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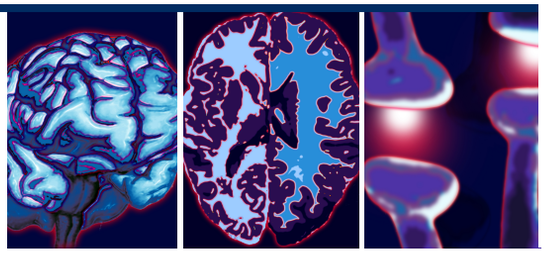

Aging changes and medical complexity in late-life bipolar disorder: emerging research findings that may help advance care

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Practice points

- Bipolar disorder (BD) is a multisystem disease that is chronic and progressive.
- Medical comorbidity occurs in most older people with BD. Cardiovascular disease and diabetes are particular concerns.
- Cognitive impairment is common in elderly individuals with BP.
- Emerging findings in later-life BP suggest potential for biomarkers for assistance with diagnosis, treatment selection and monitoring, and determining prognosis.
- Comorbidity management should be started as early in life as possible, but it is never too late to start.
- Psychotropics that minimize cardiometabolic and other medical risks should be selected.
- In BD, preventing mood relapses that may damage the brain is a key aim.
- The use of neuroprotective agents, such as lithium, lamotrigine or quetiapine, should be considered in treatment.
- Serum lithium levels may be lower than brain lithium levels and elevated brain lithium may cause neurotoxicity. When using lithium, treat the patient not the serum level.
- Nonpharmacological approaches that help the patient with self-management of BD should be used.

SUMMARY Demographic trends globally point in the direction of increasing numbers of older people with serious and chronic mental disorders, such as bipolar disorder (BD). While there has been growing sophistication and understanding in treatments for BD generally, data specific to older people with BD are limited. Recent reviews, secondary analyses and some new research confirm complexity and aging-related issues relevant to later-life

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BD. Confounding variables that must be considered when studying older BD individuals include clinical heterogeneity, medical comorbidity, cognitive impairment and concomitant psychotropic medication. This article will review current and emerging data on aging- and disease-related issues that complicate assessment and treatment of older individuals with BD. We will discuss common comorbid medical conditions that affect BD elders, how aging may affect cognition and treatment, including the effects of lithium and other psychotropic drugs on the aging brain, and recent research using neuroimaging techniques that may shed light on understanding the mechanisms of illness progression and on treatment response. Finally, we will discuss implications for future work in geriatric BD.

The elderly are the fastest growing segment of the global population, with the number of people aged 60 years or older having doubled since 1980 and the number of people age 80 years or older expected to increase more than fourfold (to 395 million) by the year 2050 [101]. Accompanying this demographic shift, the overall numbers of older adults with chronic mental illnesses, such as bipolar disorder (BD), is also expected to increase [1,2].

BD is a psychiatric illness characterized by recurrent/cyclical relapse or recurrence of either mania/hypomania or by depression. While mania is the defining feature of BD, depression is also a severe and pervasive problem among many individuals. Recent decades have seen growing sophistication in treatment approaches that may reduce symptoms and improve health outcomes for people with BD [3]; however, there is a striking scarcity of data on whether these treatments are tolerated and effective across the lifespan, and, in particular, in later life [4].

Older individuals with BD include those who develop the illness as young adults and those who experience the onset of BD later in life. In clinical psychiatric populations, presentation of BD has been reported to be 2–17% [5–7]. Unfortunately, owing to the lack of published evidence specific to older people with BD, there are still a variety of unmet needs, such as: practical clinical guidelines on the assessment and management of medical comorbidities for elders with BD; an understanding of the expected trajectory for cognitive aging in BD; an understanding of how technological advances in neuroimaging can potentially help in assessment and management; and an evidence base to guide pharmacologic and behavioral treatments. This paper will review current and emerging data on medical and aging-related issues that complicate assessment and treatment of older individuals with BD. We will discuss common comorbid medical conditions that affect BD elders, how aging may affect cognition and treatment including the effects of lithium and other psychotropic drugs on the aging brain, and recent research that may shed light on understanding the mechanisms of treatment response. We present a discussion of emerging research that suggests that BD might actually be a multisystem condition in which medical comorbidity, cognitive impairment and early mortality may have underlying common mechanistic elements. These elements are the focus of studies using neuroimaging and other techniques. Finally, we will discuss the implications for future work in geriatric BD.

Medical comorbidity in later-life BD: a progressive process that needs to be addressed as early as possible

BD has a significant and negative impact across an individual's lifespan, and individuals with BD suffer a disproportionate amount of morbidity and die earlier than the general population without BD [8–10]. Standardized mortality ratios in BD are 2.5 for men and 2.7 for women compared with the general population, with frequent causes of premature mortality being cardiovascular disorder, suicide and cancer [10]. Lifestyle variables, such as smoking, poor diet, substance abuse and metabolic abnormalities related to psychotropic drug treatments, contribute to medical complications and poor prognosis [11]. Kemp *et al.* noted that for people with BD, each 1-unit increase in BMI is associated with a decrease of approximately 7% in medication treatment response [11]. Not surprisingly, the norm in BD elders is three to four chronic medical conditions [12] with approximately two-thirds of BD elders having hypertension and a third having diabetes. Dementia is another important comorbidity for older adults with BD [12]. While one can speculate that studies carried out on BD elders could actually represent a healthier 'survivor' cohort, an important caveat is that the lack of well-performed case-controlled studies limits any ability to definitively conclude that BD elders truly have

a higher medical comorbidity than elders in the general population [12].

Recent reports in BD elders note the link between medical comorbidity and poor outcomes. A secondary data analysis of a multisite, 12-week, open-label, uncontrolled study of add-on lamotrigine in 57 adults 60 years and older with BD depression found that medical burden was associated with worse functioning [13]. In this study, each ten-point increase in the geriatric version of the Cumulative Illness Rating Scale [14] corresponded to a 7.3-point increase in the WHO-Disability Assessment Scale II [15]. The complex medical comorbidity seen in BD elders supports the notion that BD is a multisystem and progressive disorder, as has been suggested by Leboyer and Kupfer [16]. Given the general likelihood for older people to be at risk for obesity, diabetes and cardiovascular conditions, it is critical that psychotropic pharmacotherapies for BD be implemented and monitored to minimize both acute toxicity and longer-term metabolic and cardiovascular risk [17–19].

A secondary analysis from the US STEP-BD study noted that while medication treatment recovery rates in older adults were fairly good (78.5%), lower doses of lithium, valproate and risperidone were used in older BD patients than in younger BD patients [20]. In addition to aging effects that may impact psychotropic drug metabolism, tolerability and response [21], careful consideration of concomitant medication interactions is an important component of optimally managing patients with later-life BD. For example, serum lithium levels can be increased by thiazide diuretics, ACE inhibitors, COX-2 inhibitors and NSAIDs [22].

Finally, recent research on nonpharmacological approaches that may help individuals with serious mental illness and comorbid diabetes to better self-manage their complex comorbidity may be highly relevant to improving both symptomatic and functional outcomes in older adults with BD [23]. One potentially successful approach uses patients (peer educators) with mental illness and medical comorbidity to codeliver behavioral interventions with nursing staff in both group and individual settings [23]. The experience of being supported by somone who has 'been there' can be enormously powerful in helping individuals with BD and medical comorbidity make the health decisions they encounter on a daily basis and to feel encouraged and hopeful for the future. Manualizing such an approach can also increase the potential for disseminating the intervention to other settings where older adults receive care. This could include medical or primary care settings, senior centers or other locations in the community.

Neurocognitive findings in BD

Emerging work in adults with BD and in geriatric BD emphasizes the negative effects of having BD on cognitive outcomes, which may be worse for individuals who have more bipolar relapses, greater illness severity and those who are older. Over 75 studies and five literature reviews have established an association between BD and cognitive dysfunction [24–30]. Abnormalities are found in attention, working memory, executive function, verbal memory and processing speed [28], and they are an important contributor to disability [31,32]. An important limitation of the evidence base is that the majority of reports are cross-sectional, which can identify associations but not causal relationships or longitudinal patterns of development (e.g., do impairments in attention or working memory precede verbal memory deficits or executive dysfunction?). Cross-sectional reports reveal dysfunction that is present after controlling for residual mood effects, drug effects or other confounding factors. Longitudinally, dysfunction does appear to be related to illness severity; however, deficits are also apparent in first-degree relatives unaffected by BD [29,32]. To date, there is no clear consensus on the etiology of cognitive dysfunction in BD [33]. Broadly speaking, there are two non-mutual schools of thought regarding the 'intrinsic' biological mechanisms for cognitive dysfunction that include mitochondrial dysfunction and oxidative stress versus abnormal inflammation [34,35]. While not neurodegenerative, in the sense of dementia, cognitive dysfunction in BD is thought to result from multiple 'neuroprogressive' processes [36] that include neurodevelopmental aspects of BD [37], medical comorbidity and lifestyle, compounded by the effects of aging [38,39]. The limited number of longitudinal studies has failed to uniformly demonstrate a progressive decline of cognitive ability upon longitudinal follow-up, and does not support a primarily neurodegenerative process [40–42].

Cognitive aging is a complex phenomenon, consisting of regional brain shrinkage (attributed to cell body shrinkage, synapse loss, neuropil loss and white matter loss), age-related declines and changed processing strategies [43].

Loss of synaptic density, correlated with cognitive performance, is associated with white matter atrophy and with aging [43]. The effects of BD on cellular plasticity cascades may enhance neurotoxic mechanisms and impair the brain's ability to utilize repair mechanisms [33,44]. Several postmortem studies have provided direct evidence for reductions in regional brain volume, cell number and cell body size, which are more pronounced in early-onset forms of the disease [45–47]. In BD, neuronal reductions have been observed as more subtle than glial cell abnormalities, as they are limited to specific cell types in individual cortical layers [47]. Given the critical role of neuroglia in cellular support, including myelin formation, glial cell pathology may underlie the expression of aging and toxic CNS insults as increased white matter pathology observed in structural imaging. More speculatively, long periods of syndromal and subsyndromal mood symptoms may impair developing alternate processing strategies. Hence, BD may accelerate both normal age-related and pathological cognitive decline.

Neurocognitive effects of lithium, divalproex sodium & other agents used for BD

There is sparse literature on the effects of medication in older adults with BD [4], and it is not entirely clear how BD drug effects can be specifically related to multisystemic and neuroprogressive effects of BD in aging patients. Among mixed-aged adults, significant differences in the long-term impact on cognitive function among agents used for BD have not been well defined [24,29]. However, more acute effects owing to mechanistic differences and side effects are clearer [48]. Gualtieri and Johnson examined the neurocognitive effects of various psychotropic antiepileptic drugs and lithium in 159 individuals with BD (ages 18–70 years) [48]. Rank-order analysis indicated superiority for lamotrigine followed by oxcarbazepine, lithium, topiramate, divalproex sodium and carbamazepine. They suggest that medications that are predominantly GABA-ergic (e.g., divalproex sodium or benzodiazepines) are relatively sedating and associated with cognitive blunting. By contrast, glutamatergic medications (e.g., lamotrigine) are associated with activation, antidepressant effect and cognitive sparing. Medications that are more anticholinergic have a greater adverse impact on cognition [49,50]. Somewhat surprisingly, compared with anticonvulsant mood stabilizers, lithium has been found to have greater serum anticholinergic activity and this may account for its adverse short-term cognitive side effects [51].

Across the lifespan, there have been some studies examining the longitudinal course of cognitive function in BD in relation to medication exposure [24,52–58]. Among these longitudinal studies, Engelsmann *et al.* examined 18 patients with BD on long-term lithium, splitting the sample between longer and shorter durations of lithium treatment (mean: 12.9 and 5.2 years, respectively) [59]. They found no difference in cognitive performance between baseline and 6 years after initial testing on the Wechsler Memory Scale and Benton Visual Retention Test. Mur *et al.* examined cognitive function over 2 years in middle-aged adults with BD treated with lithium and found stable cognitive impairments [55,56]. Moorhead *et al.* found that mixed aged adults with BD (n = 20) had deterioration in cognitive function over 4 years of follow-up, which was associated with accelerated loss of hippocampal, fusiform and cerebellar gray matter compared with control subjects (n = 21) [54]. Psychotropic medication exposure was not related to gray matter loss. Since these studies were all limited to a follow-up of less than 10 years, the longer-term differences in cognitive function among different mood-stabilizing agents used for BD remains an open question. Furthermore, there have been no comparisons between lithium versus other drugs on longitudinal cognitive function.

Clinical correlates of structural neuroimaging findings in later-life BD

If BD is a multisystem disease that leads to neuroprogression, it might be expected the older adults with BD would exhibit the effects of key deficits and pathological processes that are demonstrated using technological advances in neuroimaging. Key points of published neuroimaging findings in later-life BD are summarized in **Table 1**. The findings may help lead to improvements in clinical assessment and the development of neuropathologically informed therapeutic interventions.

Increasingly, the pathophysiological role of cerebrovascular disease in the presentation of mood and cognitive symptoms in aging individuals with BD has been a focal point of neuroimaging studies. Neuroimaging findings include increased occurrence of white matter hyperintensities (WMHs) in the deep white matter, enlarged

Table 1. Neurocognitive findings and the effects of psychotropic treatment in older adults with bipolar disorder.

Neurocognitive findings	Psychotropic treatment effects
Cognitive findings	Executive dysfunction, impaired verbal memory, slowed information processing speed
Brain (neuroimaging) findings	Increased occurrence of white matter hyperintensities, enlarged lateral ventricles, decreased regional white matter
Effects of psychotropic treatment on cognition and brain integrity	Short term: GABA-ergic medications (e.g., divalproex sodium or benzodiazepines) are associated with acute cognitive blunting; glutamatergic medications (e.g., lamotrigine) are associated with acute cognitive sparing; medications with higher serum anticholinergicity more negatively impact cognitive function Long term: lithium is related to an increase in total gray matter and hippocampal volume as well as decreased white matter microstructural abnormalities. Antipsychotic medications have mixed effects on brain integrity

lateral ventricles and decreased regional white matter [60]. WMHs appear to represent dilated perivascular spaces, oligemic demyelination and ischemic demyelination [61]. White matter abnormalities are related to impaired cognitive performance [62]. Although findings vary, the majority of MRI studies in BD have demonstrated regional neuroanatomical abnormalities in gray matter, including frontal and subcortical structures.

Beyer *et al.* found that older patients with both early- and late-onset BD had reduced volume in the caudate, in contrast with younger BD patients [63]. While Altshuler *et al.* found significantly larger amygdala volumes in BD patients [64], a more recent large-scale study of BD patients ranging in age from 18 to 49 years found reductions in volume of the amygdala of the older BD patients compared with healthy age-matched controls, with the oldest BD patients having significant decreases in both hemispheres relative to the controls [65]. The authors speculate that volumetric differences as a function of age may be related to increased activity of the stress hormone cortisol during episodes of BD depression, which may drive cumulative excitotoxicity in the amygdala.

Recent studies have also examined the relationship of structural MRI findings and cognitive functioning in later-life BD. A recent, small cross-sectional study of 27 nondemented BD patients aged ≥50 years and 12 similarly aged mentally healthy comparators concluded that cognitive dysfunction in later-life BD does not appear to be primarily due to processes related to increased WMH or reduced gray matter volume [66].

A larger longitudinal study by Delaloye *et al.* investigated the hypothesis that a reduction in white matter volume may be associated with cognitive deficits in euthymic patients with BD over time [67]. Older BD subjects exhibited lower performance levels on measures of processing speed, working memory and episodic memory than that of controls. The findings also demonstrated that BD patients, however, do not exhibit volumetric or WMH abnormalities when compared with that of controls, contrary to findings using a younger BD sample. The authors believe that the WMH finding reflects similar medical comorbidities in the matched controls. Overall, this cross-sectional study suggests that elderly patients with BD have cognitive impairments to a similar degree as younger cohorts tested in previous studies, however, the absence of structural brain abnormalities in the MRI analyses do not support the tested hypothesis that BD has a progressive neurotoxic effect. Furthermore, after a follow-up period of 2 years, there was no observed decline in cognitive performance in any of the cognitive measures [68]. Longitudinal MRI analyses, using voxel-based morphometry and region of interest analyses of the amygdala, hippocampus, entorhinal and anterior cingulate cortex, were used to determine gray or white matter changes over the 2-year period that may relate to cognitive deficits. This volumetric MRI analysis revealed no differences between the two groups, suggesting that BD does not have a significant effect on cognition and brain aging over a short time period of 2 years. Longer longitudinal studies to identify such neuroanatomical changes and their relationship to cognitive functioning have not been completed.

Diffusion tensor imaging (DTI) is a technique that measures the diffusion patterns of water molecules, thereby providing evidence for microstructural alterations of white matter tracts. Fractional anisotropy (FA) refers to the coherence of white matter tracts with higher FA associated with greater white matter structural integrity. Higher FA represents better brain health [69]. DTI studies in adults with BD have demonstrated

altered white matter diffusivity in the orbitomedial prefrontal cortex, potentially impacting prefrontal corticolimbic connectivity and mood regulation [55]. Based on such findings, Brooks and colleagues have referred to the 'corticolimbic dysregulation hypothesis' that proposes progressive 'neurobiological disruptions' that may persist during euthymic states [70]. DTI-based measures, used in several studies of mixed-age adults with BD, have been associated with cognitive impairment, treatment response/resistance and disease severity [71].

DTI studies in older adults with BD are limited. A recent study investigated gray matter concentration changes and microstructural alterations in white matter in neocortical regions and the corpus callosum in older adults with BD compared with younger individuals [72]. Using voxel-based morphometry and region of interest analyses, the researchers determined that gray matter concentration was reduced in the right anterior insula, the head of the caudate nucleus, the nucleus accumbens, the ventral putamen and the frontal orbital cortex in euthymic BD patients when compared with that in control subjects. Tract-based spatial statistics analysis of DTI parameters was used to assess white matter changes. The findings show decreased FA in the corpus callosum in older adults with BD when compared with controls. Another DTI analysis of white matter integrity using tract-based spatial statistics techniques did not identify white matter changes over a period of 2 years in an older BD cohort compared with an age-matched population [68].

In summary, although neuroimaging studies demonstrate a reduction of regional gray matter volume and microstructural alterations in later-life BD, there are inconsistent data to support a progressive neurodegenerative process in BD. However, those studies examining longitudinal volumetric and white matter microstructural changes are limited to a relatively short follow-up period measured in a few years and not decades. Future studies examining structural MRI changes in cohorts of BD subjects over their lifespan may be a more fruitful approach to determine the evidence for BD as a neuroprogressive disorder with advancing age.

Neuroimaging findings & effects on treatment

Long-term treatment with lithium is associated with increased total gray matter [73]. Compared with BD individuals not treated with lithium, studies have shown that lithium treatment is associated with increased hippocampal volumes [74,75] and decreased white matter microstructural abnormalities [76]. It appears that the effect of lithium on hippocampal and gray matter volume is more pronounced compared with other mood stabilizers [77,78]. A recently conducted, unpublished meta-analysis and regression of DTI and MRI findings suggests that long-term use of antipsychotics may have variable impact on white matter microstructure [79]. Antipsychotic treatment was associated with FA reductions in frontolimbic regions, but increased FA in fronto-occipital regions. Mechanisms of action are not well understood; however, it is known that antipsychotic treatment can induce hyperglycemia, weight gain and the metabolic syndrome [80], which are known risk factors for cognitive dysfunction and brain changes [81]. Interestingly, lithium treatment was associated with normalization of FA in the dorsal anterior cingulate cortex.

Magnetic resonance spectroscopy markers of brain biochemistry in later-life BD

Magnetic resonance spectroscopy (MRS) is a noninvasive neuroimaging technique that can be used to measure biochemical alterations in the brain. Such alterations can serve as biomarkers for geriatric BD, thus assisting diagnostic efforts and allowing for a better understanding of neurobiological underpinnings of disease state and trait characteristics. Additionally, quantifying specific brain biochemicals may help determine the effectiveness of therapies for BD exacerbations. Research using MRS techniques in adults with BD include several proton MRS and phosphorus MRS studies examining levels of *N*-acetyl aspartate, glutamate/glutamine, choline-containing compounds, myoinositol, lactate, phosphocreatine (PCr), phosphomonoesters and intracellular pH [82]. Data from these studies may support a cohesive bioenergetic and neurochemical model that suggests mitochondrial dysfunction as a component of the pathogenesis of BD [83]. Furthermore, proton MRS studies have helped to elucidate lithium's therapeutic mechanism of action by quantifying levels of brain myoinositol and assessing evidence for lithium's effects on the phosphoinositol second messenger system [84].

Studies to identify support for bioenergetic changes with age are limited. A recent investigation by Forester and colleagues sought to determine the forward rate constant of CK (k_{for}

of CK), a catalytic enzyme that plays a major role in the maintenance of cellular energy, particularly the reversible conversion of PCr and ADP to ATP and creatine in tissues with high-energy demand, such as brain and muscle [85]. Over an 8-week period, scans were taken of ten individuals with BD depression and eight healthy controls. While both groups demonstrated an increase in the dynamic metabolite turnover of PCr to ATP, k_{for} of CK measures did not significantly differ between groups. Limited sample size and minimal control over medical comorbidities and psychotropic medications of patients may have impacted results. Pilot data from unpublished studies are suggesting baseline alterations in high-energy phosphate metabolites (PCr, inorganic phosphate and ATP) associated with the depressed phase of BD in the elderly **(Figure 1)** [86]. The goal of such research is to identify potential biomarkers of disease state that may help predict response to treatments that enhance bioenergetic metabolism.

MRS techniques have also been applied in later-life BD to quantify brain lithium in an effort to determine the impact of brain versus serum lithium levels on cognition and mood symptoms [87]. A total of 26 subjects with BD, ranging in age from 20 to 84 years, were used to investigate whether previous findings of an increasing brain lithium:serum lithium ratio from adolescence to middle adulthood held true for an older population of BD patients. Although findings identified a correlation between brain and serum lithium levels in the younger BD cohort, no such correlation was found with the older group of BD adults, suggesting that advancing age beyond middle adulthood is not correlated with a predictable brain lithium:serum lithium ratio. Although limited by the relatively small sample size and lack of replication in an older cohort, the findings from this study imply that serum lithium levels may not consistently reflect brain lithium levels. The older cohort (aged 57–85 years) from this study

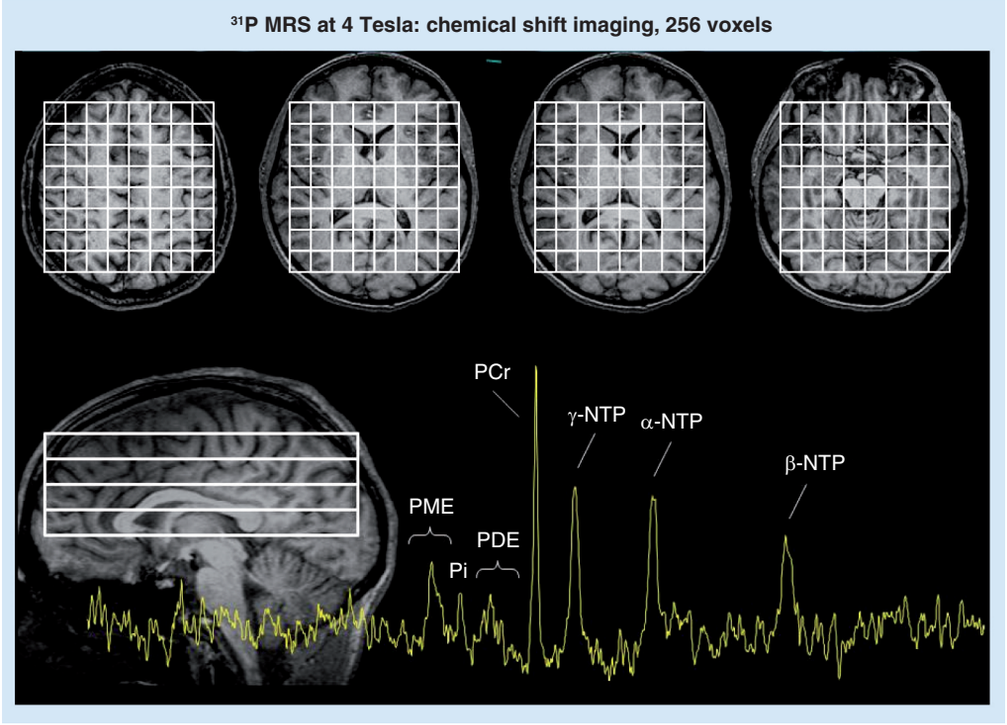

Figure 1. ^{31}Phosphorus 3D chemical shift imaging MRI scan at 4 Tesla. This spectral model acquires data from 256 voxels throughout the entire brain and quantifies ^{31}P-containing molecules including γ-, α- and β-NTP, PMEs, PDEs, Pi and PCr. The high-energy phosphate metabolites reflect bioenergetic metabolism. The grid refers to the MRS imaging acquisition matrix and allows manual optimization of voxel position with respect to anatomic landmarks.
^{31}P: ^{31}Phosphorus; MRS: Magnetic resonance spectroscopy; PCr: Phosphocreatine; PDE: Phosphodiester; Pi: Inorganic phosphate; PME: Phosphomonoester.

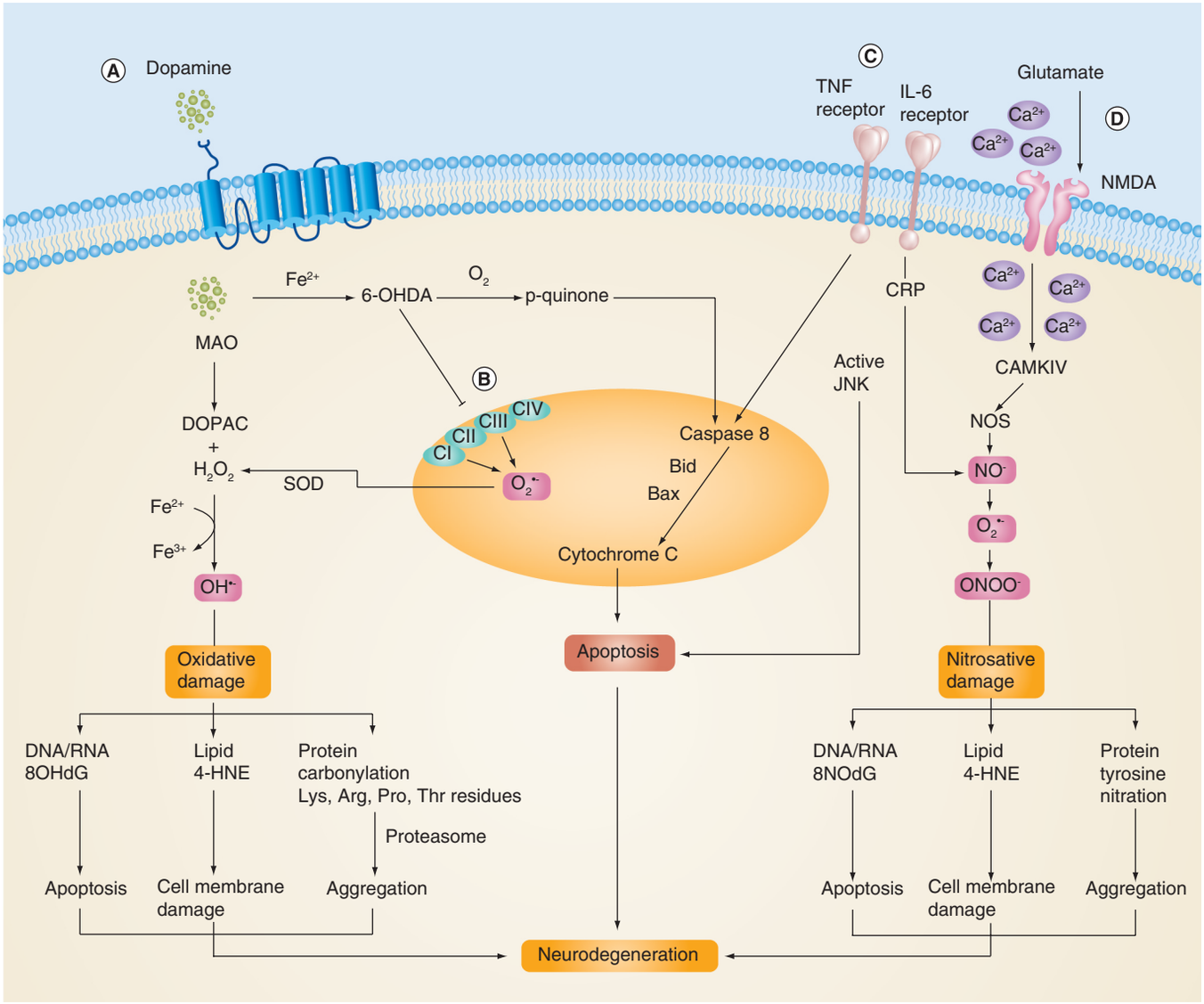

Figure 2. Pathways leading to neurodegeneration in bipolar disorder. (A) Dopaminergic system, **(B)** oxidative stress, **(C)** neuroinflammation and **(D)** glutamatergic system.
Reproduced with permission from [88].

was also given a series of neuropsychological tests to determine the association between brain lithium levels and frontal lobe functioning. Interestingly, the data suggest that brain lithium levels, but not serum lithium levels, are associated with executive dysfunction, as determined by lower scores on the Stroop Interference tests and the Wisconsin Card Sort Test in older adults with BD. Furthermore, depression symptoms, measured by the Hamilton Depression Rating Scale, were also more closely associated with brain and not serum lithium levels. Serum lithium levels alone, therefore, may not adequately predict response to treatment or the cognitive side effects of lithium and it is critical to consider the clinical presentation in older people with BD rather than relying on serum levels alone. This study also highlights the opportunities of a neuroimaging technique, MRS, to potentially help guide clinical assessment and treatment of BD in later life.

Mechanisms underlying neuroprogression of BD & their implications for treatment

A series of studies have suggested that neurochemical dysregulation, neuroinflammation, oxidative stress and mitochondrial dysfunction play a role in the etiology and course of BD [88].

Most (but not all) of these studies have focused on peripheral biomarkers and, to our knowledge, they have included very few older patients. Still, their findings suggest possible mechanisms underlying the toxic effects of depressive or manic episodes and the neuroprogression of BD. If BD is a multisystemic illness that affects both brain and body, a better understanding of the specific mechanisms may lead to more specific approaches to the treatment BD across the lifespan and the prevention of the neuropathology and cognitive decline associated with BD [89].

A reduction in interepisode durations, increased resistance to pharmaco- and psychotherapy, and accumulation of medical comorbidities are typical of the course of BD. They suggest that BD is at least, in part, a neuroprogressive disorder leading to the tissue damage and cognitive deficits described in the previous sections. In turn, this neurocognitive deterioration leads to recurrence of mood episodes and further treatment resistance, accelerating neuroprogression. Studies conducted over the past two decades have shed light on the multiple mechanisms underlying these processes, resulting in a complex model integrating the role of dysregulation of the dopaminergic and glutamatergic systems, neuroinflammation, oxidative stress and neurotrophins **(Figure 2)** [88].

Stimulants and other agents that increase dopamine may precipitate manic episodes, while dopamine antagonists (i.e., antipsychotics) are strong antimanic agents, supporting the view that an increased dopamine tone is involved in mania. An increase in dopamine also leads to oxidative stress and, ultimately, apoptosis and neurodegeneration through several pathways [88]. Similarly, an increase in glutamate is associated with elevated intracellular calcium and production of oxidative marker. BD has also been associated to increased peripheral or central levels of inflammatory cytokines (e.g., interleukins: IL-1, IL-6, IL-8 and interferon) and anti-inflammatory markers (IL-10), TNF, acute phase proteins (e.g., CRP) and complement factors (e.g., C3C and C4). These markers have been hypothesized to be involved in the cognitive changes associated with BD. Some are associated with both depression and mania, some may be more specific to one type of episode (e.g., elevation of IL-6 in mania; TNF in depression), while others may not be state dependent. In addition, some markers are elevated early during the course of BD (e.g., IL-10), others are elevated both early and late (e.g., IL-6) and some are more elevated later in the course (e.g., TNF). Oxidative stress and mitochondrial dysfunction have been fundamentally implicated in BD through a variety of pathways **(Figure 2)** with some evidence that oxidative markers change during the course of BD and underlie, in part, its neuroprogression [90–94]. Finally, neurotrophins are dysregulated in BD: for instance, BDNF is decreased acutely both during mood episodes and with progression of the disorder during euthymic (interepisode) periods.

These findings have potential implications for treatment [88]. For instance, traditional mood stabilizers – lithium, valproate, carbamazepine and lamotrigine – have specific anti-inflammatory and antioxidative properties [95]. Lithium also directly affects mitochondria and protects them against oxidative damage and it increases the production of BDNF. Lamotrigine modulates glutamate levels. While all antipsychotics reduce oxidative stress indirectly through their dopamine-blocking effects, atypical antipsychotics also do so directly (e.g., by reducing intracellular calcium or TNF). Similar to lithium and valproate, quetiapine has been shown to increase BDNF. These differing effects of various psychotropic agents attest to the importance of neuroinflammation and oxidative stress in the pathogenesis and progression of BD and are highly relevant to illness course in later-life BD. However, in the absence of pertinent head-to-head trials, they do not yet provide an undisputed rationale for favoring a specific agent when treating older patients with BD [89]. Still, clinicians could give special consideration to lithium given its favorable effect on several pathways implicated in neuroprogression. Similarly, atypical antipsychotics appear to have a broader spectrum of effect on these pathways than typical antipsychotics and lamotrigine may have a similar advantage over other anticonvulsants. These pathways also identify new therapeutic targets for other treatments that have anti-inflammatory or antioxidative effects, including novel psychotropic medications, nonpsychotropic medications (e.g., aspirin or statins), or nutritional supplements or interventions (e.g., omega-3 fatty acids vs increased consumption of fish, fruit, vegetables or olive oil) [96]. Finally, the findings extensively reviewed by Berk *et al.* summarized in this section suggest that biomarkers will have an increased role

during the coming years, not only in research studies but also in the clinic where they will be used for the selection and monitoring of treatment [88,97,98].

Conclusion & future perspective

Demographic trends globally point in the direction of increasing numbers of older people with serious and chronic mental disorders, such as BD. While there has been growing sophistication and understanding in treatments for BD generally, data specific to older people with BD are limited. Recent reviews, secondary analyses and new research confirm complexity and aging-related issues relevant to later-life BD. Confounding variables that must be considered when studying older BD individuals with neuroimaging include phenotypic heterogeneity, early- versus later-onset illness, medical comorbidity, cognitive impairment and concomitant psychotropic medication. There is a critical need for new research that aids the understanding of the BD trajectory across the lifespan from both the individual and population level. Cross-sectional studies of BD individuals in varying age ranges employing multimodal neuroimaging techniques (structural MRI, functional MRI, DTI and MRS), biomarkers of inflammatory and oxidative stress pathways, and careful clinical assessment (cognitive functioning, medical comorbidity and treatment) will help clarify the neuroprogression hypothesis of BD and potentially lead to the development of neuropathologically informed therapeutic interventions. Additionally, given the projected proportional increase in geriatric populations, the field can no longer afford to think about the elderly as a subpopulation with only limited relevance to the rest of society. Prospective treatment studies using established BD therapeutic agents, novel biological compounds and multiple behavioral interventions need to be prospectively evaluated in order to meet the substantial (and often currently unmet) needs of older people with BD.

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