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

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There is a strong association between late-life depression, cognitive impairment, cerebrovascular disease, and poor cognitive outcomes, including progressive dementia, especially Alzheimer's disease. While neuroimaging evidence suggests that cerebrovascular disease plays a prominent role, it seems that depression alone may also confer substantial risk for developing Alzheimer's disease. The relationships between the prominent cerebrovascular changes, other structural abnormalities, specific forms of cognitive dysfunction, and increased risk for developing Alzheimer's disease among those with late-life depression have been difficult to reconcile. The varied findings suggest that there are likely multiple pathways to poor cognitive outcomes. We present a framework outlining multiple, non-mutually exclusive etiologic links between depression, cognitive impairment, and progressive decline, including dementia. Importantly, the model is both testable and falsifiable. Going forward, using models such as this to inform research should accelerate knowledge acquisition on the depression/dementia relationship that may be useful for dementia prevention, monitoring the impact of depression treatment on clinical status and course of illness.

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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.[1] 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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Selected abbreviations and acronyms

AD	*Alzheimer's disease*
CAD	*coronary artery disease*
HPA	*hypothalamic-pituitary-adrenal*
MCI	*mild cognitive impairment*
MDE	*major depressive episode*
WMH	*hyperintense white matter regions*

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 processing[3-5] 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 general[10] and AD in particular.[11] Yet, many large individual studies have found no such relationship, giving rise to varying conclusions regarding the temporal and directional association between depression and mild cognitive impairment (MCI) and/or dementia.[12,13] That is, it is not clear whether prior depression is a true etiologic risk factor for dementia or rather represents a prodromal clinical manifestation of dementia neuropathology. Some evidence suggests that risk for both MCI and dementia is proportionate to cumulative depression burden in terms of symptom severity, lifetime duration of depression, or number of major depressive episodes (MDEs). In the Cardiovascular Health Study, severity of depressive symptoms independently predicted diagnosis of MCI 6 years later.[14] A large Danish case-registry study found the number of prior MDEs predicted dementia diagnosis, with a hazard ratio increasing by 13% per MDE.[15] Finally, several studies[16-18] suggest the longer the interval between onset of first depressive episode and time of assessment for dementia, the greater the risk of dementia (also see meta-analyses in refs 10,11). Overall, the weight of available evidence suggests that depression, including related pathophysiologic processes, may act as a true risk factor for MCI and dementia. However, there is no consensus as yet on this point.

Other studies have found that the shorter the interval between depression onset and assessment for dementia, the greater the risk,[19-21] while others found no such relationship between depression and cognitive impairment[22] 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. This is an important competing hypothesis to the concept of depression as a risk factor for dementia.

Overall, these findings emphasize the heterogeneity of late-life depression, its cognitive manifestations, and possible cognitive sequelae. 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 neuropatholgy 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 downregulating 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 damage[31] and memory impairment.[32] These changes have been observed concurrent with stress or exogenous

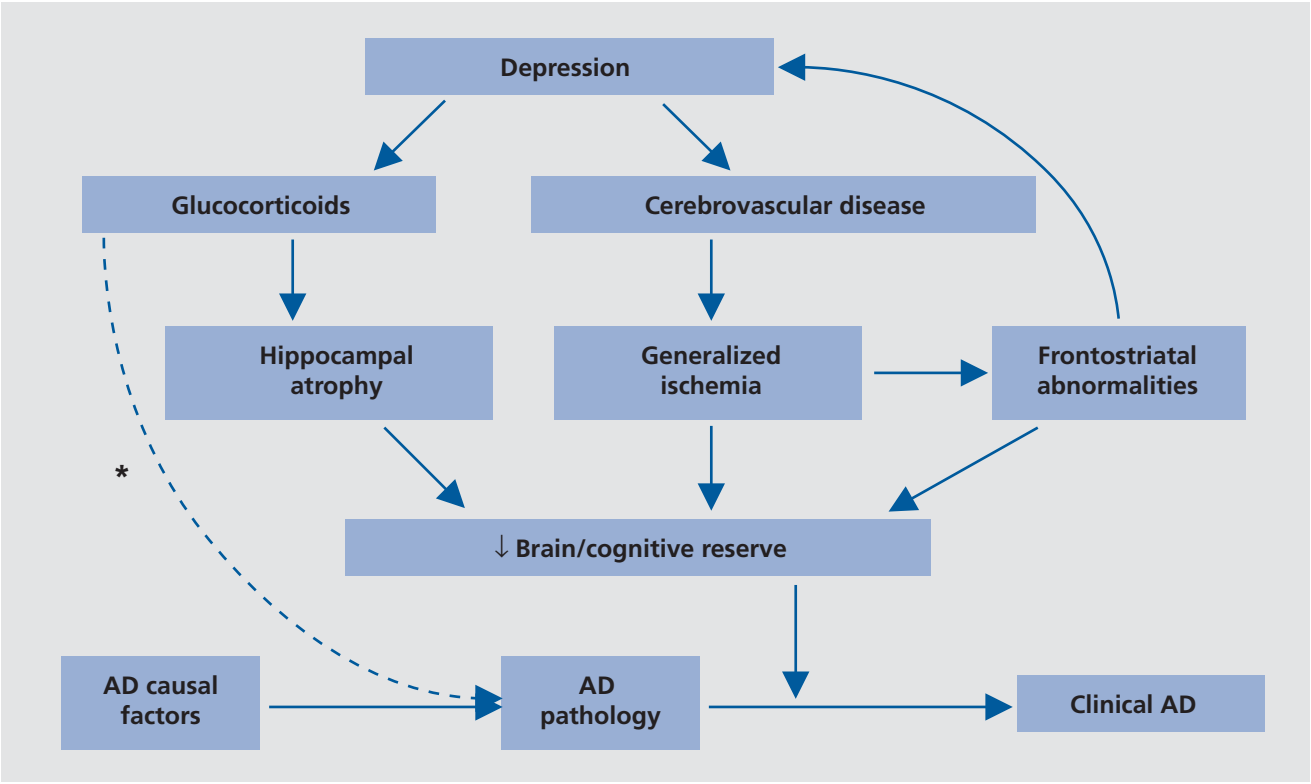

Figure 1. Proposed predominant mechanisms by which depression increases risk for Alzheimer's dementia (AD).
*The very recently postulated direct pathway leading from hypercortisolemia or elevated glucocorticoids to AD neuropathology is represented with a dashed line because, while evidence is growing, 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,[34,35] and in proportion to duration of prior hypercortisolemia.[36]

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 hypercortisolemica 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.[28,37] In addition, hypercortisolemia has been linked to a decrease in neurogenesis in the dentate gyrus.[38] 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.[39] 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,[40] atrophy of pyramidal cell dendrites,[41] derangement of glial cells,[42] 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),[43] although this finding is not universal.[44-46] Furthermore, many studies find a significant association between hippocampal atrophy and greater lifetime duration of depression, as assessed by number of depressive episodes,[43] total days depressed,[30,47] total days of untreated depression,[48] duration since first depressive episode,[49] or early-onset as opposed to late-onset depression.[50] 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.[39,51] Besides the possibility of persistent synapse 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.[52] Likewise, deficits in verbal learning and memory, similar to those described in euthymic patients with history of major depression,[30] also predict AD (eg, ref 53). While a primary causal role for depression in AD pathogenesis seems unlikely, depression-associated hypercortisolemia leading to decline in hippocampal size, connectivity and cognitive function may represent one of multiple links between depression and dementia as described below (also see *Figure 1*).

Biologic relationships between depression and Alzheimer's disease

The association between depression and dementia suggested by epidemiologic data[10,11] 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.[54,55] 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.[55] 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,[56] and more severe cortical neurofibrillary tangle pathology in the brains of AD subjects who suffered from comorbid depression.[57] The hippocampal findings, combined with the observation of marked hippocampal neurofibrillary pathology early in the course of AD,[58,59] 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 (eg, ref 60) and those with neurodegenerative diseases such as AD.[61] The prolonged hypercortisolemia associated with both diseases may partially account for these findings, as glucocorticoids can induce proinflammatory changes within the CNS.[62]

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[63] found dexamethasone administration 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[64] 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[54,55] 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,[56] 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[65] and Krishnan[66] 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,[68] 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.[67]

Diverse mechanisms have been proposed to explain the link between prior depression and subsequent vascular disease.[67,72,73] 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 hypercortisolemia 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 function[75] and may contribute over time to the development of hypertension in some cases.[76,77] Depressed subjects with coronary artery disease (CAD) exhibit autonomic dysfunction with decreased heart rate variability,[78] a condition that likely predisposes to both cardiac arrhythmias and episodic hypoperfusion. Depressed individuals with and without CAD show greater baseline platelet activation than nondepressed control subjects,[79-82] suggesting greater susceptibility to thromboembolic events. Finally, cross-sectional studies have linked depression to elevations in proinflammatory cytokines.[83] While the causal relationship between such immunologic changes and depression is unknown, a similar proinflammatory cytokine shift is observed in atherosclerotic and thromboembolic disease states.[84] 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 post-stroke 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 lesions[93] 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[98,99] and in the general population, correlating WMHs with both evidence of cerebrovascular disease[100,101] and systemic hypotensive,[102] or hypoxemic disease.[101,103]

Ischemic damage to frontostriatal brain regions may explain the executive dysfunction, psychomotor slowing and resistance to treatment common in late-life depression.[104] The few studies examining WMHs and cognition in late-life depression have found associations with psychomotor slowing,[105,106] memory, language, and executive functioning.[107,108] The relationship between WMHs and executive function may be particularly strong in individuals with late-onset depression.[106,109,110] 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).[111] In accordance with the bidirectional relationship described here, prior depression independently predicts subsequent vascular dementia (OR =2.15[112]) and individuals with late-life depression who develop clinical AD have high rates of cerebrovascular pathology upon postmortem examination.[1] Indeed, prospective community-based studies report associations between baseline systemic vascular disease/risk and both higher rates of incident AD,[113] and more rapid cognitive decline in established AD.[114] Moreover, rapid progression of cerebrovascular disease as inferred from serial MRI predicts subsequent dementia diagnosis.[115]

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.[116] 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, hypercortisolemic 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.[117] Notably, plasma levels of β-amyloid predict the extent of ischemic white matter damage in MCI and AD,[118] suggesting a reciprocal interaction between cerebrovascular and AD pathophysiology. Together these examples suggest that particular combinations of insults arising from different pathophysiologies 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.[119] Nevertheless, either may account equally well for the relationship between depression and dementia. The concept of brain reserve capacity, first proposed by Satz[120] 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 activity[126,127] 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 frontostriatal 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 activity[126,127] 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.[1] 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

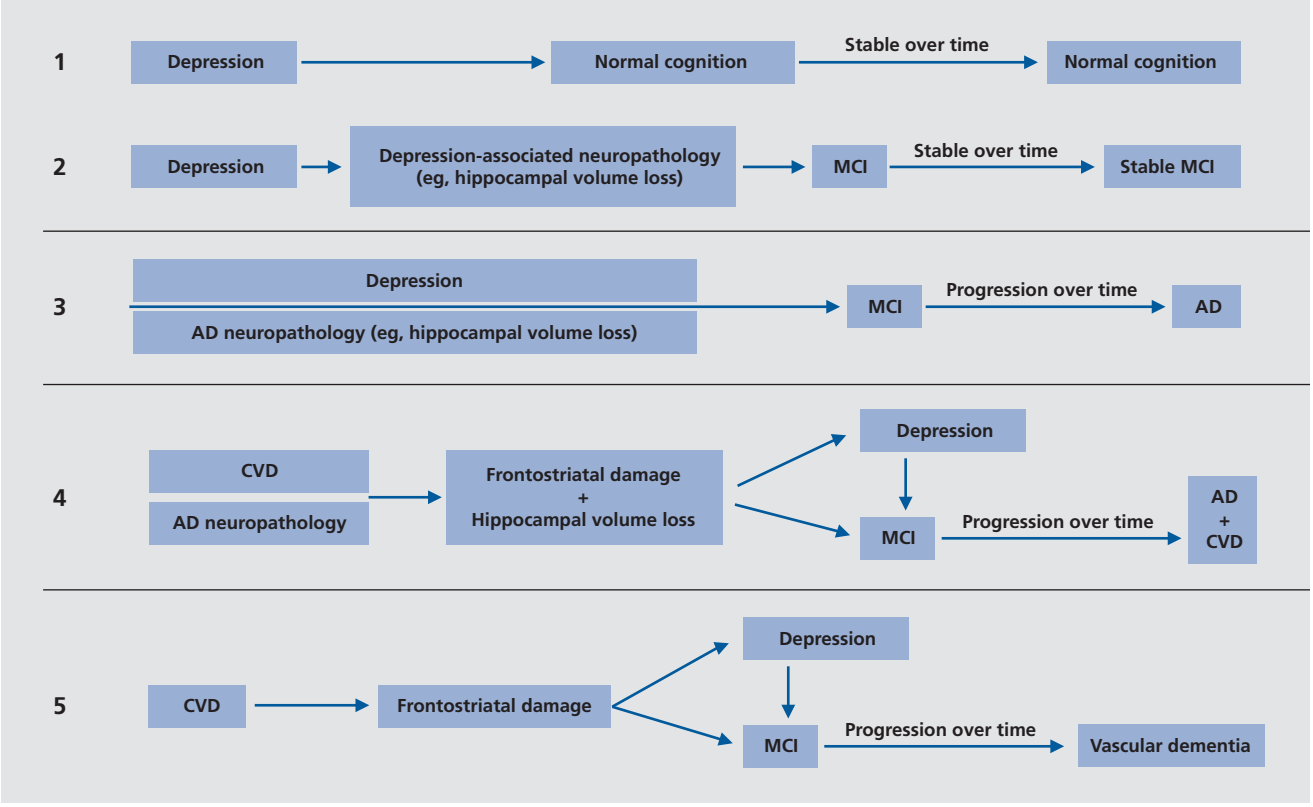

Figure 2. Pathways linking depression to predominant cognitive outcomes. MCI, mild cognitive impairment; AD, Alzheimer's disease; CVD, cerebrovascular disease.

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.

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. ❑

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Vías que relacionan la depresión de aparición tardía con el deterioro cognitivo persistente y la demencia

Existe una fuerte asociación entre la depresión de aparición tardía, el deterioro cognitivo, la enfermedad cerebrovascular y los desarrollos cognitivos desfavorables, incluyendo la demencia progresiva, especialmente la Enfermedad de Alzheimer. Aunque la evidencia de las neuroimágenes sugiere que la enfermedad cerebrovascular tiene un papel preponderante, parece que la depresión por sí misma también puede conferir un riesgo considerable para el desarrollo de la Enfermedad de Alzheimer. Ha sido difícil conciliar en los pacientes con depresión de aparición tardía las relaciones entre los marcados cambios cerebrovasculares, otras anormalidades estructurales, formas específicas de la disfunción cognitiva y el aumento del riesgo para desarrollar la Enfermedad de Alzheimer. Los variados hallazgos sugieren que probablemente existen múltiples caminos para los desarrollos cognitivos desfavorables. Nosotros presentamos un esquema que resume múltiples vínculos etiológicos no mutuamente excluyentes entre la depresión, el deterioro cognitivo y el decaimiento progresivo, incluyendo la demencia. Es importante considerar que el modelo puede ser aprobado o refutado. A futuro, la utilización de modelos como éste para dar cuenta de las investigaciones debería acelerar la adquisición de conocimientos sobre la relación entre depresión y demencia que pueda ser útil para la prevención de la demencia y para monitorear el impacto del tratamiento de la depresión en el estado clínico y en el curso de la enfermedad.

Liens entre la dépression du sujet âgé et le déficit cognitif persistant et la démence

Il existe une forte association entre la dépression du sujet âgé, le déficit cognitif, la maladie cérébrovasculaire et les faibles performances cognitives, incluant la démence progressive, et en particulier la maladie d'Alzheimer. Alors que la neuro-imagerie est en faveur d'un rôle majeur de la maladie cérébrovasculaire, la dépression seule pourrait représenter un risque substantiel de développer une maladie d'Alzheimer. Il est difficile de trouver un lien chez les sujets âgés atteints de dépression entre les modifications cérébrovasculaires marquantes, les autres anomalies structurales, les formes spécifiques de dysfonction cognitive et un risque augmenté de développer cette maladie. L'existence de résultats variés laisse supposer que les voies menant aux faibles performances cognitives sont nombreuses. Cet article présente divers liens étiologiques, non exclusifs mutuellement, entre la dépression, le déficit cognitif et le déclin progressif, y compris la démence. Il faut noter que ce modèle est à la fois testable et réfutable. En outre, l'utilisation de ce type de modèles, qui enrichissent la recherche, devrait accélérer l'acquisition des connaissances sur les liens dépression/démence, ce qui pourrait être utile à la prévention de la démence, surveillant l'effet du traitement de la dépression sur l'état clinique et l'évolution de la maladie.

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