Neuropathology of Depression in Alzheimer's Disease: Current Knowledge and the Potential for New Treatments

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Authors:

Ahmad A. Khundakar, PhD

Alan J. Thomas, PhD, MRCPsych

Institute of Neuroscience, Newcastle University

Corresponding Authors:

Dr. Ahmad A. Khundakar/Professor Alan J. Thomas

Institute of Neuroscience

Newcastle University

Campus for Ageing and Vitality

Newcastle upon Tyne

NE4 5PL

UK

Tel: 0191 2481219

Fax: 0191 2481101

e-mails: ahmad.khundakar@ncl.ac.uk; a.j.thomas@ncl.ac.uk

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Abstract

Depression is among the most common behavioural and psychological symptoms of dementia, and leads to more rapid decline and higher mortality. Treatment for depression in dementia has centred on conventional antidepressant drug treatment based around the monoamine hypothesis of depression. However, recent major studies have suggested that conventional antidepressant treatments that aim to correct underlying deficits in monoamine neurotransmitters are not effective for depression in dementia. Post-mortem studies have also suggested that depression in dementia does not arise from serotonergic or noradrenergic abnormalities, or indeed from the degenerative pathology associated with Alzheimer's disease. In contrast, considerable recent evidence has suggested that alterations in glutamatergic transmission may contribute to the pathophysiology of depression. This supports the view that treatment-resistant depressed patients, such as many dementia patients, may benefit from agents affecting glutamate transmission. This review will thus draw together the wealth of pathological data examining the basis of depression in Alzheimer's disease and relate this to current thinking on treatment, with the aim of generating discussion on potential novel therapeutic strategies.

Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting an estimated 35.6 million people worldwide [1]. Whilst AD is mainly characterized by progressive memory loss, as well as deficits in orientation, spatial awareness comprehension and language, the frequently occurring non-cognitive symptoms of dementia, termed the behavioural and psychological symptoms of dementia (BPSD), have gained increasing recognition due to their substantial physical, emotional and financial impact on patients and their carers [2]. Depression is one of the most common BPSD, occurring in about 20% of AD, 30% of vascular dementia and 40-50% of dementia with Lewy bodies patients, where its high prevalence has led to it being added as a supportive diagnostic feature [3]. The presence of depression in dementia has been associated with more rapid decline [4], higher mortality [5] and earlier institutionalisation [2]. Reciprocally, depression in late-life is frequently accompanied by deficits in performance in aspects of cognitive function [6], with an increased risk of mild cognitive impairment associated with depressive symptoms over time [7]. Whilst depression in dementia is not currently recognized as a single clinical entity, a substantial body of pathophysiological and epidemiological data suggest depression and dementia seem inextricably linked [8-10] and likely share risk factors and common pathophysiological pathways [11, 12]. Several cross-sectional and longitudinal studies have found an association between late-life depressive symptoms and subsequent cognitive decline to mild cognitive impairment and dementia [12-14]. A recent systematic review and meta-analysis found a two-fold increase in risk of dementia in depressed patients [15], and it has been suggested that greater than 10% (nearly 3.6 million) AD cases worldwide could be attributed to depression [16]. Such findings suggest the symptomatic manifestation of depression is not merely a psychological reaction to the awareness of dementia but may derive from neurobiological changes in common brain areas, which may act as either prodromal state preceding impending cognitive deficits, or an independent risk factor for the development of AD. The possible differences in the pathogenesis of late-life depression in dementia, when compared against depression in younger patients, may also explain the apparent lack of efficacy of conventional antidepressant drug therapy for depression in dementia. Recent findings from two major studies [17-19] have suggested that, contrary to previous belief, monoamine-based antidepressant treatment is not effective for depression in dementia. The poor prognosis and the lack of knowledge into the etiological and neurobiological processes has highlighted the urgent need for research into the pathological and molecular correlates of the causes of depression within the context of dementia. This review therefore seeks to appraise the current knowledge of the neuropathological and neurobiological causes of depression in AD, with the aim of offering potential avenues for antidepressant treatment.

The pathophysiological basis late-life depression

Neuroanatomy

Early primate studies identified networks of limbic, striatal and prefrontal brain regions associated with affective function [20-22]. These findings have been supplemented by clinical, neuroanatomical and imaging studies, which have helped characterize the behavioral, cognitive and visceral manifestations of mood disorders [23-25]. Five segregated,

parallel striatal-thalamocortical circuits have been delineated in primates, three of which have been associated with cognitive and emotive function in humans: the anterior cingulate cortex (ACC)-nucleus accumbens (ACC circuit), dorsolateral prefrontal cortex (DLPFC)-head of caudate nucleus (DLPFC circuit), orbitofrontal cortex (OFC)-head of caudate nucleus (OFC circuit) circuits (25). The DLPFC circuit is associated with regulating executive functions, such as problem solving, organization, working memory, and intellectual function and action (30, 32). The OFC circuit is thought to integrate limbic and emotional information into behavioral response, and is involved in sensory integration (33). The ACC circuit is an important component of reward and motivational systems in the brain. Lesion studies have shown that akinetic mutism is closely related to lesions to the ACC [26], manifesting as a wakeful state of profound apathy, with indifference to pain, thirst, or hunger.

Findings from numerous imaging and post-mortem morphological studies have led to a reappraisal of the pathophysiological basis of major depression in late-life, suggesting that neurodegenerative and vascular mechanisms may play a significant part in the manifestation of symptoms [27]. Multiple structural magnetic resonance imaging (MRI) data have revealed volumetric reductions in grey matter structures associated with affective function, including the hippocampus [28, 29], OFC [30-32], caudate nucleus [33, 34] and amygdala [35]. Furthermore, a recent systematic meta-analysis of 17 magnetic resonance imaging (MRI) studies examining volumetric changes in brain regions associated with affective function revealed significant volume reductions in the OFC, putamen, and thalamus in patients with late-life depression [36]. Neuroimaging studies have also found increased white matter hyperintensities in several key areas involved in affective circuitry in late-life depression patients. Hyperintensities are more common in late-life depression than in younger patients [37, 38] or control subjects [37, 39]. Large-scale cross-sectional studies have also reported that basal ganglia lesions [40] and subcortical white matter changes [41] are associated with depression, especially in the elderly. However, as imaging remains hampered by limitations in spatial resolution, which precludes the measurement of cellular components in circuitry involved in affective regulation, post-mortem neuromorphometry studies have offered the most suitable approach for the identification of discrete changes in the brain microstructure in depression.

Neuropathology

Advances in stereological methodology, e.g. the ‘optical disector’ (for the measurement of particle density) and the ‘nucleator’ (for the measure of particle volume) techniques, as well as technology, with the advent of sophisticated computer-based image analysis methods, has allowed the reliable assessment of potential alterations in neuronal and glial cell populations in post-mortem tissue taken from depressed patients. In general, studies conducted in cortical tissue taken from younger or mixed-age groups have revealed regional-specific decreases in packing density of glial cells in the DLPFC (BA 9) [42], subgenual [43] and supragenual [44] ACC and rostral OFC (BA 47) [42]. Such findings appear to contrast with studies conducted in tissue taken from cortical areas from patients exclusively aged 60 years or over, where no changes have been found in glial cell density in the DLPFC (BA 9) [45], caudal OFC (BA 11) [46] or subgenual ACC [47].

Unlike the disparity in glial cell pathology between the marked reductions in younger and mixed-age depression groups and the notable preservation in older patients, pathological

changes to neurons appear more discrete and of a more similar magnitude between younger and late-life depressed patients. A study examining neuronal density in all six layers of the rostral OFC (BA 47) found significant reductions in layers 3 and 5 in late-life depressed patients [42]. The study also found a negative correlation between age and overall density in both depressed and control groups. However, these findings were not replicated in a subsequent study in late life depression in the caudal OFC (BA 11) [46]. In the DLPFC, evidence of pyramidal cell pathology was found through a reduction in volume through all layers, specifically in layers 3 and, more prominently, layer 5 [45]. However, again, these findings were not replicated; no changes were found in neuronal morphology in the DLPFC in depressed patients versus control [48]. No neuronal changes have been found in late-life depression in the subgenual ACC [47].

A greater degree of inconsistency has been found in neuronal morphology in the subcortical structures in depressed patients than cortical regions. Significant increases in neuronal density have been noted in the CA1-CA3 subfields of the hippocampus, as well as the dentate gyrus, with corresponding decreases in neuronal cell body volume (51). These findings were not replicated in a more recent study [49]; however, the study did report a decrease in total hippocampal volume in a subset of recurrent/chronic depressed patients and an increase in pyramidal cell density with duration of depressive illness in the CA1 subfield, as well as an increase in granule cell and glial cell density in the dentate gyrus in patients taking antidepressant drugs [49]. Such findings may indicate an antidepressant medication-related increase in dentate gyrus granule cell proliferation. However, recent findings dispute such an effect [50]. Furthermore, a study of other limbic regions found no significant difference in neuronal density was found in the amygdala and entorhinal cortex in late-life depressed patients versus age-matched controls [51]. However, a significant reduction was found in glial cell populations in the amygdala [51]. A significant reduction in neuronal density, but not volume, has been found in the head of caudate nucleus. Reductions found in both the dorsomedial and ventrolateral aspects of the caudate nucleus, may have functional relevance due to connectivity with cortical affective circuitry. Pyramidal projection neurons emanating from layer 5 of the DLPFC and OFC send afferents to dorsomedial and ventrolateral aspects of the caudate nucleus, respectively. Thus, selective damage to pyramidal neurons in layer 5 of the DLPFC [45] and OFC [42] may indicate disturbances in affective frontal-subcortical circuitry signaling in late-life depression [52]. Such changes are in accordance microstructural alterations described earlier in the white matter adjacent to the prefrontal cortex [53-56]. Diffusion tensor imaging-based investigation has also revealed increased mean diffusivity in prefrontal areas in late-life depression, indicating impaired white matter tract integrity [55]. Furthermore, a large neuroimaging study has reported a significant correlation between increased white matter lesion volume (particularly in frontal areas) and reduced caudate nucleus volume in late-life depression [57]. Taken together, these findings indicate that the dorsal prefrontal-striatal, as well as reciprocal thalamocortical, axonal tracts mediating affective function, may be particularly prone to damage from extraneous factors, such as vascular or inflammatory events [52]. Accordingly, the presence of white matter hyperintensities has been correlated with ischemic pathology. Deep white matter hyperintensities were identified and examined microscopically and whilst some lesions in controls cases were likely to be non-ischemic in origin, all hyperintensities in late-life depressed cases were demonstrated to be ischemic and most apparent in the DLPFC [58]. However, periventricular lesions were found to be of a non-ischemic origin and more likely a result of disruption of the ependymal lining of the ventricles [59].

Neurobiology

The hypothalamic-pituitary-adrenal (HPA) axis is a major part of the neuroendocrine system that modulates stress response. Depression has long been associated with hypercortisolemia (such as found in Cushing's syndrome), non-suppression on the dexamethasone test, increased vasopressin production in cells of the hypothalamic paraventricular nucleus and loss of circadian rhythm regulating HPA function [60]. Moreover, aging itself has been shown to produce a similar pattern of events [61], meaning HPA dysfunction is heightened in late-life depression [62]. Animal studies have revealed that the hippocampus is specifically prone to the toxic effects of prolonged glucocorticoid exposure [63]. The hippocampus contains the highest concentration of glucocorticoid and mineralocorticoid receptors in the brain, which are critical regulators of dendritic spine development and plasticity [64]. Glucocorticoids also alter expression and signaling of the neurotrophin, brain-derived neurotrophic factor (BDNF). As BDNF has been shown to promote neuroplasticity, cell survival, hippocampal neurogenesis and cellular excitability, it has been hypothesized that specific adverse effects of glucocorticoids may be mediated via BDNF expression and signaling events [65]. Thus, higher cortisol levels have been shown to lower BDNF in the hippocampus, with antidepressants reversing the change [66]. Furthermore, in the absence of concomitant stress exposure, glucocorticoid exposure has been shown to result in memory disturbance [67-69]. Hippocampal atrophy has been frequently reported in depression in the elderly [70, 71] and amnesic deficits are prominent feature in late-life depression on detailed cognitive assessment. Thus, a speculative link could be made between HPA dysfunction and the amnestic aspects of late-life depression. However, at least partial, recovery of the brain atrophy has been shown to occur following cessation of corticosteroid administration [72, 73]. Thus, the atrophy observed in hypercortisolemia cannot be deemed comparable with that found neurodegenerative disorders, and may represent a contributory rather than a causative factor in hippocampal damage and corresponding memory impairment [60].

The pathological basis of AD

Senile plaques and neurofibrillary tangles (NFTs) are considered the key pathological hallmarks of AD. Early studies identified the presence of β-amyloid (Aβ) in tightly-packed deposits in the brain parenchyma and vessel wall [74, 75], coupled with genetic studies identifying mutations in genes encoding amyloid precursor protein (APP) [76] and later those for presenilin 1 and 2 [77], were proposed to result in Aβ-containing plaques and the development of early-onset familial dementia. Such findings were incorporated into the 'Amyloid Cascade Hypothesis', which postulated Aβ deposition as the initial pathological event, leading to the formation of senile plaques and then to neurofibrillary tangles, neuronal cell death, and ultimately dementia [78]. Particular cleavage of APP by secretase enzymes is thought to induce Aβ plaque formation. When APP is first cleaved by β secretase, followed by γ secretase, the Aβ (1-40) or (1-42) molecule is produced via the amyloidogenic pathway, with the Aβ (1-42) variant less soluble and more toxic [79]. Amyloid monomers aggregate to form toxic soluble oligomers, believed to mediate perturbation of synaptic connections and network dysfunction, and are associated with dystrophic neurites, activated microglia and reactive astrocytes [80, 81]. Extracellular Aβ-containing plaques follow stereotypical patterns of pathological progression, beginning exclusively in the neocortex, then spreading to allocortical brain regions, the diencephalic nuclei, striatum and cholinergic nuclei and

affecting the brainstem and cerebellum later in disease progression [82, 83]. NFTs are formed from the intracellular aggregation of the hyperphosphorylated microtubule-associated protein, tau. In normally functioning neurons, tau stabilizes microtubules forming the cellular cytoskeleton through the process of phosphorylation and dephosphorylation. Aβ interacts with signaling pathways that regulate the phosphorylation of tau [84], resulting in a hyperphosphorylated state and the polymerization with other tau molecules. In this pathogenic state, paired helical filaments are formed, which result in the accumulation of neurofibrillary tangles and toxic species of soluble tau, thus impeding normal neuronal function by disrupting axonal transport and eventually leading to cell death [85, 86]. As with plaque formation, NFTs have a well-recognized pattern of progression in AD, with neurofibrillary pathology progressing from the transentorhinal to entorhinal and hippocampal, and finally the neocortical regions [82, 87].

Whilst Aβ has been shown to play a fundamental role in AD pathogenesis, it remains unclear whether it is a primary driver in the disease trajectory. For instance, Aβ plaque density does not correlate with the severity of dementia [88, 89]. Furthermore, though it is widely assumed that NFTs are intrinsically involved in AD pathogenesis, there remains insufficient evidence to implicate them as the instigator of the neurodegenerative process. Indeed, some have speculated that Aβ plaque aggregates [90] and NFTs [91] may actually play a protective role, manifesting as a result of adaptive mechanisms to preserve endangered neurons. The apparent latency period between the appearance of AD pathology and clinical symptomatology has suggested that Aβ accumulation and NFT may occur upstream in the disease process, combining to trigger, or occur in tandem to, synaptic dysfunction, which may lead to cognitive impairment directly or indirectly via neurodegenerative processes [92].

Vascular dysfunction has long been known play a significant role in the pathophysiology of both AD [93, 94] and late-life depression [95, 96]. Preclinical and clinical imaging data has suggested deterioration of vasculature may precede cognitive decline and morphological changes in neuronal populations in AD. The lack of clearance of Aβ leads its accumulation in blood vessels and parenchyma. The resulting pathological state, cerebral amyloid angiopathy (CAA), is associated with cognitive decline and is one of the major hallmarks of AD pathology, occurring in >90% of AD-type dementias [93, 97] CAA lesions are thought to originate in the occipital lobe, followed by the frontal lobe, temporal lobe and parietal lobe [98-101]. White matter lesions, frequently resulting from ischemic insult, commonly occur in patients with suspected CAA, and are more marked in individuals with cognitive impairment [102]. Subcortical cerebrovascular disease may contribute to cognitive and behavioral deficits, via infarct damage located in frontal-subcortical circuitry, detailed earlier [20-22]. Furthermore, Binswanger's syndrome has been postulated to cause slow, progressive cognitive impairment through hypoperfusion and demyelination of the deep white matter [103, 104]. Thus, it could be postulated that subcortical atrophic changes resulting from CAA could represent a potential mechanistic point of intersection between AD and late-life depression. Nevertheless, the lack of systematic studies assessing the possible psychiatric impact of CAA [105] has highlighted the considerable need for studies examining this relationship.

Depression, mild cognitive impairment and dementia: a similar disease trajectory?

Putative neuropathological links between late-life depression, mild cognitive impairment and AD have been established from several angles. Such findings have supplemented clinical and epidemiological data that has placed depression in a continuum of events, either as a prominent risk factor or early manifestation of AD. AD patients with a history of major depression have been shown to have a greater number of hippocampal neuritic plaques and neurofibrillary tangles at autopsy than AD patients who had not experienced depression during life [106]. AD patients with a history of depression also demonstrated a more rapid cognitive decline than those who did not [106]. The presence of pathological hallmarks of AD, as well as alpha-synuclein and cerebrovascular pathology, has been demonstrated in late-onset depressed patients with a varying degree of cognitive impairment [107]. Imaging of Aβ deposits using the Pittsburgh compound-B radiotracer (PiB) has revealed that tracer retention in half of depressed subjects with MCI (3 if 6) fell within the range of AD patients. PiB retention was comparable in two depressed subjects with normal cognitive ability and non-depressed cognitively normal subjects [108]. A further study using 2-(1-[109]ethylidene) malononitrile ([(18)F]FDDNP) positron emission tomography to label amyloid and tau protein binding revealed significantly higher binding in the posterior cingulate and lateral temporal regions in late-life depressed patients [109]. Sun et al (2008) elaborated on Aβ involvement in late-life depression by examining the ratio between $A\beta_{40}$ and $A\beta_{42}$ plasma peptide [11]. Previous data [110, 111] has revealed that low concentration of $A\beta_{42}$ combined with high $A\beta_{40}$ levels increases the risk of developing AD. Accordingly, Sun et al found that late life-depression subjects had lower plasma $A\beta_{42}$ levels and a higher $A\beta_{40}$:$A\beta_{42}$ ratio than age-matched controls, in the absence of cardiovascular disease or antidepressant treatment. Depressed subjects with a high $A\beta_{40}$:$A\beta_{42}$ ratio also had greater impairment in memory, visuospatial ability and executive function, whereas depressed patients with a more comparable Aβ ratio did not have significant memory deficits [11]. Nevertheless, several pathological studies have failed to associate cognitive impairment in depression with plaque or tangle pathology [112-114] and it is likely that cognitive aspects of late-life depression arise from several inter-related pathophysiological mechanisms, which result in a wide-range of deficits requiring focused treatment strategies.

Monoaminergic systems in depression and AD

Changes to subcortical nuclei have long been thought to play a primary role in late-life depression and AD pathogenesis. AD is associated with degeneration of subcortical populations, particularly cholinergic and monoaminergic systems. Long and poorly myelinated axons, which project extensively to hippocampal and cortical regions, are particularly prone to damage in AD [115]. Early reports noted significant reductions in nucleolar volume and total RNA levels in both serotonergic and norepinephrinergic neurons in the brainstem of AD patients [116, 117]. Moreover, a reduction in inhibitory G-protein-linked 5-HT1A receptors has been found in postmortem hippocampal tissue taken from AD patients with depression [118]. Selective vulnerability of brainstem monoaminergic nuclei has been demonstrated in AD, with the rostral raphè especially prone to tangle formation, whereas others exhibit plaque and tangle expression [119]. Nevertheless, several studies examining late-life depression within the context of AD have proved more equivocal, with pathological changes frequently not varying between AD patients with depression and those without. A consistent loss of 5-HT neurons has been found in AD patients [112, 120]. However, when these patients were subdivided into depressed and non-depressed groups, no

difference in the number of neurons was found between the two groups [112]. Similarly, though reductions in the binding of protein that aids the function of 5-HT, the 5-HT transporter, have been found in AD no greater reductions were found between the AD groups with depression and those without [121]. Furthermore, although a significant loss of norepinephrinergic pigmented neurons was found in the locus ceruleus in AD, no supplementary loss of neurons was found in patients with depression and AD [122]. A recent study also found no association between brainstem tangles and depressive symptoms. However, a lower density of tyrosine hydroxylase-immunoreactive neurons in the ventral tegmental area was associated with higher level of depressive symptoms, suggesting a role for the mesolimbic dopamine system in late-life depressive symptoms. The mesolimbic dopaminergic ventrotegmental-nucleus accumbens pathway plays a crucial role in reward and associations have been made between components of the circuit and mood regulation (for a detailed review, see Nestler and Carlezon, 2006) [123]. However, post-mortem studies of the dopaminergic system in depression have been scarce and, perhaps unsurprisingly, have provided conflicting results. Nevertheless, given the high prevalence of depression in neurodegenerative disorders significantly affecting dopaminergic transmission – depression occurs in 50-60% in dementia with Lewy bodies and Parkinson's disease [124], and is more common and persistent than in AD [125] – further consideration of the role of dopamine in affective dysregulation in neurodegenerative disorders is warranted.

Despite the lack of clear evidence linking pathological changes in monoaminergic nuclei and late-life depression, especially within the context of dementia, treatment strategies for depression in AD mirror the treatment of depression alone, stemming from Schildkraut's 1965 'catecholamine hypothesis of depression' [126]. Modern selective serotonin reuptake inhibitors (SSRIs), such as sertraline, remain the first-line of treatment for depression in dementia. Until recently, it was unclear whether such conventional monoaminergic agents would be as effective in patients for depressive symptoms in dementia as they are in patients without dementia. However, two recent major studies have suggested that this is not the case. The DIADS-2 study compared the commonly-used selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline (N=67) with placebo (N=64) in depression in AD patients and found no significant change in symptoms, response or remission rates after 12 [18] or 24 weeks [19]; moreover, they found evidence that the treatment resulted in an increase in the risk of adverse events and thus concluded that this drug was not suitable for depression in AD [18, 19]. The UK-based SADD study [17] also found sertraline and another class of antidepressant drug, the noradrenergic and specific serotonergic antidepressant mirtazapine, to be ineffective, when compared against placebo, and were again associated with an increase in adverse effects.

The role of glutamatergic signalling in the pathophysiology of depression

The lack of clear evidence of pathological change in monoaminergic circuitry in brain tissue taken from late-life depressed patients *per se* or in the context of AD, coupled with the ineffectiveness of monoaminergic agents, has suggested the need for a reappraisal in research and treatment strategies for depression in dementia. Considerable interest has recently been expressed in the potential use of agents affecting the main excitatory neurotransmitter in the brain, L-glutamic acid (glutamate). Glutamate signalling occurs at both pre- and post-

synaptic sites through both ionotropic and metabotropic receptors [127]. Ionotropic glutamate receptors, which are highly permeable to Na^+ and Ca^{2+}, are the principal mediators of fast excitatory neurotransmission in the central nervous system [127]. Three subfamilies of ionotropic receptors have been identified: alpha-amino-3-hydroxy-5-methylisxazole-4-propionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors. The modulation of the NMDA receptor complex and its associated molecular mechanisms related to synaptic and neuronal plasticity have prompted a new generation of disease models of depression and antidepressant therapeutics [128-132]. Numerous imaging and post-mortem studies have highlighted glutamatergic abnormalities in major depression patients. Magnetic resonance spectroscopy studies have reported heightened cortical glutamate levels in major depression [133, 134]. Post-mortem studies have demonstrated elevated glutamate levels in the frontal cortex and a significant downregulation in mRNA transcripts for vesicular glutamate transporters and excitatory amino acid transporters [135], which are vital for the rapid removal of glutamate from synapses. This is reflected in altered post-synaptic receptor binding and expression of NMDA, and AMPA/kainate receptors in major depression [135, 136]. Preclinical models have also suggested the NMDA-mediated events are fundamental in the pathogenesis of depression and its treatment. Inescapable stress has been shown to disrupt hippocampal neuronal long-term potentiation, which is regulated through NMDA receptor activation. Considerable preclinical evidence has also demonstrated the importance of glycine recognition sites on NMDA receptors in the regulation of anxiety-related behaviors [137]. Accordingly, several functional antagonists of the NMDA receptor, including ligands at the glutamate, glycine, polyamine, vivalent cation (Zn^{2+}) and ionophore recognition sites, have been shown to exert fast-acting antidepressant and anxiolytic effects in animal models [138]. Furthermore, other preclinical model studies suggest that chronic, but not acute, administration of conventional monoamine-acting antidepressants modulate NMDA receptor activity, suggesting that post-receptor downstream neuronal adaptation processes, rather than the direct effects of extracellular synaptic monoamine levels, lie behind the therapeutic effect [139].

Increasing evidence has suggested that the clinical symptomatology of AD arises from morphological changes and associated deficits in synaptic function, which may begin several years prior to neuronal loss. Markers of synaptic degeneration have been consistently found to correlate with cognitive dysfunction [140, 141]. Abnormalities in vesicular proteins, including synaptobrevin, synaptotagmin and Rab3a [142], as well as pre- and post-synaptic proteins, such as synaptophysin [143], drebrin [144], neurogranin and synaptopodin [145] in the various brain regions of AD patients. Biochemical studies have indicated impaired glutamatergic transmission in AD. Early antemortem and postmortem studies revealed reductions in glutamate concentration in AD patients [146-149]. Furthermore, reductions in the expression of NMDA and AMPA, but not kainate, receptors have been found in AD. Such evidence pre- and post-synaptic glutamatergic is not only involved in the pathophysiology of AD [150] but also has consequent effects on neurogenesis, neurite outgrowth, synaptogenesis and neuronal cell death [151]. Hippocampal glutamatergic cell populations in the entorhinal cortex and subiculum are lost very early in AD progression, whilst the hippocampal GABAergic system remains relatively intact. Such neurodegenerative changes correlate with atrophy of astroglia, which cause disruptions in synaptic connectivity, misbalance in neurotransmitter homeostasis and neuronal death through the enhancement of glutamate-mediated neurotoxicity. Excessive overactivation of the NMDA receptor in particular leads to increased Ca^{2+}, consequent free radical damage and activation of the proteolytic processes that contribute to cell injury or death. Thus, with the disruption of

energy metabolism in AD, glutamate is not cleared and inappropriately released [152]. This state alters ionic homeostasis, meaning compromised neurons become depolarized, displacing the Mg^{2+} block from the NMDA receptor and causing excessive stimulation of glutamate receptors. This abnormal physiological state is thought to result in impairment in the NMDA receptor signalling and capacity to generate LTP, and may significantly contribute to cognitive impairment in AD [153, 154].

The accumulation of synaptic glutamate and continual receptor stimulation may also eventual neuronal damage and death via excitotoxic events. Several lines of evidence have suggested a fundamental role for glutamate-mediated excitotoxic damage in AD. Oxidative stress and increased intracellular Ca^{2+} generated in response to Aβ have been reported to enhance glutamate-mediated neurotoxicity *in vitro* [155, 156]. Furthermore, Aβ has been demonstrated to significantly affect NMDA receptor-related glutamatergic signalling, equating to cognitive loss, in the frontal and entorhinal cortex of AD patients [157]. Glutamate transporters have also shown to be downregulated in AD, and Aβ can either directly or indirectly inhibit glutamate reuptake or enhance release [158, 159]. Such excessive glutamatergic activity may exacerbate AD pathology, through heightened hyperphosphorylation of tau [160].

NMDA receptor complex signalling dysfunction: a point of intersection for depression and AD pathologies

The apparent central role for glutamatergic-mediated transmission in late-life major depression and AD offers the possibility that significant overlap may occur in the signalling transduction mechanisms in the two disorders. As mentioned, NMDA receptor antagonists have been shown to possess antidepressant and antidementia properties in age and disease-related memory deterioration. However, despite this apparent clinical success, it is unlikely that the therapeutic effect lies in merely NMDA receptor blockade alone. It is thus vital to examine the cellular signalling pathways that are influenced by such neuroadaptational processes. A remarkably consistent theme in studies examining the downstream molecular events of antidepressant function has been the overlap with molecular events involved in neuroplasticity, especially synaptic plasticity [161]. Alterations in HPA axis function have been shown to directly influence glutamate and changes in the expression of proteins involved in glutamatergic signalling have been noted in animal stress models mimicking depressed-like states [162]. Microarray analysis has also shown significant cortical downregulation of two key glutamate transporters, SLC1A2 and SLC1A3, as well the expression of L-glutamate-ammonia, the enzyme that converts glutamate to non-toxic glycine in stress models [135]. Such changes would increase extracellular glutamate and activate excitotoxic processes and affect the efficiency of glutamate signalling.

In addition to the consequences of excitotoxic damage, for example, increased intracellular calcium concentrations, mitochondrial damage, free radical generation, immune alterations and accelerated cell ageing [163], imbalances in glutamatergic signalling may diminish the normal compensatory or restorative processes essential for brain repair. For example, BDNF is regulated through the interplay of glutamate/GABA transmission [164, 165]. BDNF is a major regulator of synaptic plasticity, neuronal survival and differentiation, and mediates

advanced activities, such as learning, memory, and behaviour, in addition to its established functions for cell survival [166]. Changes in the expression and activity of BDNF have been widely described in AD and depression [167] and many studies have identified BDNF as a key target of antidepressant drug and electroconvulsive treatment [164, 168]. Moreover, genetic polymorphisms in BDNF have been found to play a role the susceptibility to both late-life depression and AD. Growth factor signalling cascades are known to have pleiotropic effects, including cell growth, survival and neuroplasticity. It has been established that activation of NMDA receptors initiates such signalling cascades and promotes the expression of BDNF [169]. Thus it is likely that disturbances in the NMDA receptor complex in depression may underlie cellular plasticity and resilience and may contribute to glutamatergic pyramidal projection cell pathology found in affective circuitry areas such as the DLPFC and OFC described earlier [42, 45, 170] (Figure 1).

The elucidation of the molecular mechanisms underlying the rapid antidepressant effect of the potent NMDA antagonist ketamine has offered novel potential therapeutic targets, whose mode of action may prove pertinent to AD treatment. The mammalian target for rapamycin signalling, mTOR is an atypical Ser/Thr kinase and a central controller of protein synthesis required for new synaptic connections [171]. mTOR signalling is influenced by the activity of NMDA, metabotropic glutamate and dopaminergic receptors, as well as BDNF, and represents a convergence point of several signalling pathways, including phosphoinositide-3-kinase (PI3K), Akt/protein kinase (Akt/PKB) [172]. A significant decrease in Akt activity has been reported in the prefrontal cortex of depressed suicide victims [173]. A large body of evidence has linked mTOR signalling with synaptic change, memory and neurological disorders. It has recently been demonstrated that the antidepressant effect of ketamine and another NMDA antagonist, Ro-25-6981, is mediated by activation of the mTOR pathway, which leads to increased synaptic signalling proteins and increased number and function of new synapses in the PFC in rats [174]. The same study showed that ketamine and Ro-25-6981 produced rapid antidepressant effects, which were blocked by the pre-treatment of the potent inhibitor of mTOR signalling, rapamycin [174]. Moreover, blockade of mTOR signalling with rapamycin completely blocked ketamine-induced synaptogenesis [174]. The activation of mTOR and associated proteins observed after treatment with another NMDA receptor antagonist, MK-801, in the rat frontal cortex suggests that the facilitation of synaptic signalling proteins is a common feature of NMDA antagonism [175]. mTOR dysregulation has also been found in AD, with several signalling proteins involved in mTOR-regulated pathways, including Akt and mTOR itself, found to be altered in the post-mortem brains of AD patients [176].

In summary, the reassessment of treatment-resistant depression, such as that found in AD, has led to several exciting lines of research beyond the monoaminergic hypothesis, which could pave the way for identification of novel biomarkers and therapeutic strategies. A substantial body of evidence suggests the involvement in shared NMDA-regulated signalling pathways in depression and AD, and may suggest an overlap of disease neurobiology. It is hoped that the potential therapies arising from this research will herald a breakthrough in what is becoming a major treatment issue within the growing global burden of AD.

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