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Author/s:

Passos, IC;Mwangi, B;Vieta, E;Berk, M;Kapczinski, F

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Areas of controversy in regards to neuroprogression in bipolar disorder

Authors: Ives Cavalcante Passos, MD, PhD^{1,2}; Benson Mwangi, PhD³; Eduard Vieta, MD, PhD⁴; Michael Berk MD, PhD^{5,6}; Flávio Kapczinski, MD, PhD^{1,2}

1. Bipolar Disorder Program, Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil
2. Department of Psychiatry, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil
3. Center of Excellence on Mood Disorder, Department of Psychiatry and Behavioral Sciences, The University of Texas Science Center at Houston, Houston, TX, USA
4. Bipolar Disorders Program, University of Barcelona Hospital Clinic, Institut d'Investigacions Biomèdiques Agustí Pi Sunyer, CIBERSAM, Barcelona, Catalonia, Spain.
5. Deakin University, IMPACT Strategic Research Centre, School of Medicine, Faculty of Health, Geelong, Victoria, Australia.
6. Orygen, The National Centre of Excellence in Youth Mental Health and the Centre for Youth Mental Health, the Department of Psychiatry and the Florey Institute for Neuroscience and Mental Health, the University of Melbourne, Parkville, Australia.

Corresponding author:

Flávio Kapczinski, MD, PhD

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Federal University of Rio Grande do Sul

Avenida Ramiro Barcelos, 2350, Zip Code: 90035-903, Porto Alegre-RS, Brazil

Phone: +55 512 101 8845

Email: flavio.kapczinski@gmail.com

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Email for all authors:

Ives Cavalcante Passos: ivescp1@gmail.com

Benson Mwangi: Benson.Irungu@uth.tmc.edu

Eduard Vieta: EVIETA@clinic.ub.es

Michael Berk: MIKEBE@BarwonHealth.org.au

Flávio Kapczinski: flavio.kapczinski@gmail.com

Abstract

OBJECTIVE: We aimed to review clinical features and biological underpinnings related to neuroprogression in bipolar disorder (BD). Also, we discussed areas of controversy and future research in the field.

METHOD: We systematically reviewed the extant literature pertaining to neuroprogression and BD by searching PubMed and Embase for articles published up to March 2016.

RESULTS: A total of 114 studies were included. Neuroimaging and clinical evidence from cross-sectional and longitudinal studies show that a subset of patients with BD presents a neuroprogressive course with brain changes and unfavorable outcomes. Risk factors associated to these unfavorable outcomes are number of mood episodes, early trauma, and psychiatric and clinical comorbidity.

CONCLUSION: Illness trajectories are largely variable, and illness progression is not a general rule in BD. The number of manic episodes seems to be the clinical marker more robustly associated with neuroprogression in BD. However, the majority of the evidence came from cross-sectional studies that are prone to bias. Longitudinal studies may help

to identify signatures of neuroprogression and integrate findings from the field of neuroimaging, neurocognition, and biomarkers.

Key Words: bipolar disorder, neuroprogression, treatment refractoriness, functional impairment, inflammation, machine learning.

Clinical Recommendations:

1. A subset of patients with bipolar disorder (BD) presents a progressive course characterized by episodes acceleration, treatment refractoriness, and functional/neurocognitive impairment.
2. Neuroprogression has been defined as the pathological brain rewiring that takes place in portion with recurrent mood episodes.
3. Manic episodes, early trauma, and psychiatric and clinical comorbidity are associated with neuroprogression in BD.

Additional Comments:

1. The course of illness is highly variable in BD and predicting cases that will follow a neuroprogressive course is a major unmet need.
2. The majority of the evidence came from cross-sectional studies that are prone to

bias. Changes in brain structures and blood biomarkers need to be longitudinally assessed in BD.

3. Differences in brain structures and biomarkers described in cross-sectional studies may reflect clinical subtypes and not necessarily neuroprogression in BD.

Introduction

Bipolar disorder (BD) affects about 2% of the world's population, with sub-threshold forms affecting up to a further 2%(1). The rates of completed suicide in patients with BD are 7.8% in men and 4.9% in women (2). Although there are several treatment options for the prevention and treatment of mood episodes, these are frequently suboptimal, and about 60% of the patients relapse into depression or mania within two years (3). In addition, although available treatments effectively reduce syndromal BD features, they are less effective in recovering functioning. This framework illustrates the caveats of the current treatment approach in BD, which focuses mainly on the stabilization of acute mood episodes and prevention of recurrence while neglecting the longitudinal course of illness and the need to promote functional recovery in many cases.

The course of BD is highly variable, and a subset of patients seem to present a progressive course associated with brain changes (4–6). The notion that multiple episodes and relapses could lead to more severe psychopathology and intellectual impairment has been stated since the work of Griesinger in 1865 (7). Also, the potentially progressive course of BD, with its neurocognitive, functional, and medical aftermaths was described in 1920 by Kraepelin and others (8). More recently, longitudinal studies have shown changes in frontal cortex and episode acceleration as a function of the previous mood episode (9,10). Given these findings, progressive changes in illness presentation have been encompassed under the concept of neuroprogression (11). The term 'neuroprogression' has been proposed as the

pathological rewiring of the brain that takes place in parallel with the clinical and neurocognitive deterioration in the course of BD (4). However, the clinical implications and molecular foundations of neuroprogression remain incompletely understood and sometimes controversial.

Aims of the Study

Here, we aim to review the concept of neuroprogression in the following aspects: **a)** clinical risk factors and outcomes associated with neuroprogression, and **b)** the environmental pathways driving neurobiological and brain changes. Finally, areas of controversy and clinical implications of the concept of neuroprogression in BD are outlined.

Methods

We systematically reviewed the extant literature pertaining to neuroprogression and BD. We searched PubMed and Embase for articles published in any language up to March 7, 2016, using the following keywords: ("neuroprogression" OR "staging" OR "illness progression" OR "progression") AND ("Bipolar Disorder" OR "Bipolar Disorders" OR "Manic Depressive Psychosis" OR "Bipolar Affective Psychosis" OR "Mania" OR "Manic State" OR "Bipolar Depression" OR "Manic Disorder" OR "Bipolar euthymic") AND ("treatment response" OR "hospitalization" OR "functioning" OR "cognition" OR "quality of life" OR "suicide" OR "recurrence of episodes" OR "inflammation" OR "oxidative stress" OR "neurotrophins" OR "cortisol" OR "neuroimaging" OR "mri" OR "Magnetic Resonance Imaging" OR "spectroscopy"). We also searched the reference lists of included studies. Two researchers (ICP and BM) independently screened and selected the studies, supervised by FK, who made the final decision in cases of disagreement. Articles from other languages were translated. We did not include grey literature in our search.

Articles met the inclusion criteria if they assessed patients with BD and the following outcomes of interest: treatment response, hospitalization, functioning, cognition, quality of life, suicide, recurrence of episodes, inflammation, oxidative stress, neurotrophins, brain changes. Preclinical studies, as well as those involving children

and adolescents, were excluded. Also, we excluded narrative review articles. We used the online version of EndNote to remove duplicate data.

Results and Discussion

Figure 1 shows the review process and study selection. The hypothesis of neuroprogression states that a subset of BD patients may experience a worsening of their condition over time. These worse clinical outcomes would include reduced inter-episode intervals, treatment refractoriness, neurocognitive and functional impairment, worse quality of life, elevated rates of hospitalizations, and suicide attempts (4). However, not all patients with BD will present these unfavorable clinical features, either as a consequence of treatment or baseline clinical characteristics (12). Therefore, early identification of which patients will develop a neuroprogressive disorder with a more pernicious course is an important unmet challenge in BD treatment. The first step to pursue this goal is identifying the risk factors associated with neuroprogression in BD. Figure 1 presents a conceptual model that integrates risk factors and outcomes related to the hypothesis of neuroprogression.

<Insert Figure 2>

Trauma exposure was associated with poor outcomes in patients with BD. A longitudinal study of 631 outpatients showed that those with childhood trauma presented increased number of manic episodes and suicide attempts, earlier onset of BD, faster cycling pattern, and comorbid substance use (13). In addition, a 24-months follow-up study of patients with BD reported that trauma predicted the severity of mood symptoms (14). Furthermore, verbal abuse has been associated with an earlier age of onset of BD and increased frequency and severity of manic and depressive episodes (15). This impact is evident as early as the first episode, with those exposed to trauma displaying poorer functional and symptomatic outcomes (16). Also, a cross-sectional study showed that childhood adverse events were associated with functional impairment and accelerating staging process of BD (17).

The number of episodes also may have predictive value for neuroprogression in BD. Kraepelin reported that the recurrence of episodes tended to accelerate over time, which leads to shortening of inter-episodic intervals (18). In this same vein, some studies using the nationwide registration of all psychiatric hospitalizations from Denmark and others showed that the rate of relapse leading to hospitalization increased with the number of previous episodes (19–24). However, it has been argued that some of these studies, and also Kraepelin's observations, may be due to a computational artifact (25). It was shown that a subset of patients with highly recurrent course skew the aggregate findings to give the impression of shortening intervals (25). In order to address these limitations, Kessing and colleagues used a frailty model called Cox regression to overcome this phenomenon (22). In this manner, Kessing et al. (2004) showed that the rate of relapse leading to hospitalization increased with the number of previous episodes in women with BD, but not for men (22). Another study from the same group used a frailty model with a sample of unipolar and bipolar patients, who were admitted between 1959 and 1963 to the Psychiatric Hospital University of Zurich with an affective episode and followed up to 1997 (21). In this study, the individual rate of subsequent recurrence was found to increase with the number of episodes (21). The effect of episodes was also the same in depressive and bipolar disorders and for men and women (21). Of note, some of these studies were conducted only in type I BD patients who were hospitalized at least for one time, which limits the scope of the neuroprogression model to more severe patients. A recent work showed that the course of BD type 1 was largely random from onset and only a subset of patients presented either cycle-acceleration or slowing (26).

Some studies also showed that successive episodes might induce treatment resistance (27). For instance, patients with an increased number of episodes have a worse response to Cognitive Behavioral Therapy (CBT) and lithium (28,29). Moreover, a study showed that response rates for olanzapine in manic and depressive episodes were significantly lower among those individuals with >5 previous episodes (30). Another study reported that a positive response to lamotrigine monotherapy was associated with fewer hospitalizations (31). Furthermore, caregiver psychoeducation appeared beneficial only in patients on Stage I of Kapczinski's model (patients with well-

defined periods of euthymia without overt psychiatric symptoms). No significant benefits from caregiver psychoeducation were found in patients in more advanced stages (32). Likewise, a 5-year follow-up study revealed that the number of previous episodes worsens response to psychoeducation (33). Another study assessed pharmacological maintenance treatment across the stages proposed by Kapczinski and colleagues (34). Authors reported that monotherapy was more frequent in stage I, and two-drug combinations in stage II, while patients at stages III and IV needed three or more medications or clozapine (35).

However, there are studies that failed to find any association between number of previous episodes and pharmacological and psychosocial treatments. In particular, one study showed no association between pretreatment episodes and poorer responses to various maintenance treatments, such as lithium and anticonvulsants, in bipolar I or II disorder (36). In addition, a longitudinal study reported that long-term response to lithium maintenance treatment is not associated with the number of frequency of episodes (37). In this sense, Rybakowski and colleagues reported that about one-third of lithium-treated, bipolar patients are excellent lithium responders; that is, lithium monotherapy prevents further episodes of BD for ten years and more. This subset of patients is clinically characterized by an episodic clinical course with complete remission, a bipolar family history, low psychiatric comorbidity, and a low number of hospitalizations in the pre-lithium period (38,39). Also, excellent lithium responders have normal neurocognitive functions and plasma BDNF levels (40). Moreover, another study showed that there was no significant effect on number of previous episodes with regard to antidepressant response in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (41). Finally, a systematic review suggested that there is no compelling evidence that the number of previous episodes could influence psychological therapies treatment response (42).

Comorbid psychiatric and clinical illnesses are also associated with poor outcomes in BD. A meta-regression analysis in children and adolescent patients with BD showed a significant association between suicide attempts and substance use disorders (43). Additionally, a machine learning study revealed that psychiatric comorbidities are associated with suicide attempts in patients with BD (44).

Furthermore, alcohol and cannabis use in patients with BD were associated with lower remission rates (45), higher severity of mood episodes, and functional impairment (46). A recent systematic review reported that patients with BD with a current or history of comorbid alcohol use disorder show more severe neurocognitive impairments especially in verbal memory and executive cognition (47). Smoking was also associated with poorer outcomes (48,49) while comorbid Attention Deficit Hyperactivity Disorder (ADHD) has been associated with suicide attempts, poor functioning, and refractory treatment (43,50). Moreover, a recent study showed evidence of cross-sensitization between number of episodes and posttraumatic stress disorder (PTSD) (51). Comorbid PTSD has been associated with higher number of manic/hypomanic episodes, lower age of onset of manic/hypomanic episodes, and earlier initiation of illicit drug use (51). In addition, comorbid PTSD is associated with worse quality of life and higher rates of suicide attempts among patients with BD (52,53).

Patients with BD presented increased rates of several medical illnesses. A recent study compared 440 patients with BD and three or more medical illnesses with 202 patients with BD and no history of medical illness (54). It was showed that medical illness burden was associated with a history of anxiety disorder, rapid cycling mood episodes, and suicide attempts (54). Moreover, a study revealed that patients with somatic comorbidity had increased rates of non-response to lithium compared to patients without (55). Notably, patients with BD are at higher risk of premature death from cardiovascular disease, diabetes, COPD, influenza or pneumonia as compared to the general population (56). These two studies confirm the hypothesis of cross-sensitization between BD and other medical diseases, showing that medical comorbidities worsen BD prognosis and vice-versa (57).

Overall, it seems that traumatic exposure, clinical and psychiatric comorbidities, and number of episodes are associated with poor outcomes in BD. Conversely, the absence of these risk predictors is associated with a more benign course of BD. In this sense, a longitudinal study of patients with BD showed that less lifetime family history of substance abuse, less history of sexual abuse, and higher age at onset of mood symptoms were associated with better prognosis (58).

Neurocognitive and functional impairment

BD is associated with neurocognitive impairments, even during euthymic periods. According to meta-analytic studies, specific domains of impairments include executive control, verbal learning and memory, working memory and sustained attention (59,60). However, recent studies have shown that the percentage of BD patients with clinically significant neurocognitive impairments may vary from 30% to 62% (61,62). To explain why not all patients with BD have neurocognitive impairments, some studies explored the relationship between illness variables and neurocognitive deficits (63–66). A study reported an association between the number of previous episodes, especially manic episodes, with neurocognitive functioning suggesting that successive episodes might be related to a progressive neurocognitive decline (64). In addition, another study assessed three groups of bipolar euthymic patients, according to the number of previous manic episodes (63). Although this was not a longitudinal study, the evidence pointed that the recurrence mania in the long-term had a negative impact on neurocognition. Those patients who had experienced three or more episodes were more impaired in attention and executive function when compared to patients who had suffered only one episode. Moreover, a machine learning study reported that euthymic patients with rapid cycling had neurocognitive impairment as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) when compared with health controls, whereas patients without did not (67). A recent work revealed that patients in early stage of BD had better performance on the total immediate free recall, in delayed free recall, and in the ability to retain words learned compared to patients at late stage as assessed by the Hopkins Verbal Learning Test-Revised (68). Notably, neurocognitive changes, albeit potentially less marked, are evident after a first episode of mania (69), which stands in contrast to at-risk studies, where individuals who transition into BD may display superior neurocognition (70). Thus the trajectory of neurocognitive change appears to begin early in the disease process, perhaps as early as the prodromal phase (71).

The above results from cross-sectional studies contrast with some findings from

other populations. A small longitudinal study did not find that the experience of successive episodes is related to a progressive neurocognitive decline (72). This study suggested that neurocognitive impairment could be the cause rather than the consequence of poorer clinical course (72). Another follow-up study did not found accelerated neurocognitive decline over 2 years in patients with BD (73). Limited sample sizes and short-interval follow-up may be potential confounders for these findings. Moreover, a cross-sectional study reported no difference in regards to neurocognitive dysfunction due to illness chronicity between elderly and young patients with BD (74). A meta-analysis reported that the evidence from longitudinal studies is not in accordance with the hypothesis of a progressive neurocognitive decline in patients with BD (75). Another recent meta-analysis found that neurocognitive dysfunction in first episode BD was comparable to that of more chronic cases of BD (76). On the other hand, a prospective 12-month naturalistic study with patients with BD revealed that neurocognitive function improves only in patients who sustain remission in the year following a first manic episode (77). Those who had a recurrence of mood episode remain impaired, with performance declines being most apparent in those who experienced longer manic episodes. Additionally, a three-year follow-up study revealed that older adults with BD had more rapid cognitive decline than expected given their age and education when compared to controls (78). A five-year follow-up study showed that a measure from the verbal memory domain, delayed free recall, worsened more in patients with BD compared to controls (79). Another follow-up study found that executive function worsened in patients with BD compared to healthy controls and was associated with duration of illness (80). Also, a meta-analysis reported that number of mood episodes was correlated with neurocognitive impairment in patients with BD (60). Finally, a systematic review of neurocognitive performance in euthymic patients suggested that only a percentage of individuals with BD are affected in a progressive manner (81).

Patients with BD may also suffer from functional impairment, even when euthymic. A longitudinal study showed that almost all first-episode manic patients with BD had syndromal recovery within 2 years, but only one-third had functional recovery (82). This pattern was confirmed by Conus and colleagues, who showed that although

90% of patients displayed syndromal recovery 6 and 12 months after a first manic episode, 40% did not recover symptomatically (83). Of note, both studies included patients with BD and psychotic symptoms. Therefore, functional and syndromal recoveries are dissociated and may need different therapeutic approaches (84). Additionally, two one-year follow-up studies reported that baseline neurocognition impairment and time spent with subsyndromal depressive symptoms predicted changes in functioning in patients with BD (85,86). Moreover, it was proposed that functional impairment might be an outcome associated with the progression of the disorder. By applying Latent Class Analysis, two subtypes of patients presenting “good” and “poor” functional outcome were identified (87). Estimated verbal intelligence, number of mood episodes, level of residual depressive symptoms, and inhibitory control were the risk predictors of functional impairment in such study (87). Of note, functional outcome was not predicted by illness duration and age of onset (87). Another study reported that patients with BD presented progressive functional impairment from stage I to stage IV of Kapczinski's model as assessed by the Functioning Assessment Short Test (FAST) (88). Previously, the same group reported that patients with BD who had only one episode experienced a greater functioning compared to patients with multiple episodes (89). Finally, some studies reported that comorbid anxiety and comorbid substance use disorders are risk factors of functional impairment (46,51,53,90).

Functional impairment is largely neglected in current BD treatment guidelines. Among the medications that could improve functioning in treatment-resistant patients with BD, clozapine showed promising efficacy (91). In a systematic review, clozapine was associated with improvement in functioning, number and length of hospitalizations, suicidal ideation, severity of mania, depression, rapid cycling, and psychotic symptoms (91) – albeit at a substantive tolerability cost. Moreover, a functional remediation therapy was recently developed to meet the psychosocial needs and functional impairment reported in BD. In a multicenter RCT, this group intervention showed significant efficacy in improving functional impairment in patients with BD (92). This means that assessment of functioning levels should be considered key factors in determining who can benefit from functional remediation in BD.

Neurobiological underpinnings of neuroprogression

The study of the biological basis of neuroprogression has the potential to aid in the identification of relevant targets for treatment and a better management of the disorder (4). Herein, we will review and discuss biological alterations that take place along with BD progression, as well as potential cellular and biochemical mechanisms associated with it.

Neuroprogression and the 'neurodegeneration vs. neuroplasticity' dualism

Bipolar patients have been shown to present several neuropathological and neuroimaging alterations in different brain structures, some of which are evident at the early stages of the illness (93). Two meta-analyses reported that patients with BD had reduced grey matter in the right ventral prefrontal cortex, temporal cortex, claustrum, left rostral anterior cingulate cortex, and right fronto-insular cortex (94,95). These findings appear driven by both glial and neuronal changes. Specifically, postmortem studies report reductions in neuronal density in individual cortical layers (96,97), lower glial cell count and density, and a decrease in the number of oligodendrocytes in different brain regions (97,98), which is in accordance with reports of reduced myelin staining in brains of bipolar patients (99). Accordingly, these observed alterations in white matter microstructures are suggestive of abnormalities in axonal myelination (100), concordant with diffusion tensor imaging (DTI) findings of disrupted white matter connectivity in BD (101,102).

Moreover, these brain reductions are in accordance with Proton magnetic resonance spectroscopy (^1H MRS) studies in patients with BD (103,104). ^1H MRS is the only non-invasive technique that can assess *in vivo* the biochemistry of altered metabolites of membrane phospholipids in the brain (105). These studies have frequently reported reduced N-acetylaspartate (NAA) and increased glycerophosphocholine plus phosphocholine (GPC+PC) in different brain regions of patients with BD, such as dorsolateral prefrontal cortex, prefrontal and anterior cingulate cortices, hippocampus, and basal ganglia (103,104). Reduced NAA levels in BD may suggest a reduction in the proliferation of dendrites and synaptic connections (106),

while Increased GPC+PC levels has been associated with increased membrane turnover (107). It is noteworthy that a prospective 12-month spectroscopy study in patients with BD following the first-manic episode revealed that NAA and the sum of glutamate plus glutamine are not altered in early stage of the disease(108). Authors reported that these findings may suggest that there may be an early window for intervention to prevent neuroprogression (108).

The hypothesis of brain reductions as an outcome of illness progression in BD is supported by findings of increased ventricle volumes in multiple-episode patients compared to those who had only one episode(109). Additionally, reductions in the volume of the left hippocampus (110,111) and corpus callosum (112) were associated with increased number of mood episodes, especially the manic ones, in patients with BD. These cross-sectional studies, however, could not establish causality between number of episodes and brain changes. This was possible only recently when a 6-year follow-up study in patients with BD type 1 showed decreased frontal cortical volume (dorsolateral prefrontal and inferior frontal cortex) as a function of previous manic episodes(9).

Of note, white matter pathological mechanisms have been hypothesized to represent early-stage alterations, whereas gray matter loss seems to be associated with more advanced stages of the illness (93,113). Multiple authors have discussed the role of neurodegeneration as a potential mechanism by which these alterations might be taking place in BD patients (114,115). A recent study has also demonstrated neurodegenerative outcomes in some cases of BD, including argyrophilic grain-type taupathy and Lewy-related alpha-synucleinopathy (116). The most accepted hypothesis, however, states that most of the alterations may result from impairments in neuroplasticity (117). That could potentially translate into shrinkage of brain structures by reducing neurites and intercellular connections in the neuronal network (4). This scenario does not exclude the possibility that brain cells might also be dying to some extent, which has been suggested by studies showing increased levels of apoptotic markers (118) in postmortem brain from BD patients. Conversely, a mechanism of 'synaptic apoptosis', which is characterized by localized apoptotic biochemical cascades in synaptic terminals, might underlie the discordance between this substantial increase

in apoptotic markers seen in patients without overt corresponding neurodegeneration(119). It is also possible that an initial white matter pathology solely based on neuroplasticity impairments might progress to gray matter pathology associated with neuronal apoptosis and a more substantial brain rewiring.

Accordingly, BD patients likely present impaired cellular resilience mechanisms and thus an increased vulnerability to cell death (120). In this same vein, late-stage patients have been shown to present an impaired unfolded protein response and thereby an increased endoplasmic reticulum stress-induced cell death when compared with early-stage patients (121), providing a cellular foundation to illness progression.

The search for biomarkers and what they tell us about BD neuroprogression

Several cross-sectional studies have compared the levels of biomarkers of neuroplasticity, oxidative stress, and inflammation between early- and late-stage patients with BD (4), but almost none of these findings have yet been confirmed by longitudinal studies.

Regarding neuroplasticity mechanisms, brain-derived neurotrophic factor (BDNF), which is the most abundant neurotrophic factor in the adult brain and is known to induce neuroprotective effects, is reduced in acute episodes of BD and is thought to play a key role in BD neuroprogression (122). Its involvement in this process was initially proposed based on a study showing that late-stage patients present decreased serum BDNF levels when compared to those at an early stage of the illness (117). However, conflicting results have been published using different populations (123,124), and a recent meta-regression study actually suggested that longer illness duration was associated with higher BDNF levels in patients with BD (125). Publication bias, low quality of studies included, and medication regime were some limitations of this study (125). Even though postmortem brains from BD patients display decreased BDNF levels (118), the exact role played by this protein in BD needs to be longitudinally assessed and previous studies comparing its levels in early and late stages needs further replication. Also, medication status, BD type, and others confounder's variables should be controlled.

Oxidative stress markers have also been studied under the concept of BD neuroprogression, and evidence points to an increase in the activities of glutathione reductase and glutathione S-transferase in late-stage patients compared to those at an early stage(126). In addition, the number of mood episodes has been associated with elevated DNA oxidation and shortened telomeres (127,128). Of note, long-term lithium treatment in BD is associated with longer leukocyte telomeres(129,130). Early-stage alterations include increased 3-nitrotyrosine levels and protein carbonylation, which suggest that oxidative and nitrosative damage to proteins is an early event in the progression of the illness (126). These findings give support to initial hypotheses regarding the potential role of mitochondrial dysfunction in BD neuroprogression (4), which has never been directly assessed in patients.

Finally, another key mechanism thought to underlie BD neuroprogression is inflammation (131). Not only do patients differ from controls in the levels of several cytokines and chemokines, but also those at a late-stage of illness seem to present increased levels of (C-C motif) ligand 11 (CCL11), and C-X-C motif ligand 10 (CXCL10), and decreased levels of CXCL827. This was verified in a recent work that found increased serum levels of CCL11 in late-stage patients with BD (132). Moreover, interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha may be increased in patients at both early and late stages, while IL-10 was only increased at the early stage of the illness (117). Another study, however, showed that IL-6 was associated only with late stage (133). Accordingly, a hypothetical model for the role of inflammation in BD neuroprogression suggests that recurrence of mood episodes might induce an excessive production of proinflammatory cytokines that would exceed the downregulatory capacity of the system to restore their normal levels, maintaining microglial cells in a constantly activated state (134).

Inflammation is closely related to the effects of stress and its hormones (135). Cortisol has anti-inflammatory properties based on the effects of the glucocorticoid receptor (GR), which inhibits nuclear factor kappa B and thus reduces the synthesis of proinflammatory cytokines (136). Interestingly, patients with late-stage BD present increased post-dexamethasone cortisol levels associated with GR resistance, which is

concordant with the hyperactive stress axis reported in patients and the seemingly contradictory increased inflammation (137).

It needs to be noted that biomarkers can reflect divergent yet overlapping clinical phenotypes, spanning risk, diagnosis or trait, state or acuity, stage or neuroprogression, treatment response and prognosis (4). So far, no single biomarker with sufficient specificity and sensitivity for neuroprogression to facilitate a clinical staging approach has been identified (138). However, the ones that have been shown to be altered between patients at different stages inform important neurobiological aspects of illness progression, and ultimately allow us to propose a hypothesis for this process (4). In summary, complimentary and interacting biological mechanisms have been proposed to explain the progressive feature of BD, but most of the evidence comes from cross-sectional studies comparing patients with different numbers of episodes or length of illness. Clarification of the operative mechanisms underlying neuroprogression will only come from well-designed longitudinal studies assessing the same group of patients for long periods of time.

Overall, it seems that number of manic episodes is the clinical marker more robustly associated with brain reductions in bipolar 1 disorder. This hypothesis is supported by cross-sectional(109–112) and longitudinal studies (9). In regards to the search for a biomarker of neuroprogression in BD, a small number of longitudinal studies support the hypothesis of inflammatory and oxidative stress changes as a function of the disease progression. However, recent evidence from a meta-regression study does not support the hypothesis of BDNF reduction(125). Medication status, type of bipolar disorder, presence of psychotic symptoms, and presence of rapid cycling are some of the confounders that should be addressed in future longitudinal studies to clarify this field.

Conclusion

In this review, we showed that illness trajectories are largely variable and it seems that illness progression is not a general rule in BD. Some hypothesis related to the neuroprogression model, such as episodes acceleration (22), progressive cortical

changes as a function of manic episodes, and the impact of early trauma on the course of BD (139) were reported in both cross-sectional and longitudinal studies. However, although a consistent relationship between number of previous episodes and neurocognitive impairment has been reported in cross-sectional studies, the direction of causality cannot be established. Conversely, a small number of longitudinal studies suggest that BD might be non-progressive in some cases, although the protective effects of medication is a substantial confound in those people responsive to therapy.

A criticism of the neuroprogressive model is the potential existence of subgroups in BD with different degrees of severity, risk factors, genetics, protective factors and demographics. Additionally, one may hypothesizes that in each individual patient the influence of clinical subtypes and neuroprogression may play a role in the determination of illness trajectories. The use of pattern recognition techniques, such as machine learning, may help to identify combinations of disease-perturbed networks that uniquely define each disease subtype and to integrate a variety of biological information to elucidate stages of progression in individual patients.

It is likely that the biological mechanisms and clinical risk factors associated with the neuroprogressive forms of BD are complex and involve differential systems in the brain and in the periphery. As no factor is singularly predictive of neuroprogression in BD, a probabilistic multi-modal data integration paradigm might predict outcomes associated to neuroprogression in patients with BD. Future studies may validate, refute, and propose new factors that may augment the modeling and predictive power of models of neuroprogression. The study of neuroprogression using multi-modal data integration could significantly advance the field of BD in the following aspects: a) implementation of personalized treatment, b) prediction of unfavorable outcomes, c) development of novel interventions aimed at inhibiting the neuroprogressive cascade, ultimately improving the quality of life of patients.

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Authors' contributions

Dr Passos participated in literature search, writing, figures, and approval of final manuscript. Dr Mwangi participated in writing, figures, literature search, and approval of final manuscript. Dr Vieta participated in writing, and approval of final manuscript. Dr Berk participated in writing and approval of final manuscript. Dr Kapczinski participated in writing and approval of final manuscript.

Conflict of interest statements

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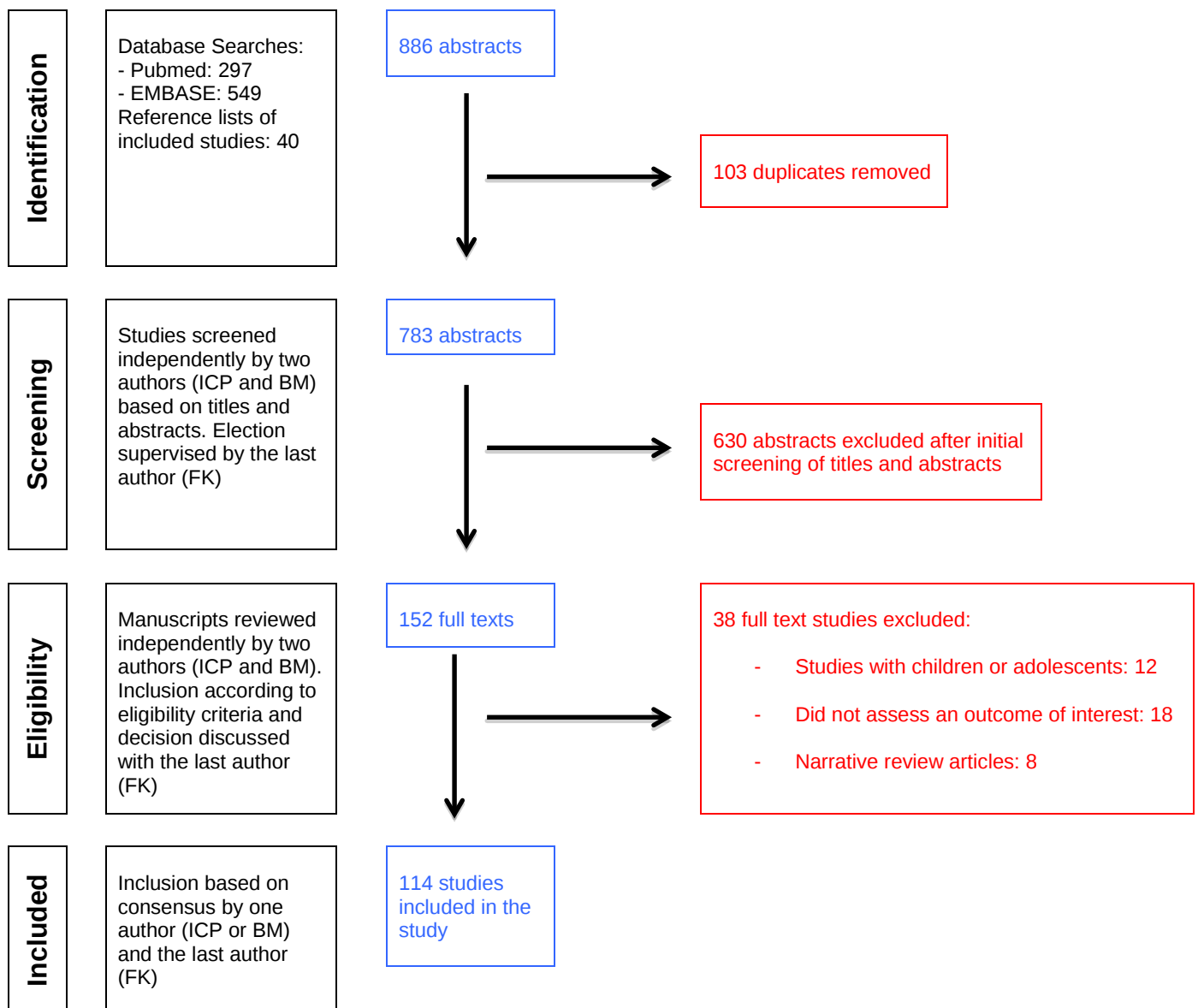


Figure 1. Flowchart of review process and study selection

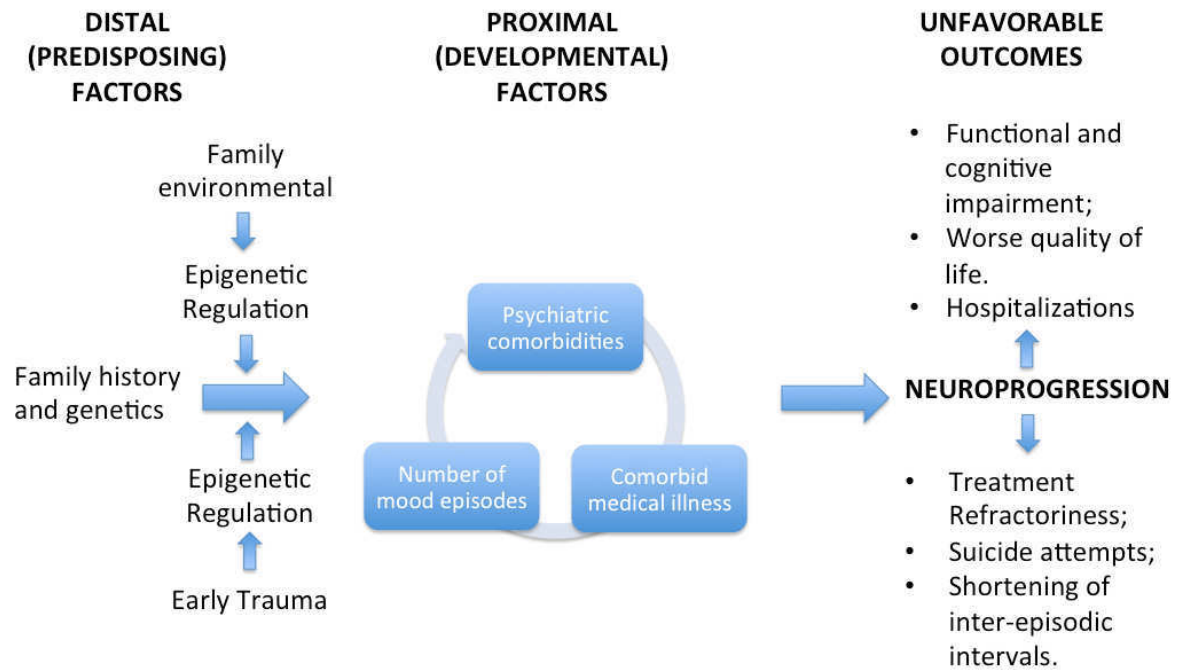


Figure 2. Risk factors and outcomes associated with the hypothesis of neuroprogression. Some patients with bipolar disorder will present a pernicious course associated with shortening of inter-episodic intervals, hospitalizations, functional and cognitive impairment, worse quality of life, treatment refractoriness, and suicide attempts. Herein, we present distal and proximal factors associated with neuroprogression. The model proposed takes into account the classic psychosocial and genetic risk for bipolar disorder and integrates findings on sensitization and cross-sensitization models to explain the unfavorable outcomes related to neuroprogression. Distal factors lead to long-term effects on gene expression and regulation. Also, distal factors may not directly lead to neuroprogression but are linked to unfavorable outcomes through the effects of proximal factors.