Neuroscience and Biobehavioral Reviews 42 (2014) 157–169

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The theory of bipolar disorder as an illness of accelerated aging: Implications for clinical care and research

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ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form
17 December 2013
Accepted 5 February 2014

Keywords:
Bipolar disorder
Aging
Biomarkers
Neuroprogression
Telomeres
Inflammation
Immunosenescence
BDNF
Oxidative stress
Amyloid
Cognition
Molecular imaging

ABSTRACT

Bipolar Disorder (BD) has been conceptualized as both a cyclic and a progressive disorder. Mechanisms involved in neuroprogression in BD remain largely unknown although several non-mutually exclusive models have been proposed as explanatory frameworks. In the present paper, we propose that the pathophysiological changes observed in BD (e.g. brain structural alterations, cognitive deficits, oxidative stress imbalance, amyloid metabolism, immunological deregulation, immunosenescence, neurotrophic deficiencies and telomere shortening) converge on a model of accelerated aging (AA). Aging can be understood as a multidimensional process involving physical, neuropsychological, and social changes, which can be highly variable between individuals. Determinants of successful aging (e.g environmental and genetic factors), may also confer differential vulnerability to components of BD pathophysiology and contribute to the clinical presentation of BD. Herein we discuss how the understanding of aging and senescence can contribute to the search for new and promising molecular targets to explain and ameliorate neuroprogression in BD. We also present the strengths and limitations of this concept.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2014.02.004
0149-7634/

1. Introduction

Bipolar Disorder (BD) is a prevalent and often severe mood disorder where individuals experience disruptive episodes of mania or hypomania and depression (Anderson et al., 2012). Causes of BD remain largely unknown but probably involve a set of genetic and environmental factors, which interact during neurodevelopment to determine vulnerability to the disease (Brietzke et al., 2012a). Genetic studies have implicated many chromosomal regions and candidate genes, but results have been inconsistent and often not replicable (Sullivan et al., 2012). Genome-wide Associantion Studies (GWAS) studies indicate that genetic susceptibility is determined by a high number of genes, each with a small effect size (Sullivan et al., 2012).

Although BD has been understood classically as a cyclic disease, in the last 10 years evidence has accumulated supporting progressive features of BD (Berk et al., 2010; Fries et al., 2012; Mansur et al., 2013), reconceptualizing BD as both a cyclic and progressive disorder. The starting point for this hypothesis was the clinical evidence that individuals in early and late stages of BD present substantial differences in the severity of clinical presentation and response to treatment (Berk et al., 2011). There are robust data suggesting that a greater number of episodes, especially those of manic polarity, are associated with a decrease in the length of the euthymic interval between episodes, worsening of neurocognitive performance, increasing risk of suicide, and poorer response to both pharmacological and psychosocial treatments (Berk et al., 2010; Magalhaes et al., 2012). Nonetheless, evidence has been mixed and progressive models of mental illness are not universally accepted (Zipursky et al., 2013). At present, operationalization of the concept of neuroprogression in clinical practice manifests mainly in the "staging" of severe mental disorders, including BD (for a detailed review, please see Kapczinski et al., 2009).

Mechanisms involved in neuroprogression remain largely unknown and only few explanatory models exist that could justify a neuroprogressive disease course. Among these, one of the most accepted is the concept of Allostatic Load (AL). AL implicates chronic stress in overactivating homeostatic mechanisms that are collectively beyond the capability of the organism, leading to progression of clinical and neurobiological parameters (Brietzke et al., 2011; Goldstein et al., 2009b; Grande et al., 2012; Kapczinski et al., 2008). However, it has been difficult to quantify the impact of stress biology on neuroprogression, in part due to mechanisms of resistance and resilience that can modulate the impact of stress (Brietzke et al., 2012b).

Another nascent theoretical framework is the concept of BD as a disorder of accelerated aging (AA) (Simon et al., 2006; Sodhi et al., 2012). Aging in humans refers to a persistent decline in the age-specific fitness components of an organism due to internal physiological degeneration (Rose, 1991). Aging can also be understood as a multidimensional process of physical, neuropsychological, and social changes. With respect to neuropsychological changes, the effect of aging is non-uniform across domains. For instance, psychomotor processing speed and verbal memory performance decline with age, while knowledge and wisdom can continue to expand. The rates of change in these domains differ between individuals and they can be modified by many intervening genetic and environmental factors. A complementary concept is the idea of *senescence*. The phenomenon of *cellular senescence* was first described by Leonard Hayflick in 1961, referring to the limited capacity of isolated cells to proliferate in culture (the Hayflick Limit) (Hayflick and Moorhead, 1961), but the concept can also be applied to whole organisms. For example, after a period of near perfect renewal (in humans, between 20 and 35 years of age), organismal senescence is characterized by the declining ability to respond to stress, increasing homeostatic imbalance and risk of disease.

Preliminary data suggest that individuals with BD present early senescent features consistent with AA. One of the most clinically conspicuous corollaries is the high prevalence and earlier age on onset of age related medical conditions e.g. cardiovascular conditions, hypertension, metabolic imbalances, autoimmunity and cancer (Crump et al., 2013; Czepielewski et al., 2013; Fagiolini et al., 2008; Goldstein et al., 2009a; McIntyre et al., 2005, 2006; Osby et al., 2001; Padmos et al., 2004; Rege and Hodgkinson, 2013; Soreca et al., 2008). In addition, the association between mood disorders and dementia has been well recognized. Most studies include individuals with Major Depressive Disorder (MDD), but a recent meta-analysis suggested that the association between BD and dementia might be stronger than that of MDD (da Silva et al., 2013). Although the degree of neurobiological overlap between the two conditions remains a matter of debate, there is evidence that inflammation, neurotrophic and amyloid cascades are altered in both conditions (Aprahamian et al., 2013; Modabbernia et al., 2013).

Here we discuss how aging and senescence may contribute to the search for new and promising molecular targets to better understand neuroprogressive features of BD. Although some findings are preliminary, we postulate they can be integrated in a new theoretical framework to better explain some elements of BD pathophysiology.

2. Neurobiological similarities between neuroprogression in BD and aging

Although there are few studies exploring aging in BD, there is a surprisingly high overlap between neurobiological mechanisms in the two conditions, including progressive changes at the molecular and cellular levels, and in the structure and function of the central nervous system (CNS) (Fig. 1).

2.1. Changes at the structural level

Normal aging is associated with alterations in brain structures. *Post mortem* and structural neuroimaging studies indicate that the human brain shrinks with age, with selective and differential