Chapter 11

Neuroprogression in bipolar disorder

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11.1 Introduction

11.1.1 Bipolar disorder

Bipolar disorder (BD) is a major psychiatric disorder frequently associated with cognitive impairment and reduction of lifespan (Soreca, Frank, & Kupfer, 2009). The significant burden of BD on the overall individual health highlights the need for the identification of clinically relevant biomarkers for better diagnosis and prognosis of patients. The prevalence of BD is around 2.1% among the general population, with a course characterized by a recurrent trend (Schaffer, Cairney, Cheung, Veldhuizen, & Levitt, 2006; Merikangas et al., 2007). BD is currently one of the most frequent, severe, and costly mental, social, and health disorders; it is also noted that there is a frequent association with high rates of disability and suicidality and numerous psychiatric and medical comorbidities in general. In addition, a thorough epidemiological evaluation estimates that 50% of patients with BD can meet the diagnostic criteria for other psychiatric disorders (Swann, 2006), as well.

According to the DSM-5 classification, BD diagnoses are currently placed in a separate category from depressive disorders. Specifically, they are strategically placed in an intermediate position between schizophrenia and depressive spectrum disorders, recognizing a continuity of BD among those classified as psychotic and neurotic disorders according to the ancient nosography. According to current knowledge, BD may be a bridge between the two diagnostic classes in terms of symptoms, genetic, epigenetic,

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molecular, anamnestic, and social aspects. Classes of diagnoses include BD type I, BD type II, cyclothymic disorder, substance/medication-induced BD, and BD induced by another medical condition. While in past centuries the classic description of BD required the necessary detection of at least one markedly expansive episode and at least one depressive episode, the current nosography allows for a diagnosis of BD after detecting a single manic episode with complete symptomatology.

11.1.2 Evidence of (neuro)progression in bipolar disorder

"Neuroprogression" is a term used to describe longitudinal and progressive alterations detectable in clinical and neurobiological variables in patients (Ruiz, Del Ángel, Olguín, & Silva, 2018). Throughout the natural history of BD, neuroprogressive mechanisms encompassing biological alterations in neuroanatomical, genetic, and biochemical markers have been reported by numerous studies, with different alterations characterizing specific stages of the illness (Berk, 2009; Schneider, DelBello, McNamara, Strakowski, & Adler, 2012). It is currently clear that the changes affecting the brain's anatomical and functional structure are not identical to changes observed at the disease's onset, but rather become evident with the chronicity and manifestation of recurrent episodes (Lyoo et al., 2006; Robinson & Nicol Ferrier, 2006). Accordingly, it is believed that neuroprogression-related changes become more evident with the sum of episodes, with a resulting accumulation of immune alterations, mitochondrial dysfunction, increased oxidative stress and damage, decreased neurotrophic support, as well as cumulative neurovascular and neurochemical alterations (Berk, Kapczinski, et al., 2011; Fries et al., 2012; Kapczinski et al., 2008; Post, Fleming, & Kapczinski, 2012).

An association between neuroprogression and reduced responsiveness to psychotherapeutic treatment, particularly with cognitive–behavioral therapy (Scott et al., 2006; Swann, Bowden, Calabrese, Dilsaver, & Morris, 1999), has also been reported. This has been thought to involve multiple episodes leading to permanent alterations in brain tissue activity and therefore resulting in more pronounced responsiveness to exacerbations and less efficient therapeutic response. Importantly, it should be noted that not all patients show the presence of neuroprogressive features, with only subsets of patients reporting progressive cognitive impairments and marked alterations in functionality (Passos, Mwangi, Vieta, Berk, & Kapczinski, 2016). This evidence raises the challenge of identifying and defining specific subgroups of patients characterized by greater sensitivity to neuroprogressive mechanisms, with the consequent need for a deeper understanding of the biological underpinnings of BD.

11.2 Clinical evidence of neuroprogression

11.2.1 Clinical features

The evolution of BD in all its forms begins in asymptomatic individuals with clinical features of risk, changing toward prodromes, and finally progressing into episodicity and chronicity. Despite considerable interindividual differences, and although many patients with BD never progress to a more dysfunctional form, BD has been repeatedly identified as a neuroprogressive disorder (Berk et al., 2010, 2014; Berk, Brnabic, et al., 2011; Berk, Kapczinski, et al., 2011).

As mentioned before, neuroprogression can be defined by a sequence of changes in the clinic and biology related to BD's pathophysiology with a variable trend over time. This theory is supported by observed pathological changes in the brain structure, both neurobiological and anatomical, which may result in a significant resistance to therapies, a reduction in the disease-free time interval, and a progressive cognitive and functional decay. Alterations of physiological functioning, combined with the lack of effectiveness of endogenous mechanisms of repair and intrinsic compensation, are considered the basis of cross-sensitivity between recurrent episodes of psychopathological exacerbations, exposure to external trauma, and comorbidity with the use of substances, whose final effect is manifested in the neuroprogression of BD (Rizzo et al., 2014; Schneider et al., 2012). Specifically, according to the "Kindling theory," psychosocial stress factors are fundamental factors for the onset of illness. In contrast, for exacerbation of subsequent episodes, the necessary factors are minor due to the increased awareness in response to recurrence and chronicity. As a result, both an increase in the episodes' frequency and an increase in their severity and dilation of recovery time (often not complete) are observed with the temporal progression of the illness (Leverich & Post, 2006; Post, 2007). Of note, the potential cross-action of psychotropic substances, of any nature, together or not with traumatic events, emphasizes the seriousness of the effects of cross-sensitization (da Costa, Passos, Lowri, Soares, & Kapczinski, 2016).

Neuroprogression has been held responsible for the acceleration of the episode−remission cycle, leading to a significant reduction in relative well-being periods (remission) and a higher tendency for future recurrence of both depressive and manic symptoms. For example, the rate of hospitalization following relapse has been shown to increase with the increase in the number of episodes, with this effect being more evident in women than in men (Kessing, Hansen, & Andersen, 2004). Besides, the onset of exacerbations' timing becomes increasingly reduced, outlining a rapid manifestation of more pronounced symptoms (Berk et al., 2007; Berk, 2009; Kapczinski et al., 2009; Post et al., 2012). These basic concepts are somewhat based on Kraepelin's observations, which suggested that the manic-depressive illness

tends to reduce time intervals between episodes and progressively continue in a more rapid course (Trede et al., 2005). Importantly, more recent studies have shown that these proposed models are not unambiguous, with existing evidence showing no support to the concept of cyclic acceleration in some cases (Baldessarini et al., 2012; Coryell, Endicott, & Keller, 1992; Kessing, Olsen, & Andersen, 1999; Maj, Magliano, Pirozzi, Marasco, & Guarneri, 1994). Nonetheless, narrative reviews overwhelmingly illustrate clinical evidence of neuroprogression in BD (Kohler & Marlinge, 2019; Morris et al., 2018; Muneer, 2016; Nascimento et al., 2019; Rosenblat & McIntyre, 2017).

11.2.2 Neurocognitive changes

Several studies have shown an association between the number of acute episodes and the development of cognitive symptoms in euthymic BD patients (Robinson & Nicol Ferrier, 2006). In particular, the relationship between the number of manic episodes and cognitive impairment has been validated by many independent studies. Euthymic patients at the time of evaluation with a history of three or more manic episodes have been shown to have a worse overall cognitive performance than patients with a history of only one manic episode (López-Jaramillo et al., 2010). It has also been reported that patients show impairments in verbal memory and cognitive functions of lesser magnitude after the resolution of a first manic episode when compared to euthymic patients with a history of multiple manic episodes. These results suggest that the sum of pathological events may have increasing repercussions over time (Torres et al., 2010).

Accordingly, many staging models of BD have been proposed to provide an analysis of the course of the pathology in a progressive sense, starting with a phase of absence of cognitive deficits in the premorbid phase, followed by an initial phase where the euthymic aspects prevail, all the way until the occurrence of severe cognitive deficits in subsequent phases of the illness (Kapczinski et al., 2009). Interestingly, the concept of preserved cognitive function that can be found in patients with BD in the first stages of the clinical history derives fundamentally from the measurement of intellect or equivalent parameters. Such evidence reflects the notion that the cognitive functioning in the phases prior to the psychopathological onset is not necessarily preserved (especially in specific cognitive domains such as selective attention, working memory or executive functions), which may already be compromised in the premorbid phase and represent a predictor of pathology (Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015; Gama, Kunz, Magalhães, & Kapczinski, 2013; Martino, Samamé, Marengo, Igoa, & Strejilevich, 2016; Rodrigues, Rosa, Kunz, Bruna, & Kapczinski, 2014).

Current neuroprogression theories state that the course of BD is characterized by relapses, increased severity of clinical symptoms over time, and general medical comorbidity (Kapczinski et al., 2009). The general condition

of the patient is typically characterized by a slower psychomotor speed both on learning tasks and on memory fixation, reenactment, cognitive flexibility, thought adaptation, and in general executive functioning (Bora et al., 2007; Halari, Leung, & Young, 2013). An inverse correlation has also been observed between the duration of illness (Martínez-Arán et al., 2004) and the acuity of higher psychic functions (Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005), such as visual memory, complex attention, and the ability to adapt to situations that require high cognitive functioning (Delaloye et al., 2011; Mora, Portella, Forcada, Vieta i Pascual, & Mur, 2012; Torrent et al., 2012). Moreover, early age of illness onset has also been strongly negatively correlated with the maintenance of neurocognitive functions, sustained attention, and verbal memory (Ancin et al., 2010; Cardoso et al., 2015; Schouws et al., 2009; Van Rheenen et al., 2020).

11.2.3 Functioning

Neuroprogression in BD has been repeatedly associated with the overall functioning of individuals (Berk et al., 2014). Through the use of data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, for instance, a higher number of episodes has been found to be associated not only with a worse functioning, but also to a lower quality of life, both through transverse and longitudinal analysis (Gitlin, Swendsen, Heller, & Hammen, 1995; Keck et al., 1998). Similarly, early-stage patients at the onset of illness, despite the first symptoms' impressiveness, have been shown to present a better general functionality than patients with multiple episodes. These findings suggest that the neurotoxicity associated with multiple acute episodes can be damaging to the brain structure, ultimately affecting functioning abilities (Perlis et al., 2006; Tohen et al., 2003).

A considerable percentage of patients find it challenging to achieve full recovery even after the first episode. At the same time, a worse psychosocial and work function is associated with recurrence and with residual symptoms after a partial recovery. Globally, it is therefore clear that the number of patients who do not achieve an adequate functional recovery after the first episodes place them in a situation of higher risk of recurrence over time, suggesting that the relationship between the number of episodes and functioning is in place since the psychopathological onset (Magalhães, Dodd, Nierenberg, & Berk, 2012; Rosa et al., 2012).

11.3 Biological basis of neuroprogression

11.3.1 Neuroanatomical changes

In most staging models proposed for BD, we find the concept of neuroprogression as a foundation. This fact includes a basic idea that departs from the

ancient conception of the disease as being immutable, in favor of a course that can be variable over time. Overall, the assumption based on neuroprogression refers to a change in the pathological reorganization of the central nervous system's structure due to biochemical insults such as stress and inflammation. In particular, it has been suggested that the neuronal architecture and neural connections, as well as the brain reactivity, are altered by a repetition of mood episodes, resulting in increased vulnerability to future episodes (Malhi, Bell, Morris, & Hamilton, 2020).

The model based on recurrence of mood symptoms suggests that BD may have a unidirectional progression that is converted into changes often irreversible in every neurobiological pathway. However, it is known that patients with BD are very different from one another both in terms of the illness onset and pathological model, with a significant variability in premorbid and syndromic states in the early stages and in individual episodes throughout the course of the illness (Berk et al., 2007). As an alternative to this immutable model, staging models based on functioning have been proposed and show a high interepisodic functioning, emphasizing that, at least in the early stages, the functioning in the disease-free intervals is almost superimposable to the nonpathological one (Malhi et al., 2020). Cognitive deficits in BD patients have been shown to be independent of the phase of the disease, with subjects with a history of more than one manic episode showing greater deficits in verbal and working memory, executive function, reasoning and problem solving (Vrabie et al., 2015).

Many staging models of BD are based on the assumption that there is a single process underlying the disease's progression, with each model emphasizing one major aspect of neuroprogression (Malhi et al., 2020). A comparative evaluation of the models leads to BD in the same way that current medicine understands most complex diseases. Specifically, basic and clinical instrumental research has led to the concept of a multifactorial genetic basis of complex diseases. In the course of life, an individual can be subjected to multiple triggering factors, starting from childhood and adolescence, where even the occurrence of an isolated depressive episode can act as a trigger in a nervous system vulnerable to environmental, genetic, and epigenetic factors, and eventually precipitate a mood episode later in life. The hypothesis of the action of multiple factors is also corroborated by the presence of numerous compensatory mechanisms in the brain that try to remedy the succession of events triggering the pathology, suggesting the high unlikelihood of a unique BD-specific neuroprogressive process (Malhi et al., 2020).

Finally, many clinical staging models do not include in their definitions the presence and especially the combined action of clinical comorbidities and other psychiatric diseases. Arguably, such incorporation would make the models poorly assessable and possibly make the high number of variables as factors of confusion. This consideration leads in contrast to the confrontation with the clinical reality, where BD patients typically present high

comorbidity with mental and nonmental conditions. As a consequence, the effectiveness and clinical utility of existing models that do not recognize this complex nature of the genesis and development of BD are limited. It should also be noted that models rarely define the effects of various personality traits and different personal temperaments and socioenvironmental factors.

Several risk factors are thought to contribute to the genesis of BD and its significant clinical variability in its subgroups. Similarly, the current level of knowledge of environmental and genetic risk factors' pathological contribution is limited due to the highly nonspecific nature of many risk factors. At present, it is especially challenging to determine which are the links that can cause specific pathogenic mechanisms of BD; therefore existing staging models are only partially able to identify groups of patients at risk, with a low predictive capacity at the moment (Malhi et al., 2020).

11.3.2 The dualism of neurodegeneration versus neuroplasticity

The presence of neuropathological and neuroimaging alterations affecting multiple brain structures has been consistently demonstrated in BD patients, and for some of them, the presence of such alterations already at early stages of the disease has been demonstrated. For instance, decreased gray matter volume has been reported in the right ventral prefrontal cortex, temporal cortex, claustrum, left anterior rostral cingulate cortex, and right anterior frontoinsular cortex of patients (Bora, Fornito, Yücel, & Pantelis, 2010; Lin, Reniers, & Wood, 2013; Selvaraj et al., 2012). Together with these changes, a series of alterations at both the glial and neuronal levels have been observed in BD, in particular through postmortem studies, with evidence of marked reductions in neuronal density in the individual cortical layers, a reduction in the number and density of glial cells, and a reduction in the number and density of oligodendrocytes (Benes, Vincent, & Todtenkopf, 2001; Öngür, Drevets, & Price, 1998; Rajkowska, Halaris, & Selemon, 2001; Regenold et al., 2007). As a result, microstructural alterations of the white matter have also been identified, suggesting abnormalities in axon myelination that are in agreement with results obtained by diffusion tensor imaging on the interrupted connectivity of the white matter in patients with BD (Benedetti et al., 2011; Bora & Pantelis, 2011; Lagopoulos et al., 2013).

These reductions in the central nervous system are consistent with proton magnetic resonance spectroscopy (^{1}H MRS) studies in patients with BD; this is particularly important because this is currently the only noninvasive technique available for the in vivo assessment of the biochemistry of altered membrane phospholipid metabolites in the brain. Through this type of study a significant reduction of N-acetyl aspartate (NAA) and an increase in glycerophosphocholine plus phosphocholine (GPC + PC) have been observed in various brain regions (Kraguljac et al., 2012), particularly in the dorsolateral

prefrontal cortex, hippocampus, basal ganglia, and anterior cingulate cortex (Yildiz-Yesiloglu & Ankerst, 2006). A reduction in NAA levels in BD has been correlated with a reduction in dendritic and synaptic proliferation. Similarly, an increase in GPC + PC has been considered responsible for an increase in membrane turnover (Skripuletz et al., 2015), especially in the early clinical stages of illness (Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007; Stanley, 2002). Based on these findings, it is clear that a well-defined time interval can be suggested for early intervention to prevent neuroprogression. These hypotheses regarding macrostructural alterations of the brain are corroborated by the finding of an increase in ventricle volume in patients after multiple episodes compared to patients with a single recorded episode (Cao et al., 2016; Javadapour et al., 2010; Lavagnino et al., 2015; Silveira et al., 2017; Strakowski et al., 2002). In further analyses, the volume reductions at the left hippocampal level and corpus callosum have also been associated through cross-sectional and longitudinal studies, with an increase in the number of mood episodes, especially in the manic and hypomanic phases. In addition, the presence of changes in neurons and glial cells are the basis of the neuropathological aspects of BD. Through the use of a three-dimensional stereological cell counting method, it has been demonstrated that the Brodmann area 9 of BD patients is characterized by significant reductions in glial density, with increased size and changes in the shape of glial nuclei compared to healthy controls (Rajkowska et al., 2001). It has also been proposed that microstructural neuroanatomical alterations in the white matter are more representative of the early stages of the disease, whereas alterations in the gray matter are more indicative of advanced stages of the disease (Lin et al., 2013).

Interestingly, a connection between episodes of psychopathological acuity and argyrophilic grain type tauopathy and Lewy's alpha-synucleinopathy has also been observed (Gildengers et al., 2014). At the moment, the most accepted hypothesis regarding most of these alterations is attributable to alterations of neuronal plasticity with a consequent shrinkage of brain structures and reduction of neurons and neuronal intercellular connections (Passos et al., 2016) (rather than a proper "neurodegenerative"-like progression as seen in traditional neurodegenerative diseases, such as Alzheimer's disease). There is also the possibility that an apoptotic process occurs in central nervous system cells as evidenced by postmortem studies of patients with BD (Berk, Kapczinski, et al., 2011; Frey et al., 2008; Jakobsson et al., 2013; Kauer-Sant'Anna et al., 2009). Among the proposed hypotheses, there is also the possibility that a pathology initiated at the white matter level (substantially due to alterations in neuroplasticity) may evolve and lead to the pathological involvement of gray matter associated with neuronal apoptosis and a more substantial rewiring of the brain with the consequent marked psychopathological alteration (Passos et al., 2016).

11.3.3 Molecular changes associated with the progression of illness

An in-depth analysis of peripheral blood samples from patients with BD at late stages has suggested mechanisms underlying the observed reduction in neuronal density and viability in cell cultures. These studies have mainly focused on mechanisms related to oxidative stress and low-grade inflammation in glial and neuronal plasticity (Kapczinski et al., 2010; Rajkowska, 2002; Wollenhaupt-Aguiar et al., 2016).

Biomarkers involved in oxidative stress and inflammation are thought to play a fundamental role in the cell degenerative process, and have been shown to be altered in patients at different stages of illness progression. For instance, alterations in oxidative stress markers associated with BD neuroprogression have been found in the glutathione system (including increased levels of glutathione reductase and glutathione S-transferase, enzymes involved in the pathway of reduction-detoxification) (Andreazza et al., 2008; Andreazza et al., 2009; Kauer-Sant'Anna et al., 2009), in the levels of C-C ligand-11 and C-X-C ligand 10 (proinflammatory cytokines based on the PI3K-Akt signaling pathway), among others. The action of these molecular compounds on neuroprogression is being further studied in order to ascertain their ability to overcome the blood−brain barrier (BBB) and trigger neuroinflammation (Panizzutti et al., 2015; Patel & Frey, 2015). Signs of microglial activation have been detected with positron emission tomography, and the presence of focal neuroinflammation in particular in the right hippocampus of patients has been demonstrated, emphasizing the need for further studies on the role of in vivo immune activation in the pathophysiology of BD (Haarman et al., 2014). These data confirm the hypothesis that oxidative stress and inflammation can act as triggers and amplifiers of the immune system activation with a consequent increase in systemic toxicity in BD (Haarman et al., 2014; Stertz et al., 2015). In BD patients, increased levels of damage-associated molecular patterns (DAMPs) have been reported when compared to healthy subjects, particularly of cell-free nuclear DNA, heat-shock protein of 70 kDa (HSP70), and heat-shock protein of 90 kDa (HSP90). These DAMPs (originally intracellular molecules presenting with immunogenic activity once in the extracellular and peripheral spaces) can be of multiple forms (sugars, metabolic byproducts, lipids, RNA, and DNA) and present a common binding affinity with specific toll-like receptors (TLRs). Their binding the TLR in the periphery can activate signaling cascades within the immune system with production of an (sterile) inflammatory response. Of fundamental importance is the connection with the neuroprogression provided by DAMP activation of TLR reporting cascades, potentially leading to the generation of a cytotoxic insult. This mechanism may be activated by various factors such as drug abuse, high stress, or affective

episodes, subsequently leading to a systemic inflammatory response (Kapczinski et al., 2010) (as repeatedly observed in BD).

11.3.4 Insulin signaling and hypothalamic–pituitary–adrenal axis dysregulation

The overlap of biochemical processes that occur in the central nervous system in both BD and insulin resistance can lead to significant cognitive impairment, which is of particular relevance for BD neuroprogression (as discussed in Section 11.2.2). These mechanisms include insulin signaling, oxidative stress, mitochondrial dysfunction, dysregulation of the hypothalamic–pituitary–adrenal axis (HPA), and as the last step, neuroinflammation.

Cellular studies carried out in human cells have revealed that the chronic stress-induced increase in corticosteroid levels, as observed in subjects with insulin resistance, is responsible for the alteration of normal neural processes leading to the increased release of corticotropin (CRH) levels (Reagan, Grillo, & Piroli, 2008). This modified hormonal release process involves altered neurogenesis at the hippocampal level, and murine studies have shown an involvement of neurotrophic factors, such as synaptophysin, in the alteration of synaptic architecture with consequent impairment of neuronal plasticity and ultimately neurogenesis (Gaspar, Baptista, Macedo, & Ambrósio, 2016; Joëls & Baram, 2009; Joëls, Karst, Krugers, & Lucassen, 2007; Stranahan et al., 2008). The HPA axis' role in BD has been thoroughly evaluated in the literature, showing that BD is associated with higher levels of cortisol and adrenocorticotropic hormone (ACTH) (van den Berg et al., 2020). Moreover, BD patients at a late stage have been shown to present increased postdexamethasone cortisol levels and an epigenetically mediated hypoactivity of the glucocorticoid receptor (GR) when compared to early-stage patients, stressing the potential key role of the stress axis in BD neuroprogression (Fries et al., 2015). In addition, polymorphisms within the CRH receptor 2 (*CRHR2*) gene have been found to confer an increased risk of suicide in BD (De Luca, Tharmalingam, & Kennedy, 2007). The presence of a history of adverse events such as childhood trauma has also been associated with a worse outcome in BD, which has been hypothesized to be mediated by the HPA axis. Further analysis has also shown that childhood trauma is correlated with a more marked cognitive impairment of memory and executive function in patients with BD (Calkin, Gardner, Ransom, & Alda, 2013; Cuperfain, Kennedy, & Gonçalves, 2020; Dauvermann & Donohoe, 2019; De Luca et al., 2007; Fish et al., 2004; Murri et al., 2016; Passos et al., 2016).

Genetic analyses have suggested a strong link between insulin pathways and BD, including the presence of variants within the insulin-like growth factor 1 (*IGF-1*) gene region in patients (Pereira et al., 2011). The increased

oxidative stress seen in BD can also lead to insulin resistance and increased neuroinflammation, both locally and systemically. In particular, in the early stages of the disease, the increase in glycemic values may lead to an activation of metabolic pathways, with ROS generation and an increase in circulating inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-8, and monocyte chemoattractant protein 1 (MCP1; also called CCL2) (Dinel et al., 2011; Donath, 2014; Sima, Zhang, Kreipke, Rafols, & Hoffman, 2009).

The connection with BD is evidenced by the fact that, as in diabetes mellitus and insulin resistance, bipolar patients have an association with a chronic proinflammatory state. This proinflammatory state is more pronounced during manic episodes when compared to euthymia, while there are fewer associations available in the literature regarding the depressive phases of the disease (Barbosa, Bauer, Machado-Vieira, & Teixeira, 2014; Goldsmith, Rapaport, & Miller, 2016; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013). An increase in TNF-α and other inflammatory cytokines, as well as a reduction in BDNF and antiinflammatory cytokines, such as IL-10, have been reported in advanced stages of BD (Kauer-Sant'Anna et al., 2009). Postmortem studies have further validated these data, with results showing an increase in inflammatory markers in the frontal cortex of BD patients (Rao, Harry, Rapoport, & Kim, 2010). Given the proposed relationship between neuroinflammation and cognitive deterioration (Rao et al., 2010), patients have also been found to present increased CC, IL-6, and TNF-α, sCD40 and hsCRP, microglial activation, as well as an increase in cerebrospinal fluid levels of YKL-40 (a microglial marker), with consequent worsening of the executive function (Rolstad et al., 2015; Rosenblat et al., 2015). It has also been found that high levels of TNF-α are associated with marked cognitive deterioration, even in the early stages of BD (Chakrabarty, Torres, Bond, & Yatham, 2019). Overall, it can be stated that the presence of neuroinflammation in both BD and insulin resistance can lead to cognitive impairment observed in both conditions, with a reduction in overall functioning.

11.4 Future perspectives of the field

Current knowledge of BD suggests that the development of a hypothetical staging model must necessarily fully represent the multisystemic disruption that generates it, leading to the complete integration of all available biological measures. Chronic disorders such as BD require that the adherence of the research model to the real construct of pathology is taken into account, which must consequently consider the extensive amount of physical and psychopathological comorbidities of the disorder (Chang et al., 2009; Kupfer, 2005). Although there is no universally recognized consensus model, the

model proposed on the basis of allostatic load markers has several advantages (Kupfer, Frank, & Ritchey, 2015). For instance, the factors that make up this model include measures of cardiovascular function such as heart rate variability, blood pressure, metabolism, sympathetic nervous system activity, HPA activity, and inflammation (Bizik et al., 2013). Moreover, the use of this model as a tracking method for alterations related to BD seems to be of interest since the constitutive markers are largely dysregulated, to varying degrees, in patients with BD. Accordingly, their study would lead to a differentiation of disease stages and a consequent better identification of subgroups of patients on which to apply targeted treatments, with a change in disease progression trajectories (Grande et al., 2014; Pfaffenseller et al., 2013; Pfennig, Frye, Köberle, & Bauer, 2004).

A combination of multiple markers could be a more pronounced predictor of BD-associated functional damage than a single marker. Although the allostatic load model is promising, there are still several barriers to its clinical use and application, including the absence of a universal agreement on the markers constituting a precise measurement of the allostatic load itself. Several authors have written significant contributions on allostatic load in different patients' groups (Danese & McEwen, 2012; Duru, Harawa, Kermah, & Norris, 2012; Gallo, Fortmann, & Mattei, 2014; McEwen, 1998; Vieta et al., 2013; von Thiele, Lindfors, & Lundberg, 2006). However, the lack of a single research consortium and the scarce availability of a single line emphasize the possibility of slight differences in the use of markers, making it difficult to compare the data obtained by independent groups. One of the main drawbacks of the models proposed to date is the attribution of a homeostatic health model instead of an allostatic one. A homeostatic model starts from the basic assumption that every physiological variable is configured in a normal range of values, and deviating from these could lead into the pathological field. On the contrary, an allostatic model identifies health and well-being as the organism's anticipatory ability to predict the appropriate responses to each situation, thus defining a healthy value for any variable as entirely context-dependent. Together with this, it is necessary to consider how the aggregation of the data of every single variable can depend on analyses such as the rapid ecological evaluation in the assessment of markers in different situations (Gallo et al., 2014).

The predictive validity of individual markers in the context of cumulative dysregulation in BD's neuroprogression remains a matter of debate; this could, according to some, emphasize the greater validity of individual markers in the current state compared to a combined measure due to the greater experimentation of the former compared to the latter. However, it seems necessary to point out the validity of the combined model as a biopsychosocial representation of disease that takes into account exogenous factors such as environmental, occupational, and social stress and endogenous ones (Kupfer et al., 2015).

11.5 Conclusions

There is a strong correlation between biological factors, functional, and cognitive damage in the genesis and clinical course of BD. These data imply the need for advanced staging models and the development of models increasingly defined by molecular, genetic, and structural variables. In currently existing models, the patient is included in a classification that follows a space-time continuum concerning the anatomical and functional mapping of the brain and the course of the pathology describing premorbid phases, the onset, and the clinical course, including manic, depressive, and partial or complete remission phases.

The current knowledge available in the literature agrees that early intervention provides a better outcome (Post et al., 2010). In this sense, possible interventions should be established as early as possible in the onset phase, together with the appropriateness of treatments. Such a precision medicine approach may provide precise results in terms of reduction of relapse, the possibility of prevention of the disease in its most severe aspects, and slowing down the neuroprogression of the disease.

Primary prevention in this perspective is necessary, starting from the complete avoidance of the triggering factors in subjects considered at risk, starting from the stressors, through the use of substances of abuse and delay in diagnosis. Moreover, clinical and preclinical staging models can be used as irreplaceable tools in the treatment planning as targeted and effective as possible and can be used in the psychoeducational field as a means of information for patients and their families to obtain better compliance.

A position of caution and realism on the current state of scientific research is necessary as a limitation. A decidedly complex etiopathology characterizes mental pathology, and this aspect is not unequivocally acclaimed; combined action of exogenous and endogenous aspects makes it extremely complex to accurately design curative and preventive programs on a large scale. It is therefore essential for translational work to integrate multiple lines of research and to create consortia that aim to define reliable, theoretically impeccable, and clinically usable models of neuroprogression and staging of BD.

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