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The heterogeneity of late-life depression and its pathobiology: a brain network dysfunction disorder

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Abstract

Depression is frequent in older individuals and is often associated with cognitive impairment and increasing risk of subsequent dementia. Late-life depression (LLD) has a negative impact on quality of life, yet the underlying pathobiology is still poorly understood. It is characterized by considerable heterogeneity in clinical manifestation, genetics, brain morphology, and function. Although its diagnosis is based on standard criteria, due to overlap with other age-related pathologies, the relationship between depression and dementia and the relevant structural and functional cerebral lesions are still controversial. LLD has been related to a variety of pathogenic mechanisms associated with the underlying age-related neurodegenerative and cerebrovascular processes. In addition to biochemical abnormalities, involving serotonergic and GABAergic systems, widespread disturbances of cortico-limbic, cortico-subcortical, and other essential brain networks, with disruption in the topological organization of mood- and cognition-related or other global connections are involved. Most recent lesion mapping has identified an altered network architecture with "depressive circuits" and "resilience tracts", thus confirming that depression is a brain network dysfunction disorder. Further pathogenic mechanisms including neuroinflammation, neuroimmune dysregulation, oxidative stress, neurotrophic and other pathogenic factors, such as β-amyloid (and tau) deposition are in discussion. Antidepressant therapies induce various changes in brain structure and function. Better insights into the complex pathobiology of LLD and new biomarkers will allow earlier and better diagnosis of this frequent and disabling psychopathological disorder, and further elucidation of its complex pathobiological basis is warranted in order to provide better prevention and treatment of depression in older individuals.

Keywords Late-life depression · Cognitive impairment · Neuroimaging · Neuropathology · Brain network disconnections

Abbreviations

5-HTT	Serotonin transporter
Aβ	β-Amyloid
AD	Alzheimer disease
CAA	Cerebral amyloid angiopathy
CBF	Cerebral blood flow
CBT	Cognitive behavior therapy
CI	Cognitive impairment
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
CVD	Cerebrovascular disease
DMN	Default mode network
DS	Depressive symptoms close to death
ECN	Executive control network
ECT	Electroconvulsive therapy
FA	Fractional anisotropy
FC	Functional connectivity
GM	Gray matter
ICN	Intrinsic connectivity network
LC	Locus ceruleus
LLD	Late-life depression
MCI	Mild cognitive impairment
MDD	Major depressive disorder
SMA	Supplementary motor area
SMN	Somatomotor network
SN	Salience network
SNAP	Suspected non-Alzheimer pathophysiology
STD	Subthreshold depression
WM	White matter
WMH	White matter hyperintensities

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Introduction

Late-life depression (LLD) is one of the most common mental disorders among the older adults. Its pathophysiology and pathogenesis are multifactorial and complex. This common mood disorder is a heterogenous group, affecting individuals in whom the initial depressive symptoms occur after age 60 years and those with no depressive episode earlier in life (Sekhon et al. 2021). LLD is often associated with cognitive and executive deficits (Alexopoulos 2019; Koenig et al. 2015; Köhler et al. 2010; Manning et al. 2023; Rajtar-Zembaty et al. 2022), with functional disability, lower quality of life (Chachamovich et al. 2008), and may lead to a higher mortality risk (Cuijpers and Smit 2002; Katon et al. 2003; Laborde-Lahoz et al. 2015; Roebuck et al. 2023). In older individuals, depressive symptoms are usually chronic (Comijs et al. 2015; Schaakxs et al. 2018). LLD has been suggested to increase the risk of subsequent dementia or to represent an early manifestation of Alzheimer disease (AD) or other cognitive disorders (Barnes et al. 2012; Butters et al. 2008; Crocco et al. 2010; Geerlings et al. 2008; Geraets et al. 2022; Invernizzi et al. 2021; Kuring et al. 2020; Lauriola et al. 2018; Mendez 2021; Ochi et al. 2022; Ohanna et al. 2011; Ownby et al. 2006; Weisenbach et al. 2012; Wu et al. 2022a; Diniz et al. 2013), whereas others have not found such relationships (Chen et al. 1999; Ganguli et al. 2006; Naismith et al. 2012). A recent review stated that there is an association between depression and AD, but more appropriately as a risk factor and not as a predictor or clinical marker of the development of AD (González Hernández et al. 2022). Several pathways connecting LLD and dementia/AD have been discussed (Guo et al. 2022; Hakim 2022; Harerimana et al. 2022; Lee et al. 2021; Linnemann and Lang 2020; Mendez 2021; Ni et al. 2018; Ye et al. 2016; Zhang et al. 2022; Mendes-Silva et al. 2016), and there are overlaps between depression and symptoms of AD, although different depressive symptoms in AD may have different etiology (Amidfar et al. 2023; Novais and Starkstein 2015). However, despite extensive clinical, neuroimaging, and neuropathological studies, the pathophysiology and molecular basis of LLD are still poorly understood (Disabato and Sheline 2012; Jellinger 2013, 2022a, b; Kuo et al. 2021; Saberi et al. 2022). The essential neuroimaging and neuropathological correlates of LLD and their relevance in the pathogenesis of LLD will be critically reviewed. Depressive symptoms associated with AD will not be considered (seeBotto et al. 2022; Guo et al. 2022; Robinson et al. 2021; Sinclair and Ballard 2023; Cheng et al. 2021; Du et al. 2023).

Prevalence and incidence

Among older individuals, the prevalence of major depressive disorder (MDD) varies from 0.9 to 42%; clinically relevant depressive symptoms between 7.2 and 49% (Djernes 2006). Others reported a prevalence of depressive symptoms among older adults of 20% with high heterogeneity (Tang et al. 2022). Its average prevalence is 12% and in long-term care institutions 35%, while its average prevalence in the community is about 12% (Kuo et al. 2021). Depressive disorders in geriatric age are found in 3–4.5% of the population (Aziz and Steffens 2013). Worldwide the prevalence of LLD is increasing, particularly in lower income countries, which reflects the overall growth and aging of the global population (World Health Organization 2017). The epidemiology of depressive disorders in people aged 65+ presents notable differences among European countries, with incidence of 6.62 (99.9% Cl 6.61–6.63/100 person-years). Regarding the differences between European regions, the incidence and rates (4.93 to 7.43) followed the same ascending order: northern, eastern, continental and southern. In countries of eastern and southern Europe the most important predictors were female gender and impairment in activities of daily living (ADL), while poorer self-rated health and older age were more relevant in northern countries (Conde-Sala et al. 2019). Depression rates ranged from 18.1% in Denmark to 36.8% in Spain, reflecting a north–south gradient (Ladin 2008). The incidence rate of LLD in community-dwelling adults aged 60+ years was 7 per 1000 person-years and the recurrence rate 27.5 per 1000 person-years, both rates more than doubled when episodes of depressive symptoms were included (Luijendijk et al. 2008). For persons aged 70 years or older at baseline, the incidence rate was 0.2–14 per 100 person-years, and the incidence of clinically relevant symptoms was 6.8 per 100 person-years (Büchtemann et al. 2012). Its incidence increases with age, with the greatest increase (9.6%) in the age group 86–90 years (Mossaheb et al. 2009; Solhaug et al. 2012). Among primary-care attendants aged 75 and older, the incidence of depression was 36.8 per 1000 person-years and increased from 35.4 per 1000 person-years at age 75–79 years to 75.2 per 1000 person-years for subjects aged 85 and older (Weyerer et al. 2013). In another cohort aged 75+ years, the incidence of depressive symptoms was 39 per 1000 person-years (Maier et al. 2022). LLD often affects individuals with multiple health problems (Lyness et al. 2006) and complex somatic co-morbidity/multi-morbidity (Alexopoulos et al. 2002; Triolo et al. 2023; Qiu et al. 2023). Prevalence of depression among older adults in nursing homes was 36.8%: mild to moderate forms 29.1% and severe ones 9.1% (Tang et al. 2022), whereas higher physical activity

was linked with lower depressive symptoms in older European adults (Felez-Nobrega et al. 2023). Population aging, social stress, and the COVID-19 pandemic have significantly affected the emotional health of older people, resulting in a worldwide prevalence of LLD (Zhao et al. 2023). The prevalence of clinically significant depressive symptoms among older adults in USA was 7.2%, but more than doubled to 19.8% during the COVID-19 pandemic. Age > 70 years was independently associated with depressive symptoms during this pandemic (Briggs et al. 2021). The cardiovascular risk group showed slightly higher levels of depressive symptomatology even in the beginning of the pandemic (Gerhards et al. 2023).

LLD and cognitive impairment

Cognitive impairment (CI) is a frequent component of LLD and depression may confer a greater risk of cognitive decline in an intact elderly population compared with that without depressive symptoms (Ismail et al. 2014). The central symptoms of CI among elderly with MDD concern memory and information-processing speed, and over half of the subjects meet the criteria for mild cognitive impairment (MCI) (Panza et al. 2010; Steenland et al. 2012). Executive dysfunction and processing speed appear to be the core neurocognitive deficits in LLD (Manning et al. 2023; Rajtar-Zembaty et al. 2022). In a recent case–control study, 26.6% of LLD patients had CI, and showed significant impairment of all cognitive domains (Wang et al. 2022). Depressive symptoms are frequent in MCI and remain stable throughout the cognitive spectrum, except for an increase in the Cornell Scale for Depression in Dementia (CSDD) score in severe dementia (Wiels et al. 2021), whereas according to others, the frequency of depression (and other neuropsychiatric symptoms) increases with the severity of cognitive decline (Siafarikas et al. 2018). On the other hand, elevated depressive symptoms impact cognitive function in non-demented individuals. A follow-up showed that the presence of significant depressive symptoms in elderly subjects with MCI was associated with progression to AD, suggesting that depressive symptoms in MCI may be predictors for progression to AD (Van der Mussele et al. 2014). A meta-analysis of longitudinal studies detected that the association between depression and subsequent CI/dementia was stronger in studies with shorter follow-up periods and for severe and late-onset depression (Stafford et al. 2022). Among cognitively unimpaired and non-depressed older adults (50–90 years) with at least 4 years follow-up almost 40% developed incident depression. This group showed mild cognitive decline before depression onset. Cerebrospinal fluid (CSF) β-amyloid (Aβ) levels and white matter hyperintensities (WMH) suggested that subtle cognitive changes that occur prior to LLD may be explained by the underlying pathological aging process, disrupting brain networks involved in emotional and cognitive processing, thus disposing older adults to depression (Almdahl et al. 2022). In older age bipolar disorder, cognitive dysfunction is more severe than in LLD, but in the same domains as in LLD, which cannot be fully explained by the severity of depressive symptoms (Orhan et al. 2023). Important problems are the relationship between depression and CI, particularly in elderly individuals without overt neurocognitive disorders. One possibility is that some pathological processes that predispose aged individuals to depressive disorders may exacerbate cognitive changes in the presence of other co-morbidities, such as hypertension, diabetes or vascular disorders, and may contribute to the cognitive heterogeneity associated with cerebral dysfunctions inducing impairment in higher-order cognitive domains (Geraets et al. 2022; Jellinger 2021; Kim et al. 2018; Kim and Han 2021). Accelerated aging processes in LLD may be driven by altered proteostasis control, inflammatory mechanisms, and systemic oxidative stress (Kuo et al. 2021; Wolkowitz et al. 2010), and linked to enhanced senescence processes compared with healthy individuals (Diniz et al. 2021; Seitz-Holland et al. 2023). There is a complex relationship between depression and incident CI across races as follows: previously established risk factors between depression and dementia were not found among African Americans and non-hispanic Whites, while Hispanics and Asians had a higher hazard for progression to incident CI (Babulal et al. 2022).

Structural brain abnormalities in LLD

Structural and functional imaging studies provide informations about cerebral changes in LLD (Sexton et al. 2013), with impact on the heterogeneity of changes in regional gray (GM) and white matter (WM) that may explain the clinical and neuroanatomical heterogeneity in LLD (Wen et al. 2022). The structural brain anomalies in "vascular depression", a subtype of LLD related to cerebrovascular disease (CVD) and vascular risk factors (Aizenstein et al. 2016; Alexopoulos et al. 1997), were reviewed recently (Jellinger 2021, 2022b; Rushia et al. 2020).

Early MRI data documented no significant differences between LLD and control groups, suggesting non-specificity of structural brain changes in geriatric depression, although patients with LLD showed significantly more left temporal and caudate atrophy than early-onset depression (Greenwald et al. 1997). Cortical thickness in frontal lobe structures in LLD was found to be similar to healthy old people, while subcortical GM and WM changes appeared to be related with LLD (Colloby et al. 2011). Others described right frontal lobe atrophy (Almeida et al. 2003), reduction

of orbitofrontal cortex volume related to subcortical lesions (Lee et al. 2003), medial orbitofrontal lesions (MacFall et al. 2001), or reduction of dorsolateral frontal cortex in LLD (Chang et al. 2011). More recent studies described decreased cortical thickness in the prefrontal and orbitofrontal cortex, anterior and posterior cingulate cortex, several temporal and parietal regions, hippocampus, amygdala, striatum, thalamus, and insula. These structural findings were also associated with cognitive dysfunction, which is a prominent clinical feature in LLD (Kim and Han 2021). LLD-MCI interactions are associated with widespread cortical and subcortical GM loss in right inferior frontal gyrus (anterior insula and left medial frontal gyrus clusters) (Xie et al. 2012). LLD was correlated to atrophy in the precuneus, superior frontal gyrus, and ventromedial cortex (Boccia et al. 2015). The role of hippocampal atrophy in relation to LLD is a matter of discussion. The frequently reported hippocampal volume reduction was associated with later age of depression onset, duration of illness (McKinnon et al. 2009) or increased risk of relapse (MacQueen and Frodl 2011), which may explain the association between smaller hippocampal size and LLD (Steffens et al. 2011a). However, a prospective long-term study did not confirm this relationship (den Heijer et al. 2011). Others found that higher depression scores were associated with less age-related volumetric decreases in the right subiculum and CA1 sector of the cornu ammonis (Szymkowicz et al. 2017), or did not observe effects of hippocampal or WMH volume on changes in depression severity (Ahmed et al. 2022). Another study demonstrated that a considerable proportion of patients with LLD and MCI had hippocampal atrophy, but tested negative for brain Aβ (Wu et al. 2018). A recent study using ^{18}F-flutemetamol amyloid PET imaging showed no association of lower hippocampal volume with AD pathology in depression in old age (De Winter et al. 2017). It is not known, however, whether hippocampal atrophy in these depressed persons might lead to dementia in later life (Videbech and Ravnkilde 2004).

Modern analysis confirmed previous findings implicating the left and right hippocampus and anterior cingulate in LLD and showed that late onset was significantly associated with widespread structural abnormalities in LLD (Zhukovsky et al. 2021). Severe LLD showed no hippocampal volume loss but increased WM lesion volume over time, and it appeared that hippocampal atrophy and LLD are independent predictors for increased risk of dementia at long follow up (Gerritsen et al. 2022).

While some authors could not demonstrate any effect of WMH severity or location on depressive symptoms (Versluis et al. 2006; Whyte et al. 2004), WM and subcortical GM volume changes were associated with both aging and LLD (Chen et al. 2006). A multicenter longitudinal study showed that WMHs predated the development of depressive symptoms (Teodorczuk et al. 2007). Progression of WMH volume was associated with poor outcomes in LLD (Schweitzer et al. 2001; Taylor et al. 2003). The volume of WMHs, in particular frontal deep ones, was greater in older individuals with depression than in controls (MacFall et al. 2006); it correlated with baseline severity of depressive symptoms in elder people with MCI and seemed to be associated with persistent depression at follow-up (Soennesyn et al. 2012). Progression of WMHs was associated with incident depression, but not with the history of depression at baseline (Firbank et al. 2012), while others reported contradictory findings (Delano-Wood et al. 2008; O'Brien et al. 2001). Cross-sample entropy analysis of fMRI signals, used for the automatic analysis of LLD by 3D convolutional neural networks, showed that volumes in the left inferior parietal lobule, parahippocampal gyrus and postcentral gyrus performed best in predicting depressive symptoms (Lin et al. 2023). Large confluent WMHs were associated with persistent depression, and poorer executive function (Geraets et al. 2021a, b; Prins and Scheltens 2015), with higher incidence of depression in older individuals (van Agtmaal et al. 2017), and with subcortical lacunar infarcts (van Sloten et al. 2015). A population-based study showed that reduced total brain volume, larger WMH volume, presence of cortical microinfarcts, and higher levels of mean diffusivity (indicating WM microstructural integrity) were cross-sectionally associated with higher depressive symptoms. These associations were more pronounced in older age, indicating that damage of WM structure might be crucial for the pathogenesis of LLD (Özel et al. 2022). On the other hand, LLD accentuates cognitive weaknesses in older adults with small vessel disease (Oberlin et al. 2022). WMHs and disconnection of WM tracts have been regarded as main contributors to the vascular hypothesis of LLD (Rushia et al. 2020; Salo et al. 2019; Steffens et al. 2002; Blöchl et al. 2023).

Since vascular pathology is common in LLD, assessment of cerebral blood flow (CBF) is of interest. Reduced anterior CBF in depressed elders reflects decreased metabolic activity in frontotemporal and cingular cortex, while higher posterior CBF (in the parietal lobe, thalamus and hippocampus) may represent compensatory processes or different activity of these neuronal networks (Abi Zeid Daou et al. 2018).

Fractional anisotropy (FA), an index of WM integrity, was significantly associated with executive function in WM tracts in LLD cases (He et al. 2021). Severity of depression in mid- and late life was associated with WM integrity in association fibers and thalamic radiations, while greater subject variance was associated with decreased WM microstructure within projection fibers (Shen et al. 2019). Depression symptoms were significantly related to low FA in the ventral anterior cingulate (Bijanki et al. 2015).

Hyperintensities in deep brain structures are associated with depressive symptoms, mediated via cognitive ability and impaired physical health, while persons with higher

cognitive ability and better physical health are at lower risk of depressive symptoms (Murray et al. 2016). On the other hand, neither depressive symptoms nor apathy that are highly overlapping in older patients with severe LLD were found to be related to WMH, only periventricular WMH being associated with depression severity. These findings suggested that radiological markers of CVD, such as WMH, may not be useful in predicting these symptoms in severe LLD (Oudega et al. 2021), whereas FA mean diffusivity and WMH volume are predicting cognitive performance and dysexecutive behaviors in LLD patients (Oberlin et al. 2022).

LLD and brain circuit disturbances

LLD is mediated by dysfunction of multiple brain mechanisms causing functional connectivity (FC) disturbances in mood-related and many other essential brain networks. LLD is associated with disruption in the topological organization of intrinsic connectivities in cortical and subcortical GM and WM areas. Early multimodal examinations supported the hypothesis that WM anomalies in the fronto-subcortical and limbic networks play an important role in LLD, even in the absence of changes in the resting functional networks (Sexton et al. 2013). LLD was correlated with FA in frontal tracts, anterior thalamic radiation, corpus callosum, fornix, and disturbed FC between the left ventrolateral prefrontal cortex, amygdala and hippocampus, based on the structural connection of the ventral prefrontal cortex to temporal region by the uncinate fasciculus (Steffens et al. 2011b). Specific fronto-limbic vulnerabilities with decreasing FA in the uncinate, incorporated in a large network of WM vulnerability, were associated with LLD (Lamar et al. 2013). Resting-stage functional MR imaging (fMRI) showed increased connectivity between the default mode network (DMN) and the posterior superior temporal sulcus (Eyre et al. 2016), and between frontal, sublobar (thalamus, insular), limbic and temporal areas, indicating increased connectivity in specific brain regions in LLD (Kenny et al. 2010). Connections within the DMN were decreased between the posterior cingulate cortex and the medial prefrontal cortex, between posterior cingulate cortex and the right inferior parietal gyrus/angular, and between the left thalamus and cerebellar tonsil. FCs between left thalamus and cerebellar tonsil revealed a negative correlation with clinical Hamilton Depression Rating Scale (HDRS) scores. These findings indicate abnormal FC within DMN in LLD (Chen et al. 2015). Reduced GM volumes in the DMN, lateral prefrontal regions and ventrolateral prefrontal cortex-caudate connectivity alterations were reported in patients with LLD with suicidal thoughts (Shao et al. 2022). Others reported structural alterations in frontal executive and cortico-limbic circuits in LLD (Rashidi-Ranjbar et al. 2020). LLD subjects showed decreased inter-network connectivity between the bilateral executive control network (ECN) and default mode subcortical (thalamus and ventral striatum) networks, and between the left ECN and salience networks (SN) insula components. Pronounced intra-network connectivity differences within the ECN, and fewer but significant DMN and SN disruptions correlated with LLD (Li et al. 2017), and decreased WM microstructure in association fibers and anterior thalamic radiation was associated with severity and course of depressive symptoms in late life (Shen et al. 2019).

In LLD, WMHs are associated with region-specific disruptions in cortical and subcortical GM areas involved in attentional aspects of cognitive control systems (Respino et al. 2019). An interactive effect in education on the association between WMH, depression severity and language domain has been observed, suggesting that cognitive reserve moderates the effects of WMH on depressive symptoms and neurocognition (Lin et al. 2020). Higher cognitive and brain reserve may be protective particularly for those who had experienced clinically relevant depressive symptoms before (Zijlmans et al. 2023).

A meta-analysis of 143 articles including 14,318 subjects confirmed previous findings implicating the left and right parahippocampus and anterior cingulate in LLD. In contrast, coordinate-based network mapping showed differences in frontoparietal attention network in LLD. Late onset of depression was associated with abnormalities in the anterior cingulate (Brodmann area 32) and dorsolateral prefrontal cortex (Brodmann area 9). These data highlight some unique circuitry relevant to LLD, which also may explain some of the risk for cognitive decline (Zhukovsky et al. 2021). Recent evidence from a multi-site data set showed that LLD patients had alterations in nodal network metrics, which mainly involved the DMN and somatomotor network (SMN). The above changes were present in both first-episode drug-naive (FEDN) and non-FEDN patients and were correlated with depression severity, altered topologic changes were found only in late-onset patients (Tan et al. 2023). These results may help to strengthen our understanding of the underlying neuronal mechanisms and biological heterogeneity of LLD (Tan et al. 2023).

Accumulating evidence from structural and functional imaging supports a "network dysfunction model" for understanding the biological mechanism in LLD. Four major neural circuits have been shown to be involved in LLD: DMN, cognitive control network, affective/frontolimbic network, and corticostriatal circuits. These are related to specific GM and WM structural abnormalities and resting state and task-bases functional changes in each of these affected networks (Tadayonnejad and Ajilore 2014). LLD patients show extensive alterations in the intrinsic brain FCs, especially significant decreases within

the DMN and within the SMN, as well as alterations in several global brain network metrics, such as significant decreases in global efficiency, local efficiency, etc. Moreover, significant alterations in nodal network metrics were found in LLD patients, which mainly involved the DMN and SMN. Changes in FC strength were found in both early- and late-onset (after age 50 years) patients, while altered topological metrics were obvious only in late-onset patients. These results may help our understanding of the underlying neuronal mechanisms and biological heterogeneity of LLD (Tan et al. 2023), the latter already having been emphasized by others (Wen et al. 2022). Lesion-symptom mapping was used to identify brain regions significantly associated with depression severity. In the lesion analysis, the most robust "risk" regions include the bilateral mid-to anterior insula, the left prefrontal WM, along with the bilateral dorsolateral prefrontal cortex, and left dorsomedial prefrontal cortex. Functional network mapping demonstrated that these "risk" regions localized to nodes of the SN, whereas peak "resilience" regions include right orbitofrontal, medial prefrontal, and inferolateral temporal cortices. Structural lesion network mapping implicated dorsal WM tracts as "risk" ones and ventral WM tracts as "resilience" tracts. In the structural lesion network mapping (LNM) analysis, "risk" tracts were the bilateral dorsal frontal WM pathways, while "resilience" tracts were the cerebellar outflow and ventral frontal WM tracts. In the functional LNM, the "risk" network was most similar to the SN while the "resilience" network was most similar to the DMN. These results demonstrated that lesions to special nodes of the SN and DMN are associated with greater risk versus resilience for depressive symptoms in the setting of focal brain lesions (Trapp et al. 2023). These findings, that complement those of other recent studies on depression following brain injury, also based on indirect functional connectivity. A "depression circuit" based on resting state connectivity with an a-priori region of interest—in the left dorsolateral prefrontal cortex—was derived and network scores from this circuit were used to predict depression risk (Padmanabhan et al. 2019). This map of "risk" and "resilience" circuits could help to localize the therapeutic effects on the altered network architecture of depression (Klingbeil and Saur 2023).

On the other hand, a recent meta-analysis of multiple databases emphasized that functional imaging experiments revealed no significant convergent regional abnormality in LLD. This inconsistency was suggested to be due to clinical and biological heterogeneity of LLD, as well as experimental (image modalities, etc.) and analytic flexibility. These findings highlight the need for more reproducible research by using standardized protocols on more homogenous populations to identify potential consistent brain abnormalities in LLD (Saberi et al. 2022).

Neuropathological correlates of LLD

Neuropathological studies gave conflicting results about the morphological basis of LLD (see Jellinger 2013). The first report of two cases of LLD with cognitive decline showed cerebral atrophy, extensive WM changes, signs of cerebral and generalized vascular disease, but no Alzheimer pathology (Lloyd et al. 2001), while another study showed no increased Alzheimer or cerebrovascular lesions (O'Brien et al. 2001). Comparison of 38 autopsy cases of LLD and 20 age-matched controls showed no association of LLD with CVD (Santos et al. 2010), while others found no association between depressive symptoms and AD pathology (Tsopelas et al. 2011; Wilson et al. 2003). Postmortem morphometry studies identified discrete changes in the brain microstructure in depression, suggesting that varying neuronal and glial cell pathology, combined with vascular factors may play a greater role in LLD (Khundakar and Thomas 2014).

A review of structural changes, despite MRI-assessed WM changes, emphasized that lacunes, periventricular and deep demyelination were unrelated to LLD (Xekardaki et al. 2012). These data were confirmed by personal clinico-pathological studies of 20 patients with LLD (mean age 77 ± 5 years) without dementia and 20 age-matched controls, showing that the frequency and severity of WMHs, lacunes in basal ganglia and frontal WM as well as of cortical microinfarcts were similar in both groups. Neuritic Braak stages were lower in the LLD group (1.65 vs 2.5), while cerebral amyloid angiopathy (CAA) showed no differences. Lewy bodies were seen in 10% of LLD and in 18% of controls, and there was no TDP-43 pathology in either of these brains (Jellinger 2013). Other postmortem studies of clinically well-documented cases of LLD did not confirm that diffuse WMHs, subcortical microvascular lesions, cortical microinfarcts or AD pathology including CAA are essential factors for the development of LDD (Beekman 2011; Xekardaki et al. 2012), challenging the "vascular depression hypothesis". Other studies emphasized that MDD in older adults without dementia was not associated with smaller brain volume, while this was associated with risk factors for neurodegeneration (Nunes et al. 2018). In a large study of 582 older individuals with depression (52% with MCI and 17.9% with incident dementia), none of the neuropathological markers (amyloid plaque and tau tangle density, Lewy bodies, hippocampal sclerosis, gross or microscopic cerebral infarcts) was related to the level of depressive symptoms. It was argued that in old age, depressive symptoms are associated with cognitive decline that is independent of neuropathological markers of dementia (Wilson et al. 2014). The same group published the results of

longitudinal cohort studies with 657 autopsy cases (4% MDD, 8.6% chronically elevated depressive symptoms). Higher amyloid plaque burden was associated with higher likelihood of MDD (present in 11%) but not with elevated depressive symptoms (present in 11.3%), whereas none of the other pathological markers were related to either depressive measure. Neither dementia nor antidepressant medication modified these pathological changes. These results did not support the idea that LLD is associated with dementia-related pathology (Wilson et al. 2016). Another cross-sectional study of 407 older adults without dementia showed that those with recently acute depression (within 2 previous years) were more likely to have higher Thal phase scores compared to those with a history of depression ($p = 0.028$). These findings indicate that the association between LLD and AD pathology is associated with spread of amyloid pathology beyond the neocortex to include allocortical and subcortical regions critical for regulation of mood and cognitive behavior (Kim et al. 2022). Another study using neuropathological data from the National Alzheimer's Coordinating Center (NACC) reported that depression in early AD appeared to be independent of neuritic plaque and tangle pathology (McCutcheon et al. 2016). On the other hand, a longitudinal study of depressed cognitively healthy subjects found significantly higher baseline Geriatric Depression Scale (GDS) scores for those with both greater CERAD scores and greater neuritic Braak stage than those with lower tau burden. This suggested that early AD-related changes produce raised GDS scores due to an overlapping neural basis with depression (Robinson et al. 2021). A large postmortem study of 741 individuals (age at death 72 ± 11.7 years) (MDD 7.3%, LLD 10.8%, depressive symptoms close to death/DS/ 22.7%) showed that LLD and DS were associated with small vessel disease, brain infarcts and Lewy body disease ($p = 0.003$, $p = 0.018$ and $p = 0.002$, respectively); DS was associated with amyloid plaque burden and CAA ($p = 0.027$ and $p = 0.035$) in cognitively normal individuals. Vascular brain pathology was the strongest correlate of clinical depression in the absence of dementia, corroborating the vascular hypothesis of depression (Nunes et al. 2022). The elevated frequency of vascular depression in people with HIV disease is also consistent with the vascular depression hypothesis of LLD (Beltran-Najera et al. 2023).

Pathogenic factors in LLD

Vascular factors

Whereas some neuropathological studies failed to verify the vascular hypothesis of LLD (Beekman 2011; Xekardaki et al. 2012), others have provided evidence that co-morbid cerebral small vessel disease (CSVD), marked by large WMH volumes, subcortical lacunes or microinfarcts are associated with increased risk for depressive symptoms in older subjects (with and without CI) (Geraets et al. 2021a, b; Jellinger 2021, 2022a, b). This has been confirmed in the above cited large postmortem study of non-demented older individuals with depression (Nunes et al. 2022). These microstructural lesions disturb cortico-subcortical neuronal circuits causing interruption of major connections involved in emotions and behavior, indicating an association between CSVD and depression in older subjects (Empana et al. 2021; Kim and Han 2021). However, there is evidence that other, non-vascular factors are important in the pathogenesis of LLD. In older adults, MDD is associated with accelerated physiological and cognitive aging, generating pathobiological pathways that potentially target common changes between depression and accelerated aging (Mastrobattista et al. 2023).

Amyloid hypothesis of LLD

Previous studies found a significant positive relationship between Aβ deposits in precuneus/posterior cingulate cortex and depressive symptoms in older cognitively normal subjects (Yasuno et al. 2016), and that Aβ deposition occurs during a long predementia period when depression is prevalent, causing disrupted FC, that impairs networks implicated in depression (Mahgoub and Alexopoulos 2016). Elevated Aβ levels were associated with a 4.5-fold increase in likelihood of developing clinically significant depressive symptoms in cognitively normal older adults (Harrington et al. 2017). Others suggested that increased PiB (Pittsburg compound B) retention may be related to LLD via prefrontal neuronal injury in the MCI stage, whereas vascular processes are associated with LLD via prefrontal neuronal injury even in cognitively intact individuals (Byun et al. 2016). Greater Aβ in the left parietal cortex was found in LLD patients compared with controls, and was correlated with more severe depressive symptoms (Smith et al. 2021b, c). Others suggested that the presence of depressive disorder or even increased depressive symptoms are unlikely a direct consequence of increased Aβ in cognitively normal older adults (Perin et al. 2018).

Topological features of brain networks were different in the presence of Aβ accumulation. Combined fMRI and ^{18}F-flutemetamol PET studies in 235 cognitively normal adults with and without depression showed increased anterior DMN FC and decreased posterior DNM FC in the depression group. Cerebral Aβ retention was positively correlated with anterior and negatively with posterior DMN FC. Anterior DMN FC was positively correlated with severity of depression, whereas posterior one was negatively correlated

with cognitive function. In addition, the effects of global cerebral Aβ retention on severity of depression were mediated by subgenual anterior cingulate FC. These results may link Aβ pathology and LLD (Wang et al. 2021), but the relevance of cerebral Aβ pathology for the pathogenesis of LLD is a matter of controversial discussion. Aβ increases glutamate release leading to long-term depression, which in turn drives hyperphosphorylation of tau, thus supporting a possible causal chain (Taylor et al. 2021).

Studies using ^{11}C-PIB-PET showed a positive correlation between depressive symptoms and mean cortical amyloid load, which was localized to the precuneus/posterior cingulate cortex, indicating that older, cognitively normal patients with depressive episodes were more likely to have underlying AD pathology (Yasuno et al. 2016). In another study LLD patients showed greater Aβ load in the left parietal cortex compared with controls, and this was correlated with greater depressive symptoms and poorer visuo-spatial memory, but not with improvement after treatment (Smith et al. 2021b). Elderly subjects with MDD or amyloid deposition showed greater volume reduction in the left middle temporal gyrus; they had lower FC than those with subthreshold depression (STD) in the frontal cortical and limbic areas. The STD-MCI-A(+) group showed greater FC reduction than the STD-MCI-A(−) and MDD-MCI-A(−) groups, particularly in hippocampus, parahippocampus, frontal and temporal cortices. The functional differences associated with amyloid plaques were more evident in the STD than in the MDD group. Regional GM loss and alterations in brain networks may reflect disorders caused by Aβ deposition and depression (Hyung et al. 2021).

A longitudinal study of older adults showed that baseline cortical Aβ burden, CSF amyloid levels and WMH were significant predictors of incipient depression. Compared to the non-depressed group, hippocampal volume was not reduced before onset, but was reduced following depression (Almdahl et al. 2022). Conversely, two other studies showed that LLD was associated with reduced cortical Aβ burden. In a large group of older adults with a current diagnosis of LLD, 33% met ADNI (Alzheimer's Disease Neuroimaging Initiative) criteria for MCI; 19.3% were Aβ-positive compared to 31.1% of non-depressed. Among LLD patients global Aβ was not associated with lifetime number of depressive episodes, length of depression, or antidepressant use, but with worse memory performance. Contrary to expectation, the LLD group showed less Aβ load than the non-demented one, and Aβ deposition was not associated with depression history features, but with memory decline (Mackin et al. 2021).

A study of MDD patients with suspected non-Alzheimer pathophysiology (SNAP) exhibited significantly decreased ^{18}F-florbetapir uptakes in most cortical areas, but not in the parietal and precuneus cortex, as compared with the Aβ-negative/ND-negative MDD and control subjects. No correlation of neuropsychological tests or depression characteristics with global amyloid uptakes, but significant positive correlations between cognitive functions and hippocampal volumes were observed. Decreased cerebral Aβ deposition in SNAP patients with a lifetime history of MDD suggested a non-amyloid-mediated pathogenesis of LLD (Wu et al. 2022a). A recent study by the same group showed that SNAP-MDD patients had a characteristic pattern of atrophy extending from the hippocampus to the medial temporal and dorso/ventromedial prefrontal cortex. In addition, hypometabolism involved large parts of the prefrontal, bilateral temporal, parietal and precuneus cortices (Wu et al. 2023), whereas a non-depressed SNAP cohort showed relatively restricted hypometabolism in the temporal and parietal cortex (Chiaravalloti et al. 2019). Depressed SNAP patients showed greater atrophy and hypometabolism in the temporal and insula cortices compared to Aβ-positive/ND-negative LLD subjects (Wu et al. 2023).

In a large community-related autopsy series of 1013 older subjects, in whom depressive symptoms and CI had been determined, moderate or frequent plaque density was not associated with LLD or current depressive symptoms but with CI ($p < 0.001$). It was concluded that in this large community sample different clinical forms of depression were unrelated to Aβ pathology in the brain areas studied (Saldanha et al. 2021). In conclusion, the impact of cerebral Aβ deposition in depression in old age is still controversial and needs further elucidation.

Neuroinflammation and immune reactions

Recent studies have provided evidence that neuroinflammation and immune dysfunctions contribute to the pathobiology of LLD (Hodes et al. 2015; Kalkman 2020; Wohleb et al. 2016). It has been associated with elevated levels of proinflammatory cytokines but often depressed individuals have co-morbid conditions that are associated with immune dysregulation. These conditions are associated with weakening of the blood–brain barrier that facilitates the passage of pro-inflammatory factors. Microglia has been shown to play an important role in neuronal cell death, neurogenesis, and synaptic interaction. Besides their involvement in immune response-generating proinflammatory cytokines (Hodes et al. 2015; Wohleb et al. 2016), the release of which by microglia and activated astrocytes induces alterations in many brain functions (Tonhajzerova et al. 2020). These changes are associated with significant reduction in connectivity between prefrontal cortex and ventral striatum (Felger et al. 2016). Moreover, sustained exposure to proinflammatory cytokines can alter the microglial function and the expression of enzymes responsible for amyloid peptide metabolism, aggravating the pathological process in both depression and dementia (Carrera-González et al. 2022). In

addition, activated pro-inflammatory mediators in depressed individuals have been shown to lead to CSVD with the consequent reduction in CBF, which is known to precede cognitive decline (Hakim 2022). On the other hand, recent studies in patients with LLD showed that at baseline, circulating cytokines were low and similar to healthy controls and did not change significantly after treatment with antidepressants or placebos though depression improved after non-placebo treatment. Analysis of CSF in a subset of individuals for IL-1β revealed low levels in both LLD and controls. These data suggested that depression itself does not result in systemic or intrathecal elevations in cytokines, thus indicating negative findings for increased inflammation in a carefully screened depressed population (Luning Prak et al. 2022).

Biochemical deficits

Neuroimaging and neuropathological studies have provided insights into dysfunction of various biochemical systems in patients with LLD. PET images revealed lower serotonin transporter (5-HTT) availability in frontal, temporal, and parietal cortical regions that distinguishes LLD patients from healthy controls and the expression of this pattern may be associated with greater depressive symptoms. PET images in unmedicated LLD patients showed higher Aβ in temporal, parietal and occipital cortices associated with lower 5-HTT in putamen, thalamus, amygdala, hippocampus, and raphe nuclei, indicating a covariance of Aβ deposition and serotonin degeneration (Smith et al. 2021b). On the other hand, serotonergic system modulation has been implicated in alteration of Aβ production, whereas noradrenaline is considered to be involved in compensatory mechanisms, leading to increased Aβ degradation via microglia and other mechanisms. This indicated modulation of depression by the monoaminergic system (Morgese and Trabace 2019). Furthermore, affection of the mesolimbic dopamine system and other, hitherto unknown changes of the monoaminergic system, may be contributing factors to the development of LLD (Medina et al. 2016; Paradise et al. 2012; Torres-Platas et al. 2016). Lower density of tyrosine hydroxylase-immunoreactive neurons in the ventral tegmental area was associated with higher levels of depressive symptoms (Wilson et al. 2013).

The serotonin hypothesis of depression, first proposed in 1967, was later replaced by complex neurobiological theories, e.g., the chemical imbalance theory, which included additional neurotransmitters (Licinio and Wong 2020). Recently, an umbrella review summarizing the results of all existing reviews and meta-analyses on the serotonin hypothesis of depression provided negative results and did not support the hypothesis that depression is caused by lowered 5-HTT activity or concentration (Moncrieff et al. 2022), which, however, was criticized by others (Möller and Falkai 2023; Riederer 2022).

Another aspect linking LLD and cognitive deterioration is norepinephrine-related degeneration in the locus ceruleus (LC). Recent studies, using neuromelanin-sensitive MRI, did not identify an effect of LLD diagnosis on LC integrity and cognition, but correlation analysis showed a significant relationship between LC integrity and cognition. This confirmed prior evidence of LC involvement in cognition of healthy older adults and extended its association in individuals with LLD (Calarco et al. 2022). Studies with proton magnetic resonance spectroscopy (^{1}H-MRS) in MDD patients showed significantly lower N-acetylaspartate/creatine ratio in the left prefrontal WM, indicating dysfunction of neuronal viability in MDD patients (Zhong et al. 2014). Post mortem examination of patients with LLD identified four brain microRNAs in the prefrontal cortex associated with LLD symptoms, while lower levels of miR-484 were associated with faster decline of cognition over time (Wingo et al. 2020).

The gut-brain axis

Recent studies detected a significant difference in the gut microbial composition between patients with LLD and healthy controls, suggesting an association between depressive symptoms, brain structures and gut microbiota (Tsai et al. 2022). These data and studies in rats showing that multi-strain probiotics ameliorated depression-like phenotypes (Dandekar et al. 2022), suggest that gut microbiotic changes may play a role in the communication between the gut and the brain, thus enlarging the pathogenic spectrum of LLD.

Brain changes following LLD treatment

Treating LLD is complex, but there are several therapy options with good efficacy and tolerability. Neuroimaging studies documented the heterogeneity of the treatment response in LLD patients. Measurement of cortical thickness showed no baseline differences between responders and non-responders and no changes in cortical thickness after 8 or 16 weeks of escitalopram monotherapy (Suh et al. 2020). On the other hand, whereas remitted patients showed a volumetric reduction in the orbitofrontal cortex bilaterally and in another cluster in the right middle temporal pole, non-remitters showed a greater volumetric reduction in the bilateral orbitofrontal cortex compared with controls (Ribeiz et al. 2013). Longitudinal analysis of cortical thickness following 8-week antidepressant treatment showed that remittent patients had significantly greater right cerebral cortex thickening, especially in superior temporal, rostral middle

frontal cortex, precuneus and pars opercularis of rostral frontal, parietal and supramarginal cortex than non-responders (Saricicek Aydogan et al. 2019).

Prior to treatment, 5-HTT was lower in LLD patients, mainly in temporal cortex and limbic region (amygdala, hippocampus). Regional 5-HTT occupancy by antidepressants was 70% or more across cortical and subcortical regions; the greater one correlated with greater improvement in depressive symptoms and memory performance. This supports the hypothesis that serotonine degeneration and variability in 5-HTT occupancy may contribute to heterogeneity in treatment response in LLD patients (Smith et al. 2021a). Earlier studies showed that mean striatal 5-HTT occupancy at high therapeutic dose was 85%, which provided a rationale for raising the dose in special circumstances (Voineskos et al. 2007).

Studies using fMRI reported lower task-based activity in the prefrontal and limbic regions after pharmacotherapy (Aizenstein et al. 2014), whereas activation of the frontal and medial temporal, middle cingulate and visual cortices, hippocampus, parahippocampus, caudate and thalamus predicted remission (Karim et al. 2018), as did intact activation in the frontoparietal network during response inhibition (Gyurak et al. 2016).

Significant decreases were found in the right supplementary motor area (SMA) at baseline, while in the responder group after 2 weeks of SSRI therapy, the right SMA was thinner than in the non-responder group. There was a negative correlation between the cortical thickness of SMA and reduction of depressive symptoms in the responder group. The extent of thinner cortical thickness in the SMA at baseline may predict improved SSRI response in MDD (Wu et al. 2022b). LLD is associated with CI and reduced gray matter volume (GMV), which, after a 12-week antidepressant pharmacotherapy, in the superior orbital frontal gyrus was associated with less improvement in depression severity, and increased GMV in the same region was associated with greater improvement in depression severity (Droppa et al. 2017). Furthermore, after citalopram treatment in LLD, improvement of mood and cognition were associated with higher GMV in primary frontal areas and normalization of glucose metabolism in these brain regions (Marano et al. 2015). Recent brain imaging suggested that the activity of brain regions in LLD is organized into functionally distinct networks, termed intrinsic connectivity networks (ICNs). Treatment response following glutamatergic modulation alters FC of limbic nodes within ICNs, that could exert downstream effects on the nodes within other brain networks of relevance to MDD that are structurally and functionally interconnected through glutamatergic synapses. Understanding ICNs features underlying treatment response will positively impact the outcomes for adults suffering from LLD, and will facilitate the development of biomarkers to enable glutamate-based precision therapeutics (Demchenko et al. 2022). The topological architecture of functional brain networks that has been disrupted in drug-naive patients, after antidepressant therapy globally shifted towards recovery, whereas the local efficiency, the clustering coefficient of the network, the path length, and the normalized characteristic path length decreased, suggesting a correlation between recovery of retardation symptoms and global efficiency (Dai et al. 2023).

In a small study, remitters showed increases in ECN connectivity in the right precentral gyrus and decreases in DMN connectivity in the right inferior frontal and supramarginal gyrus. The ECN and DMN in some regions (middle temporal and bilateral fusiform gyrus) showed reversed effects (decreased ECN and increased DMN, respectively). Early changes in FC can occur shortly after antidepressant treatment (Karim et al. 2017). Following electroconvulsive therapy (ECT), right hemispheric GM volume was increased in the caudate, medial temporal lobe including hippocampus and amygdala, insula, and posterior superior temporal regions, but did not correlate with MADRS score. This shows that ECT in patients with LLD is associated with significant GM increase, which is most pronounced ipsilateral to the stimulation side (Bouckaert et al. 2016a). On the other hand, a small study of severe LLD patients treated twice weekly with ECT, resulted in no association between baseline hippocampal volume, WMH volume and total Aβ load, and response or remission at 1 and 4 weeks after ECT (Bouckaert et al. 2019). However, another study following ECT showed a significant decrease in MADRS scores and a significant increase in hippocampal volume, while brain-derived neurotrophic factor (BDNF) levels remained unchanged. Hippocampal volume increase following ECT is an independent neurobiological effect unrelated to the severity of depressive symptoms, suggesting a complex mechanism of action of ECT in LLD (Bouckaert et al. 2016b).

In addition to structural changes after ECT, it reversed the functional network connectivity from negative to positive between two pairs of networks (Yrondi et al. 2018). Recent studies demonstrated links between ECT therapy response and multimodal brain networks in LLD. Volume increases in the hippocampal complex and thalamus were antidepressant response-specific, while functional decreases in amygdala and hippocampus complex were CI-specific, the overlap between antidepressant-response and CI networks challenges parameters of ECT implicating individualized treatment modules (Qi et al. 2022).

Significant ECT effects were seen on FC in the DMN, central executive and sensorimotor networks, and cerebellar posterior lobe; these networks were enhanced, and the changed FC between medial and ventrolateral prefrontal cortex was negatively correlated with depressive symptom improvement (Pang et al. 2022). Six types

of psychotherapies were found to be effective for LLD (Ji et al. 2023). Responders demonstrated less thinner cortex in bilateral posterior cingulate and parahippocampal cortices, left paracentral, precuneus, cuneus and insular cortices, right medial orbitofrontal and lateral occipital cortices relative to non-responders (Mackin et al. 2013).

Mindfulness-based cognitive therapy (MBCT) strengthened functional and structural connections between amygdala and middle frontal cortex as detected by MRI analysis, and this increase in communication correlated with improvements in depressive symptoms (Li et al. 2022). A significant interaction effect of MBCT was found in the change of activation of the superior temporal gyrus to negative emotional expression, while a decrease in activation of the left superior temporal gyrus to negative emotional expression was correlated with increase in the positive affect score (Liu et al. 2022).

The resting state FC with the bilateral subcortical cingulate cortex, the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain and the left ventromedial prefrontal cortex was differentially associated with remission and treatment failure to cognitive behavior therapy (CBT) and antidepressant medication. Positive FC was associated with remission to CBT and failure with medication, whereas negative FC scores were associated with remission to medication and treatment failure with CBT (Dunlop et al. 2017).

FC analysis of rostral anterior and anterior subcallosal cingulate correlated inversely with baseline depression severity, and increased following CBT (Pantazatos et al. 2020), while problem solving therapy increased resting state FC between subgenual anterior cingulate cortex and a structure within the DMN, resulting in benefit from CBT (Solomonov et al. 2020).

Relative to healthy controls, treatment-resistent patients after 8 weeks MBCT showed marginally less amygdala activation, which was associated with greater depression severity (Ferri et al. 2017).

Lower FA in multiple frontal limbic areas (cingulate, prefrontal cortex, genu of corpus callosum, WM adjacent to hippocampus, multiple posterior cingulate cortex, and insular WM) was associated with poor antidepressant response of LLD, and may represent a morphological substrate that predisposes to this disorder (Alexopoulos et al. 2008). Relative to treatment responders, treatment-resistent ones showed increased FC in the left striatum. When adjusted to WMH burden, these differences lost significance for the precentral but not for the striatum FC. The post-treatment "frontalization" of the DMN connectivity suggests a normalizing effect of antidepressant treatment (Andreescu et al. 2013).

A recent meta-analysis of various antidepressant treatments revealed that that clinical response to all treatments could be predicted by baseline DMN connectivity in patients with depression. The repetitive transcranial magnetic stimulation (rTMS) had a larger effect size compared to other treatment strategies, which was related to changes in connectivity of perigenual anterior cingulate and ventromedial prefrontal cortex, thus highlighting the crucial role of DMN, especially the perigenual anterior cingulate cortex in the understanding the underlying treatment mechanisms in depression (Long et al. 2020). Siddiqi et al. (Siddiqi et al. 2021) demonstrated that lesions, as well as transcranial magnetic and deep brain stimulation sites converge on a common 'depression circuitry', which can be used to predict the efficiency of neurostimulation. There are obvious spatial similarities between the 'depression circuitry' described in these studies and the results from Trapp and coworkers (Trapp et al. 2023).

Conclusions and outlook

Depression is common in older individuals, often associated with cognitive decline, and is associated with high disability and shortened lifetime. LLD occurs in up to 38% of community samples and often affects people with multiple health problems. Subtle cognitive changes may occur prior to LLD, but the relationship between depression and CI is not fully understood, although depressive symptoms may be predictors for progression to AD (or other dementias). Structural and functional imaging studies, in addition to cortical and subcortical GM loss (atrophies), predominantly involving frontal and limbic systems including the hippocampus, have demonstrated widespread disorders of WM integrity with decreased microstructures, manifesting as WMHs that often correlate with depression severity. Depression is a network dysfunction, and resting state function connectivity appears to be well suited for describing the large-scale network dysfunctions in MDD (Kaiser et al. 2015). An imbalance between the DMN and the SN has been implicated in repetitive negative thinking (Lydon-Staley et al. 2019). These lesions are often associated with CSVD, impairment of cerebral hemodynamics with reduction of CBF, subcortical lacunes, microinfarcts and disorders of the blood–brain barrier, although the "vascular depression hypothesis" is still under discussion (Aizenstein et al. 2016; Jellinger 2021, 2022a, b). The disease-specific pathologies of LLD, in addition to biochemical abnormalities involving serotonergic and other systems, are characterized by widespread disturbances of cortico-limbic, cortico-subcortical networks, with interruption of inter-network connectivities, involving mood, executive and cognition-related relays. In addition to age-related mechanisms including Alzheimer-related changes—the role of amyloid pathology in LLD is controversial—and cerebrovascular lesions, other pathogenic factors including neuroinflammation, neuroimmune mechanisms, disturbances of BDNF and other co-morbidities are involved in the complex

and multifactorial pathobiology of LLD. In addition, psychobiological factors include a variety of genetic, endocrine, inflammation, metabolic, neural, cardiovascular, and other processes that bidirectionally interact to affect the risk for LLD and the course of illness (Laird et al. 2019), and which may influence the risk of future suicidal behavior (Galfalvy et al. 2023). Recent autopsy studies in large cohorts, in addition to vascular and AD-related pathologies observed a variety of lesions, although not all of them appear related to depressive symptoms. The variable effects of antidepressant therapies in responders and non-responders on the structural and functional cerebral changes support the pathobiological heterogeneity of LLD. Despite enormous progress of neuromaging and neuropathological studies, the complex and multifactorial pathogenesis of LLD and its interaction with other age-related co-morbidities is not fully understood, and treatment effectiveness appears rather modest. Better clinical, neuropsychological, neuroimaging indicators and modern biomarkers will allow that patients with LLD may be better evaluated for this disorder. Multifactorial long-term clinicopathological studies may provide further insight into the complex pathophysiology and pathogenesis of LLD as a basis for earlier diagnosis, prevention and successful treatment of this highly debated and devastating disorder.

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Declarations

Conflict of interest The author declares that he has no conflict of interest.

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