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Biological Basis of Late Life Depression

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Abstract

Late life depression (LLD) is an important area of research given the growing elderly population. The purpose of this review is to examine the available evidence for the biological basis of LLD. Structural neuroimaging shows specific gray matter structural changes in LLD as well as ischemic lesion burden via white matter hyperintensities. Similarly, specific neuropsychological deficits have been found in LLD. An inflammatory response is another possible underlying contributor to the pathophysiology of LLD. We review the available literature examining these multiple facets of LLD and how each may affect clinical outcome in the depressed elderly.

Keywords

Late life depression; LLD; Elderly; Ischemic lesion burden; White matter hyperintensities; Neuropsychological factors; Cognitive deficits; Inflammatory markers; Treatment outcome; Structural neuroimaging

Introduction

Late life depression (LLD), most commonly defined as depression occurring at age 60 or older, is an area of great research interest because of its clinical significance and because of the insights it can provide into the biological basis of depression. While beyond the scope of this article, there are multiple hypotheses regarding the biological basis of depression in general. One hypothesis proposes that the hypothalamic–pituitary–adrenal (HPA) axis plays a role in the pathophysiology of depression across an individual's lifespan. The vascular depression hypothesis argues that an underlying cerebrovascular etiology differentiates late-onset (LOD) from early-onset (EOD) depression, with LOD having increased rates of comorbid vascular disease. Neurodegenerative illness is another mechanism that may be related to the development of LLD. The purpose of this review was to examine the current evidence for the biological basis of LLD, focusing on structural neuroimaging, neuropsychological factors, and biochemical inflammatory mediators and how those factors influence treatment outcome.

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Neuroimaging

Structural MRI

Structural neuroimaging studies provide information about the underlying neuroanatomical changes in LLD, including changes in anatomical size and shape of brain regions of interest (ROI) and white matter ischemic lesions as measured by the occurrence of white matter hyperintensities (WMH). Grey matter structural changes are seen in LLD compared with controls, especially in areas of the frontolimbic pathway. This pathway includes the orbitofrontal cortex, anterior cingulate cortex (ACC), basal ganglia, hippocampus, parahippocampus, and amygdala. Multiple studies have shown smaller orbitofrontal cortex [1–4], ACC [2, 4, 5], hippocampal [6, 7], parahippocampal and caudate [8, 9], and amygdala volumes in LLD than in controls [8, 10]. However, some studies report no differences in these volumes in LLD, although results may have been influenced by study methodologies. The recent Women's Health Initiative magnetic resonance imaging (MRI) study by Goveas et al. [11], which comprised 1,372 postmenopausal women, examined the relationship between depressive symptoms at study onset and brain volumes as well as ischemic lesion burden measured an average of 8 years later. ROI comprised frontal lobe regions, amygdala, and hippocampal volumes as measured by cross-sectionally obtained MRIs. The authors reported smaller superior, middle, and inferior frontal gyral volumes, but no difference between hippocampal or amygdala volumes or ischemic lesion volumes between women with depression symptoms and those without evidence of depression on questionnaire. One important limitation in that study was that depressive symptoms were based on questionnaire rather than a semistructured clinical interview. Similarly, a study by Dotson et al. [3] that failed to find hippocampal decreases included subsyndromal depressive symptoms also obtained via questionnaire rather than clinical diagnosis. In contrast to the smaller amygdala volumes reported in multiple studies, Tamburo et al. found no difference in amygdala volume but did find a significant difference in amygdala shape, with contraction of the basolateral nuclei in LLD individuals [12]. There were no studies identified reporting no difference in orbitofrontal cortex or ACC volumes.

A few studies examined how structural changes seen in LLD may influence clinical outcome [3, 13, 14]. Gunning et al. found an association between smaller dorsal and rostral anterior cingulate volumes and poorer treatment response to escitalopram in individuals with LLD compared with controls [15•]. Hsieh et al. [16] reported that smaller hippocampal volumes were related to decreased response to antidepressants, whereas Janssen et al. reported no structural differences between remitted and nonremitted LLD individuals [17]. Overall, the relationship between grey matter structural differences and treatment outcome in LLD remains an intriguing area of research.

White Matter Hyperintensities

One possible etiology of LLD strongly supported in the literature, the vascular depression hypothesis [18, 19], proposes that cerebrovascular disease causes ischemic lesions in limbic structures involved in mood regulation, disrupting their projections to the frontal cortex. WMH on T2-weighted MRI are used as a measure of ischemic lesion burden. Medical conditions such as hypertension [20], diabetes mellitus [21], cardiovascular disease [22], and higher Framingham vascular risk factor scores [22, 23] contribute to WMH pathology. They occur in up to 60 % of healthy elderly patients, as well [24–27].

Multiple studies report increased WMH in LLD [28–34, 35•, 36]. A review examining WMH in LLD demonstrated both periventricular and deep WMH are more common and more severe in LLD patients compared to controls. The authors found that WMH are more common and more severe in LOD than in EOD, supporting the hypothesis that LOD is

pathophysiologically different from EOD. Multiple studies have reported no difference in WMH in regards to age at onset of depression [37–40], but small sample sizes may account for the negative findings. Recent studies have also reported increased WMH severity in LOD compared with EOD [41, 42].

The severity of WMHs has been found to predict clinical outcome in LLD patients; specifically, more severe WMH are associated with worse treatment outcome [35•, 43–52], although there are studies reporting no association between WMH and treatment outcome [41, 53–55]. The Leukoaraiosis And Disability (LADIS) study, a longitudinal European study examining the relationship between white matter lesions, depression, and disability, found that WMH severity at baseline predicted depressive symptoms 2 and 3 years later. Disability increased over time, and by 3 years, baseline white matter changes did not significantly predict depressive symptoms when adjusted for disability. The study concluded that over time, disability may be the mediator between white matter changes and depression [56]. In a treatment study with escitalopram, Gunning-Dixon et al. [57] found that individuals with LLD had more severe lesion burden than controls, with the nonremitted depressed accounting for much of this difference. The remitted depressed did not have a significant difference in signal hyperintensities compared with controls. A 12-week antidepressant treatment study with sertraline and nortriptyline demonstrated that individuals with increased deep WMH, periventricular hyperintensities, and total lesion volumes had a four- to seven-times increased likelihood of poor treatment outcome than individuals with low hyperintensities [58•]. Interestingly, the authors argued that it was total lesion volume, not lesion location, that mediated treatment response. These recent studies add to the growing literature demonstrating the role of WMH in LLD pathophysiology and clinical outcome.

Neuropsychological Factors

Multiple studies demonstrate that neuropsychological deficits underly LLD and that these deficits may include multiple cognitive domains [59–62, 63•], including episodic memory, executive functioning, and processing speed [64]. These cognitive deficits may persist despite improvement in depressive symptoms [65–69]. Studies suggest that processing speed may be a strong contributor to the cognitive deficits seen in LLD [70, 71] but may have a stronger mediating effect on executive functioning than episodic memory [72]. Slowed processing speed also may be associated with a worse natural course in those with LLD [73].

A recent study comprising 67 LLD patients and healthy controls compared global cognition, memory, executive functioning, and processing speed over time [62]. The study found persistent cognitive deficits across all domains in individuals with LLD compared with controls, regardless of current mood, remission status, or antidepressant treatment. Later age of onset was associated with worse episodic memory. Processing speed was a significant mediator of executive functioning and memory but did not fully explain executive dysfunction or memory impairment in LLD. Whereas that study found minimal improvement in cognition with antidepressant treatment, the authors note that lifetime antidepressant treatment did not have a negative effect on cognition at any time point in the study and that other studies have noted improvement in cognition with antidepressant treatment [65, 74, 75]. A recent study by Sexton et al. [63•] examined multiple neuropsychological factors, including executive function, processing speed, episodic memory, language skills, visuospatial skills, and MRI correlates. All domains were significantly impaired in those with LLD, but executive functioning was the key factor. MRI results showed executive functioning correlated with the anterior thalamic radiation and processing speed with the genu of the corpus collosum, which the authors note is in

agreement with Shimony et al. [76]. These results provided further support that structures in the frontolimbic pathway are involved in the pathophysiology of LLD.

Multiple studies examined the effects of neuropsychological function on treatment outcome in LLD and found that executive dysfunction negatively affected treatment outcome [45, 50, 55, 77–79]. In a 1-year treatment study examining cognitive deficits and treatment response, Story et al. concluded that individuals with LLD with poorer baseline verbal memory and processing speed had worse treatment response regardless of baseline depression severity [80]. Similarly, Sheline et al. found that both baseline neuropsychological function and WMH scores predicted Montgomery–Åsberg Depression Rating Scale (MADRS) scores over a 12-week course of sertraline, indicating cognitive deficits and increased ischemic lesion burden lead to poorer response to antidepressant treatment. This study also found a larger effect on treatment outcome with processing speed than with other cognitive domains. Neuropsychological function and WMH scores were correlated with each other and with vascular risk-factor scores, lending further support to the hypothesis that LLD is strongly associated with vascular disease.

Inflammatory Mediators

Inflammation as a possible etiology for LLD provides an interesting avenue of research. There is some evidence that inflammation may be associated with multiple serious illnesses in the elderly, including cardiovascular illness, cognitive decline, and overall mortality [81]. Cytokines, specifically interluken-6 (IL-6), stimulate the production of C-reactive protein (CRP) in the liver, initiating the inflammatory response. IL-6 crosses the blood–brain barrier, acts as a neuromodulator, and stimulates the HPA axis [82–85]. Whereas multiple studies report positive associations between inflammatory mediators and LLD [85–93], some do not [94]. Thomas et al. reported elevated levels of two adhesion molecules in postmortem dorsolateral prefrontal cortex [95, 96] and elevated serum IL-1B levels [97] in LLD patients, but a follow-up report found no elevated serum levels of adhesion molecules previously found in the post mortem study [98]. As part of the Longitudinal Aging Study Amsterdam (LASA), a long-term study of the elderly in The Netherlands, Bremmer et al. [85] reported an association between IL-6 and LLD; specifically, LLD patients with high IL-6 levels were at increased risk for major depressive disorders (odds ratio 2.49) independent of age, chronic diseases, Mini Mental Status Exam (MMSE), and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antidepressants. Neither CRP nor IL-6 levels were associated with specific depression symptoms. Inflammatory mediators as a possible mechanism of LLD remain an interesting area of future research. No published studies have thus far been found examining the association of inflammation with antidepressant treatment outcome.

Conclusion

LLD is a heterogeneous disorder, with conflicting findings regarding structural brain imaging, ischemic lesion burden, neuropsychological factors, and inflammatory markers. However, the studies reviewed here lend to our understanding that, indeed, LLD is a unique illness compared with EOD, with a unique pathophysiology. Structural neuroimaging provides further support that the frontolimic pathway is involved in LLD, although studies may differ in specific ROIs affected. Research supports increased WMH in LLD, specifically in LOD, suggesting that ischemic burden is related to depressive symptoms and treatment outcome. Similarly, neuropsychological deficits are a core feature of LLD and also affect clinical outcome. The role of inflammation in LLD is less well investigated but remains an interesting avenue of future research.

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