, Lange KL, Salmon DP, et al. The effects of prolonged stress and APOE genotype on memory and cortisol in older adults. Biol Psychiatry. 2007;62:472-428.
35. Lee BK, Glass TA, McAttee MJ, Wand GS, Bandeen-Roche K, Bolla K, Schwartz BS. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry. 2007;64:810-818.
36. Lupien SJ, de Leon M, De Santi S, et al. Cortisol levels during aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998;1:69-73.
37. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000;57:925-935.
38. Elder GA, De GR, Gama Sosa MA. Research update: neurogenesis in adult brain and neuropsychiatric disorders. Mt Sinai J Med. 2006;73:931-940.
39. Miller DB, O’Callaghan JP. Aging, stress and the hippocampus. Ageing Res Rev. 2005;4:123-140.
40. Tata DA, Marciano VA, Anderson BJ. Synapse loss from chronically elevated glucocorticoids: relationship to neuropli volume and cell number in hippocampal area CA3. J Comp Neurol. 2006;498:363-374.
41. Fuchs E, Flugge G, Ohl F, Lucassen P, Vollmann-Hondorf GK, Michaelis T. Psychosocial stress, glucocorticoids, and structural alterations in the tree shrew hippocampus. Physiol Behav. 2007;73:285-291.
42. Muller MB, Lucassen PJ, Yassouridis A, Hoogendijk WJ, Holsboer F, Swaab DF. Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus. Eur J Neurosci. 2001;14:1603-1612.
43. Videbech P, Ravnikilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry. 2004;161:1957-1966.
44. Ashari M, Greenwald BS, Kramer-Ginsberg E, et al. Hippocampal/amygdala volumes in geriatric depression. Psychol Med. 1999;29:629-638.
45. Greenwald BS, Kramer-Ginsberg E, Bogerts B, et al. Qualitative magnetic resonance imaging findings in geriatric depression. Possible link between later-onset depression and Alzheimer’s disease? Psychol Med. 1997;27:421-431.
46. Axelsson DA, Doraiswamy PM, McDonald WM, et al. Hypercortisolemia and hippocampal changes in depression. Psychiatry Res. 1993;47:163-173.

47. Sheline YI. Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity? Mol Psychiatry. 1996;1:298-299.

48. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry. 2003;160:1516-1518.

49. Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF, Becker JT. Brain morphometric abnormalities in geriatric depression: Long-term neurobiological effects of illness duration. Am J Psychiatry. 2002;159:1424-1427.

50. Janssen J, Hulshoff Pol HE, de Leeuw FE, et al. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. J Neurol Neurosurg Psychiatry. 2007;78:638-640.

51. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: implications for the field of brain and cognition. Brain Cogn. 2007;65:209-237.

52. Jack CR, Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology. 2000;52:1397-1403.

53. Tierney MC, Szalai JP, Snow WG, et al. A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment [see comments]. Neurology. 1996;46:149-154.

54. Steffens DC, Byrum CE, McQuoid DR, et al. Hippocampal volume in geriatric depression. Biol Psychiatry. 2000;48:301-309.

55. Lloyd AJ, Ferrier IN, Barber R, Ghoklar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. Br J Psychiatry. 2004;184:488-495.

56. Rapp MA, Schneider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry. 2006;63:161-167.

57. Rapp MA, Schneider-Beeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. Am J Geriatr Psychiatry. 2008;16:168-174.

58. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. Eur Neurol. 1993;33:403-408.

59. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging. 1995;16:271-278.

60. Miguel-Hidalgo JJ, Baconn C, Dillely G, et al. Glial fibrillary acidic protein immunoreactivity in the prefrontal cortex distinguishes youngsters from older adults in major depressive disorder. Biol Psychiatry. 2000;48:861-873.

61. Mrak RE, Griffin WS. Common inflammatory mechanisms in Lewy body disease and Alzheimer disease. J Neuropathol Exp Neurol. 2007;66:683-686.

62. Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun. 2007;21:259-272.

63. Green KN, Billings LM, Roofzaad B, Mcgaugh JL, Laferla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer’s disease. J Neurosci. 2006;26:9407-9416.

64. Kang JE, Crrito JR, Dong H, Csernansky JG, Holtzman DM. Acute stress alters inflammatory mediators in different brain regions. J Neurosci. 2007;27:1313-1317.

65. Muselman DL, Tamer A, Manutang AK, et al. Exaggerated platelet reactivity in major depression. Am J Psychiatry. 1996;153:1313-1317.

66. Muselman DL, Marzec U, Davidoff M, et al. Platelet activation and secretion in patients with major depression, thoracic aortic atherosclerosis, or renal dialysis treatment. Depress Anxiety. 2002;15:91-101.

67. Leonard BE. Inflammation, depression and dementia: are they connected? Neurochem Res. 2007;32:1749-1756.

68. Kim JS. Cytokines and adhesion molecules in stroke and related diseases. J Neurol Sci. 1996;137:69-78.

69. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Soron F. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. Lancet Neurol. 2005;4:371-380.

70. Kip KE, Marroquin OC, Shaw LJ, et al. Global inflammation predicts cardiovascular risk in women: a report from the Women’s Ischemia Syndrome Evaluation (WISE) study. Am Heart J. 2005;150:900-906.

71. Aben I, Verhey F, Strik J, Lousberg R, Podder J, Honig A. A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. J Neurol Neurosurg Psychiatry. 2003;74:581-585.

72. Park JH, Lee SB, Lee TJ, et al. Depression in vascular dementia is quantitatively and qualitatively different from depression in Alzheimer’s disease. Dement Geriatr Cogn Disord. 2007;23:67-73.

73. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24:1069-1078.

74. Hippisley-Cox J, Fielding K, Pringle M. Depression as a risk factor for ischaemic heart disease in men: population based case-control study. BMJ. 1998;316:1714-1719.

75. Vinkers DJ, Stek ML, Van der Most RC, et al. Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age. Neurology. 2005;65:107-112.

76. Hermann LL, LeMasurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neurol Neurosurg Psychiatry. 2007;79:619-624.

77. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. Stroke. 2009;30:2159-2166.

78. de Groot JC, de Leeuw FE, Oudkerk M, van Gijn GJ, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol. 2000;47:145-151.
109. Krishna MS, O’Brien JT, Firbank MJ, et al. Relationship between periventricular and deep white matter lesions and depressive symptoms in older people. The LADIS Study. *Int J Geriatr Psychiatry*. 2006;21:983-989.

110. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke*. 2002;33:1635-1644.

111. Teodorczuk A, O’Brien JT, Firbank MJ, et al. White matter changes and late-life depressive symptoms: longitudinal study. *Br J Psychiatry*. 2007;191:212-217.

112. Hebert R, Lindsay J, Verreault R, Rockwood K, Hill G, Dubois MF. Vascular dementia: incidence and risk factors in the Canadian study of health and aging. *Stroke*. 2000;31:1487-1493.

113. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*. 2005;65:545-551.

114. Miekle MM, Rosenberg PB, Tschanj J, et al. Vascular factors predict rate of progression in Alzheimer disease. *Neurology*. 2007;69:1850-1858.

115. Steffens DC, Potter GG, McQuoid DR, et al. Longitudinal magnetic resonance imaging vascular changes, apolipoprotein E genotype, and development of dementia in the neurocognitive outcomes of depression in the elderly study. *Am J Geriatr Psychiatry*. 2007;15:839-849.

116. den Heijer HT, Launer LJ, Prins ND, van Dijk EJ, Vermeere SE, Hofman A, Koudstaal PJ, Breteler MM. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*. 2005;64:263-267.

117. Capiziano AA, Acion L, Bekinschtein T, et al. White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer’s disease. *J Neurol Neurosurg Psychiatry*. 2004;75:822-827.

118. Gurol ME, Irizarry SM, Smith EE, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology*. 2006;66:23-29.

119. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20:112-117.

120. Sztajzel P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology*. 1993;7:273-295.

121. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8:448-460.

122. Stern Y. The concept of cognitive reserve: a catalyst for research. *J Clin Exp Neuropsychol*. 2003;25:589-593.

123. Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol*. 1988;23:138-144.

124. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med*. 1999;131:165-173.

125. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*. 2001;58:498-504.

126. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348:2508-2516.

127. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002;69:364-370.

128. Kaze AM, Johnson EM. Alzheimer’s disease pathology in non-demented elderly. *J Alzheimers Dis*. 1998;1:81-89.

129. Morris JC, Storandt M, McKeel DW, et al. Cerebral amyloid deposition and diffuse plaques in “normal” aging: evidence for presymptomatic and very mild Alzheimer’s disease. *Neurology*. 1996;46:707-719.

130. Schmitt FA, Davis DG, Wnekstein DR, Smith CD, Ashford JW, Marksberry WR. “Preclinical” AD revisited: neuropathology of cognitively normal older adults. *Neurology*. 2000;55:370-376.

131. van der Flier WM, Barkhof F, Scheltens P. Shifting paradigms in dementia: toward stratification of diagnosis and treatment using MRI. *Ann N Y Acad Sci*. 2007;1097:215-224.

132. Tarter RE;Butters MA, Beers SR. *Medical Neuropsychology*, 2nd ed. New York, NY: Plenum; 2001.