Current Understanding of the Neurobiology and Longitudinal Course of Geriatric Depression

Sara L. Weisenbach, Ph.D.[1,2] & Anand Kumar, M.D.[1]

1. University of Illinois at Chicago, Department of Psychiatry
2. Jesse Brown VA Medical Center, Research & Development Program

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Correspondence to: Sara L. Weisenbach, Ph.D., University of Illinois at Chicago, Department of Psychiatry, 1747 W. Roosevelt Rd., Suite 155, Chicago, IL 60607, Telephone: 312-413-4470, Fax: 213-413-1703, Electronic mail: sweisenbach@psych.uic.edu

Anand Kumar, M.D., University of Illinois at Chicago, Department of Psychiatry, Psychiatric Institute, 1601 W. Taylor St., Chicago, IL 60612, Telephone: 312-996-7383; Electronic mail: akumar@psych.uic.edu

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Abstract

Late life depression is a complex disease associated with a number of contributing neurobiological factors, including cerebrovascular disease, neurodegeneration, and inflammation, which also contribute to its longitudinal prognosis and course. These factors create a context in which the brain is more vulnerable to the impact of stress, and thus, to depression. At the same time, some individuals are protected from late life depression and its consequences, even in the face of neurobiological vulnerability, through benefitting from one or more attributes associated with resilience, including social support, engagement in physical and cognitive activities, and brain reserve. Enhanced understanding of how neurobiological and environmental factors interact in predicting vulnerability and resilience is needed to predict onset and course of depression in late life and develop more effective interventions.

Introduction

Late-life depression (LLD; defined as depression occurring in individuals age 65 or older, and distinct from late onset depression, which is a subtype of depression with onset after the age of 65) has been associated with high incidence of chronic illness, cognitive dysfunction, disability, and poor prognosis [1-5]. There has been a great deal of interest in understanding the neurobiological and psychosocial contributions to onset and maintenance of depression and depressive symptoms in older adults, in an attempt to identify more effective treatments and prevention strategies. In this paper we will begin by describing three plausible neurobiological avenues to onset and maintenance of LLD that have gained traction in the literature, including vascular, neurodegenerative, and inflammatory mechanisms. It is important to consider that, while described separately, these pathways likely interact in a dynamic fashion, and may overlap considerably in a given individual. Alexopoulos [6] proposes a model in which factors contributing to LLD be separated into "mediating mechanisms" (e.g., hypometabolism of dorsal cortical regions and hypermetabolism of ventral limbic regions), "predisposing brain abnormalities" (e.g., abnormalities in frontostriatal and limbic circuitry, heredity and psychological vulnerability), and "etiological contributors" (e.g., age-related brain changes, disease-related changes, and allostatic response to adversity). We urge the reader to consider this model in our discussion of plausible mechanisms of LLD. For example, vascular changes may be an etiological contributor, occurring as a result of disease-related changes, such as hypertension

or cardiovascular disease. These vascular changes may then predispose to disruption and abnormal metabolism in fronto-striatal regions [7, 8]. Under the umbrella of this model, one or more of these aforementioned factors creates a context in which the brain is more vulnerable to the impact of stressors. In the second section of the manuscript, we discuss factors that have been shown to confer resilience to affective and cognitive changes, even in the face of vulnerability, including psychosocial factors, lifestyle factors, and brain reserve. We propose a model in which factors contributing to depression in late life can create an increasingly vulnerable brain, but which can be buffered by factors associated with resiliency (see Figure 1).

Three Plausible Mechanisms of Depression in Late Life

Vascular

It has been recognized for some time [9, 10] that individuals with vascular risk factors, including hypertension, atherosclerosis, and/or history of transient ischemic attacks or surgery for vascular disease are at greater risk for depression than those not experiencing vascular risk factors. Prominent symptoms of LLD, including cognitive deficits, anhedonia, psychomotor retardation, poor insight, and functional disability are similar to what might be anticipated from lesions to striato-pallido-thalamo-cortical pathways [11-14]. The vascular depression hypothesis states that "cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes" [15, p. 915]. The evidence supporting the vascular depression hypothesis is substantial, including clinical, behavioral, and structural and functional neuroimaging studies. For a more complete review of

supporting evidence, we refer the interested reader to Taylor and colleagues [16]. Here, we focus on the mechanisms underlying the relationship between vascular risk factors and depression, including disconnection and hypoperfusion, as thoroughly detailed in [16].

Disconnection. When vasculature that serves cerebral areas important for cognition and affective functioning is compromised, it can disrupt neural connections in and between these regions and impact behavior. There is evidence that cognitive performance and affective functioning are negatively impacted when specific fiber tracts and neural circuits are damaged, [12]. For example, a recent study by Lamar and colleagues [17] found that lower fractional anisotropy (FA) in the uncinate fasciculus predicted poorer performance on a measure of executive functioning among 26 patients with LLD. Also, in a study of 145 healthy and cognitively impaired older adults, Smith and colleagues [18] measured global and focal white matter hyperintensity (WMH} volume, and found that WMH in bilateral temporal-occipital, right parietal periventricular, and left anterior limb of the internal capsule were associated with episodic memory performance, while WMH in bilateral inferior frontal, bilateral temporal-occipital, right parietal periventricular, and bilateral anterior limb of the internal capsule were predictive of executive function performance, independent of total white matter volume. Finally, Dalby and colleagues [19] demonstrated a positive relationship between depression severity and fiber tracts intersected by white matter lesions in the left superior longitudinal fasciculus and the right uncinate fasciculus among 22 patients with LLD.

Hypoperfusion. Another potential mechanism to account for the relationship between cerebral vascular pathology and depression is reduced perfusion of blood to key brain regions integral to affective and cognitive processing. One such measure of cerebral hemodynamics is that of carotid intima-media thickness (IMT), which encompasses the innermost two layers of the arterial wall, is a reflection of atherosclerosis and vascular disease risk [20], and correlates strongly with atherosclerosis itself [21]. Studies have shown IMT to be higher among older adults with LLD (relative to comparisons), and to correlate with WMH among patients with LLD [22]. IMT is also associated with later of age depression onset [23], and is positively associated with non-response to antidepressants [24].

Arterial endothelial function is another way to assess vascular function and pathology. Vascular endothelium are the thin layer of cells that line the inner surface of blood vessels and form an interface between blood and the rest of the vessel wall. They are involved in a number of important functions, including the inflammatory response and control of blood pressure [25]. While it is not possible to directly assess the functioning of endothelia within the brain, it is often reflected in gluteal fat [26]. A study of older patients with LLD found that endothelial function was poorer in depressed relative to (NDC) comparisons, independent of response to antidepressant therapy [24]. Another study of LLD patients found reduction in the dilation response to acetylcholine (a vasodilator) in preconstricted small arteries [27, 28]. Given that that this did not correlate with the severity or volume of WMH [28], Taylor and colleagues [16] suggested that WMH may actually be an endpoint to

perfusion deficits, which do not need to cause ischemia to impact brain functioning. B

Blood flow velocity using cerebral transcranial Doppler ultrasound is also capable of reflecting vascular function. Among a large sample of NDC older people, lower peak-systolic, end-diastolic, and average blood flow velocities at baseline were associated with higher depression symptom severity at the follow-up visit approximately 3-6 years later. Moreover, mean blood flow velocity and decreased baseline vasomotor reactivity, which compensates for maintaining cerebral blood flow during mental activity, predicted incident depressive symptoms during the span of the follow-up period [29].

In summary, there is wide support for the suggestion that for at least a subset of individuals with LLD, vascular changes, including hypoperfusion of and disrupted connection between regions relevant to cognition and affective regulation are one mechanism of depression in late life and its associated symptoms.

Neurodegenerative

Epidemiology. There have been many studies investigating depression as a prodromal symptom and risk factor of neurodegenerative diseases, such as Alzheimer's disease (AD; for review, [30]), with mixed findings. A systematic review, meta-analysis, and metaregression analysis of prospective studies of risk of developing dementia among individuals with and without depression concluded a pooled odds ratio (OR) of 2.03, with 1.73 for case-control and 1.90 for cohort studies. Interestingly, the longer the interval between the diagnosis of depression and development of dementia, the higher was the risk of developing AD, suggesting

that AD is a risk factor, as opposed to a prodromal state of AD. Similarly, a more recent systematic review and meta-analysis in 23 prospective population-based studies found that LLD was associated with significantly increased risk for all-cause dementia (1.85 OR), and clinical diagnoses of Alzheimer's disease (1.65 OR), and vascular dementia [31].

Structural neuroimaging. Supporting a neurodegenerative path to AD, there have been a multitude of studies demonstrating cerebral atrophy in LLD patients, in regions that play a critical role in memory, executive functioning, and other cognitive processes known to decline in early AD [32-35]. Interestingly, among 334 participants with Mild Cognitive Impairment (MCI) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, depression symptom severity was associated with reduced entorhinal cortex thickness at baseline, as well as accelerated atrophy over an average of 30.5-month follow-up [36]. It is important to note that neurodegenerative and vascular changes, while both present in those with LLD, may be independent processes. A study by Kumar and colleagues [33] found smaller frontal lobe volumes and larger whole brain lesion volumes among those with LLD, relative to NDCs. After controlling for medical comorbidities, however, the relationship between whole brain lesion volume and LLD was reduced to non-significance, while lower frontal lobe volume continued to be associated with LLD. Moreover, frontal lobe volume and brain lesion volume were not correlated. Together these findings suggest that vascular and neurodegenerative processes may be autonomous pathways contributing to LLD, independent of one another in the context of LLD.

Neuropathology. Given structural imaging findings and results from epidemiological community studies suggesting an increased risk of AD among those with depression, there has been work investigating the presence of neuropathological features of neurodegenerative disease in post-mortem-brain tissue, although these studies are limited in number and sample sizes are small. In the first study to characterize neuropathologic diagnoses in a group of LLD patients (n = 10), Sweet and colleagues [37] found that of the seven patients with dementia at death, six met neuropathologic criteria for AD, which was similar to the rate of AD in patients with dementia without a history of mood disorder. Among the six LLD patients with dementia, all had comorbid Dementia with Lewy Bodies (DLB) or cerebrovascular disease. Other studies of post-mortem brain in LLD have failed to show an association between the presence of depression prior to death and Alzheimer's pathology [38, 39], although these studies excluded individuals with dementia, eliminating the group most likely to show such neuropathological changes. Interestingly, in one of these studies, individuals with history of depression were more likely than never-depressed comparisons to show neuropathology associated with DLB [38], while in the other study, those with history of depression had more atheromatous disease [39]. Taking a different approach, Rapp and colleagues [40] found that AD patients with a history of depression had higher levels of plaque and tangle formation than did AD patients with no history of depression. While studies of neuropathology in LLD have begun to provide some support for findings of increased risk of dementia in larger, community-based, epidemiological studies, methodological limitations preclude drawing any conclusions at the current

time regarding the actual prevalence of neuropathological features in the brains of patients with LLD or history of depression.

Positron emission tomography (PET). Newer imaging techniques, such as PET scanning, have allowed investigators to study, in-vivo, the presence of neuropathological features of Alzheimer's disease in living humans. The first study, by Butters and colleagues [41] used Pittsburgh Compound-B ([^{11}C]PiB) to visualize β-amyloid plaque accumulation in the brains of eight individuals with remitted Major Depressive Disorder (MDD; six with comorbid MCI) compared to eight never-depressed elders (none with MCI). Results demonstrated that one-half of subjects with comorbid MCI and depression history had [^{11}C]PiB retention in the range of what is typically seen in AD, while the other half had values that were intermediate to those typically observed in healthy comparison and AD subjects. The two non-MCI patients demonstrated values that were similar to healthy comparisons. A second study by Kumar and colleagues [42] used [^{18}F]FDDNP to image amyloid and tau in the brains of 20 LLD patients (one with comorbid MCI) and 19 never-depressed comparisons. They found greater [^{18}F]FDDNP binding in the posterior cingulate and lateral temporal regions in the LLD group. Similarly, Wu and colleagues [43] studied 25 LLD and 11 comparison subjects (none with comorbid MCI), and found increased ^{18}F-Florbetapir (AV-45/Amyvid) binding (to amyloid plaques) among LLD patients. In contrast, another group found no association between previous depressive episodes and increased [^{11}C]PiB binding [44]. It is notable that individuals in this latter study could not have had depression for at least six years prior to enrollment in the study, and thus may represent a group of

LLD individuals who are at less risk of going on to develop cognitive decline and/or dementia.

Plasma studies. The aforementioned PET studies provide some evidence that neuropathological features of AD are more prevalent in the brains of individuals with LLD relative to NDC individuals, though are limited by small sample sizes and heterogeneous methodologies, with some studies including patients with MCI, others including few with MCI, and still others excluding those with MCI altogether. Some groups have chosen to use plasma and/or CSF to quantify β-amyloid. Changes in plasma Aβ40, Aβ42,and Aβ42/40 ratios may be linked to increased risk for incident AD [45, 46], while reduced levels of CSF Aβ42 are associated with Aβ deposition in brain senile plaques [47]. In a study of 48 LLD patients relative to 35 NDC, elevated levels of plasma Aβ42 and Aβ42/40 ratios were found in the LLD group, and this was associated with greater severity of white matter hyperintensity burden, but not age of onset of first depressive episode [48]. A review by Osorio et and colleagues [49] concluded, however, that the relationship of LLD with plasma Aβ levels is equivocal, with some studies demonstrating higher levels of Aβ in the LLD group, relative to the NDC group (or positive associations between Aβ and depressive symptoms), some finding the opposite relationship, and others finding no differences. At the same time, baseline Aβ42 [50] and Aβ42/40 ratios [51] have been shown to be predictive of new onset of future depressive symptoms, although this may be specific to ApoE4 carriers [51]. The authors cite between-study methodological differences, heterogeneity of LLD, in addition to disease-stage

dependent differences in the trajectory of Aβ changes as possible explanations for disparate findings. [49].

Cerebrospinal fluid studies. CSF markers of Alzheimer's disease are more reliable indicators than plasma studies of CNS amyloid deposition [48]. In one study, Pomara and colleagues [52] detected significantly lower levels of Aβ42 in a group of 27 cognitively-intact women and men with LLD, relative to the NDC group. In contrast, Gudmundsson and colleagues [53] found higher levels of CSF Aβ42 among a small group of women with depression (n = 14), relative to those with without LLD. Importantly, the former study included individuals with more chronic forms of depression, whereas the latter study were community volunteers who may have had more acute forms of depression [52]. Importantly, none of the three studies of CSF markers in MDD to date have detected significant between group differences in Aβ40, total tau, or phosphorylated tau, which are also markers of Alzheimer's disease [53, 54], suggesting that the absence of these markers may distinguish LLD without AD from the comorbid condition. However, tau pathology may be a downstream effect of amyloid beta deposition [55], so may not be particularly useful as a biomarker of early AD.

Given the association between depression and risk for dementia, in addition to mixed evidence of increased amyloid burden in older adults with history of depression, there has been interest in the mechanisms underlying these relationships. One theory that has been proposed is HPA-axis dysfunction, known to be associated with depression [56] and hippocampal volume loss [57]. This theory is supported by studies of animal models. In a mouse model, stress-level

glucorticoid administration was associated with increased amyloid-β and tau-pathology [58]. Further, acute stress (i.e., three months of isolation) has been shown to increase levels of amyloid in the brain [59, 60]. Follow-up study suggested that the relationship between stress and amyloid deposition may be mediated by increased corticosterone levels [59].

In summary, large-scale studies suggest that depression is associated with increased risk of dementia, and some studies have demonstrated neuropathological changes associated with neurodegenerative diseases in LLD in autopsied human brain, in-vivo imaging, and studies of CSF and plasma. Animal studies suggest that HPA-axis dysfunction may be one mechanism by which LLD is associated with neurodegenerative changes.

Inflammatory Processes

Plasma studies. Inflammatory explanations for depression across the lifespan have gained a great deal of traction in recent years. In a seminal review, Alexopoulos and Morimoto [61] suggest that inflammatory processes related to aging and disease may provoke neural and/or metabolic changes that predispose to the development of depression in late life. A multitude of studies have demonstrated an association between levels of peripheral pro-inflammatory cytokines and depressive symptoms in older people [62-71]. While a variety of pro-inflammatory markers have been studied, interleukin-6 (IL -6) has been most reliably associated with depressive symptoms after possible confounding variables, such as age chronic disease, cognitive functioning, and anti-depressants have been covaried. There may be an interaction of inflammatory and vascular processes predisposing to LLD, as

higher levels of IL-6 and C-reactive protein have been associated with greater white matter pathology [72-75]. IL-6 levels have also been negatively associated with memory performance in depressed and NDC older adults [76]. Pro-inflammatory cytokines also impact monoamine neurotransmitter pathways [77-79], resulting in reduced tryptophan and serotonin synthesis [77, 80]. In addition, they disrupt function of glucocorticoid receptors and decrease hippocampal neurotrophic support [81]. Alexopoulos and Morimoto [61] propose that dramatic and prolonged CNS immune response can impact emotional and cognitive network functions that are relevant to depression, and can contribute to the etiology of at least some LLD syndromes.

Interestingly, chronic inflammation has also been associated with increased risk of vascular dementia and AD, with an increased incidence of vascular events and smaller hippocampal volume. Leonard [82] hypothesized that the progression of depression to dementia may be mediated by the activation of macrophages and microglia in the brain, linked to chronic inflammation. In their review of the literature, Hermida and colleagues [83] propose that individuals with LLD and activation of the inflammatory pathway may be most vulnerable to vascular events, the amyloid cascade, or both processes.

Resilience

The three neurobiological processes reviewed (vascular, neurodegenerative, and inflammatory), likely increase the vulnerability of the brain to the adverse impact of stressors, both psychosocial and physiological. Yet, there are individuals who, even with the accumulation of apparent neurobiological predisposition, do not

develop depression or cognitive decline. For example, in one study, 40% of non-depressed, cognitively normal older adults displayed the presence of at least one AD-sensitive biomarker (i.e., hippocampal volume, gray matter thickness, and glucose tolerance) [84]. Findings such as these suggest moderating variables that might increase or decrease the likelihood of cognitive decline and depression, even in the face of neurobiological vulnerability.

Psychosocial Factors. There is a large literature on the protective effect of psychosocial variables to cognitive and emotional health in aging. In one study of 234 older people residing in two independent living facilities, scores on a depression symptom severity rating scale were significantly predicted by three psychosocial-oriented variables, including fewer neighbor visitors, less participation in organized social activities, and less church attendance [85]. A second study of 889 community-dwelling individuals found that lack of contact with friends was a significant risk factor for the development of depression over one year, and maintenance of depressive symptoms was predicted by low levels of social support and social participation [86]. Social support has also been demonstrated to buffer against the effects of disability on depression in late life [86, 87].

Lifestyle Factors. Physical and cognitive engagement have been associated with reduced risk for AD and cognitive decline in a multitude of studies, and are now widely cited as potentially modifiable risk factors of dementia [88]. In a study of 92 cognitively normal older adults, those with higher lifetime cognitive activity and higher current physical activity had fewer white matter lesions (WML). In turn, WML were associated with a composite measure of neural integrity and better

cognitive functioning. Additionally, less Aβ burden buffered against the negative impact of poor neural integrity on cognitive functioning. The authors concluded that cognitive and physical activities may protect against cerebrovascular and Aβ pathology, and potentially the development of dementia, in late life [89]. Depressive symptoms were not measured in this study, though volunteers reported no current psychiatric symptoms.

Physical activity has been demonstrated as an effective intervention for depression in older adults in at least nine studies [90], although it is not yet clear from the literature whether lifetime physical activity prevents the onset of depressive symptoms. Conceptually, however, given the relationship of depression with cerebrovascular pathology and overall neural integrity, one would expect that lifetime physical activity would also be protective of depression onset in late life.

Brain Reserve. Brain reserve theory [91] hypothesizes that individuals with high brain reserve, typically defined by education, which is associated with greater synaptic density, are less likely to exhibit behavior associated with dementia when faced with neurological insult. There has been a great deal of study on the effect of brain reserve on delaying clinically relevant cognitive deficits in dementia [92-94]. There has been little study, on the other hand, as to the impact of cognitive reserve on the expression of depressive symptomatology. An interesting study using the Health and Retirement Survey, that includes 1355 stroke-free women greater than 80 years of age studied over six years found that level of education (i.e., brain reserve), and the interaction of cerebrovascular burden (by self-report and smoking history) interacted with level of education in negatively predicting depressive

symptoms at baseline. While the protective effect of brain reserve diminished over the study period, these results suggest that brain reserve may buffer against the effects of cerebrovascular burden on depressive symptoms, and should be replicated in other studies that include men [95].

Conclusions

LLD is a complex, heterogeneous disease with a multitude of dynamic and likely overlapping etiologies. Vascular, neurodegenerative, and inflammatory factors have gained the most traction in the literature as to possible mechanisms by which depression in late life develops and persists. However, this is certainly not an exhaustive list, and there are likely other less studied or never studied factors that also contribute. Psychosocial factors, such as social support, as well as lifestyle choices (e.g., physical activity), and cognitive reserve may protect against the effects of adverse neurobiological events in what would otherwise by a brain vulnerable to depression and cognitive decline. Future research would benefit from measuring multimodal neurobiological and environmental factors to better understand how they interact in predicting onset and course of depression in late life.

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