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Review

Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: Evidence, pathophysiology and treatment implications

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ABSTRACT

Background: Bipolar disorder (BD) has been associated with cognitive impairment during depressed, manic and euthymic periods. Inflammation has been shown to be involved in the pathophysiology of BD and cognitive impairment.
Methods: For this systematic review, the MEDLINE/PubMed, Embase, Google Scholar and ClinicalTrials.gov databases were searched for relevant articles assessing the association between cognitive function and inflammatory markers in BD subjects. A discussion of potential mechanisms and therapeutic implications is also included to provide further context to the subject matter.
Results: Eight studies, including a total of 555 BD subjects, assessing the association between cognitive function and inflammatory markers were identified. Cognitive dysfunction was associated with elevated levels of pro-inflammatory markers YKL40, IL-6, sCD40L, IL-1Ra, hsCRP and TNF-α. Mechanistically, elevation in inflammatory cytokines alters monoamine levels leading to cognitive and affective dysfunction. Neuro-inflammation, manifesting as microglial activation, leads to increased oxidative stress, pathologic synaptic pruning and impaired neuroplasticity in key brain regions sub-serving mood and cognition. Immune dysfunction also activates the hypothalamic–pituitary–adrenal (HPA) axis leading to hypercortisolemia and metabolic dysfunction, further promoting neuronal dysfunction. Anti-inflammatory agents are therefore currently being investigated in the treatment of BD and appear to exert an antidepressant effect; however, cognitive outcomes have yet to be reported.
Conclusion: Several studies suggest that immune dysfunction is associated with cognitive impairment in BD. Several neurobiological pathways have been identified whereby immune dysfunction may promote cognitive impairment in BD. Future investigations of anti-inflammatory agents targeting cognitive function as a treatment outcome are merited.

Contents

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1. Introduction

Bipolar disorder (BD) is a highly prevalent and disabling illness associated with significant morbidity and mortality (Kupfer, 2005; Fagiolini et al., 2013). In the last twenty years, cognitive deficits have been well established as a core characteristic of BD and have been recognized as an important predictor of functional impairment in personal, occupational and social domains (Green, 2006; Tse et al., 2014). Because of this, cognition became a significant target for both pharmacological and non-pharmacological interventions. Moreover, cognitive dysfunction has both mood-dependent and mood-independent aspects in BD, as evidenced by the persistence of cognitive dysfunction throughout periods of euthymia (Bourne et al., 2013). Several cognitive domains have been shown to be consistently and robustly affected in BD, including but not limited to verbal memory, attention and executive function (Martinez-Aran et al., 2004; Robinson and Ferrier, 2006; Bourne et al., 2013). Although multiple original studies as well as meta-analyses have now confirmed the presence of significant cognitive impairment in BD (Robinson and Ferrier, 2006; Bourne et al., 2013; Lee et al., 2014; Samame et al., 2014), the neurobiological substrates sub-serving this observed impairment have yet to be fully elucidated.

Immune dysfunction has been proposed as a potential key neurobiological substrate of cognitive impairment in BD (Barbosa et al., 2014b; Bauer et al., 2014). Over the past several years, inflammation has been repeatedly shown to play a significant role in the pathophysiology of mood disorders (McNamara and Lotrich, 2012; Rosenblat et al., 2014; Rosenblat and McIntyre, 2015). As such, several inflammatory medical co-morbidities including inflammatory bowel disease (IBD), systemic lupus erythematosis (SLE), autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), migraine, rheumatoid arthritis (RA), obesity, atherosclerosis and type II diabetes mellitus have been associated with increased rates of BD (Lilliker, 1980; Cassidy et al., 1999; Kupka et al., 2002; Edwards and Constantinescu, 2004; McIntyre et al., 2005; Bachen et al., 2009; Calkin et al., 2009; Eaton et al., 2010; Han et al., 2011; Hsu et al., 2014; Perugi et al., 2014). Epidemiological studies revealing these associations between inflammatory comorbidities and BD provide the impetus for further investigations of the interaction between BD and inflammation {Rosenblat, 2015 ; Eaton, 2010}. Aside from inflammatory medical comorbidities, several other factors may result in inflammation, including but not limited to undiagnosed inflammatory medical comorbidities, history of early childhood adversity, chronic oxidative stress, a dysfunctional gut-microbiota and low-grade, idiopathic systemic inflammation (Bercik, 2011; Brietzke et al., 2012; Cryan and Dinan, 2012; Fagundes et al., 2013; Post et al., 2013).

Several studies have now shown pro-inflammatory cytokines to be elevated during periods of depression, mania and euthymia, indicative of a chronic, low-grade inflammatory state (Breunis et al., 2003; O'Brien et al., 2006; Brietzke et al., 2009a, 2009b; Drexhage et al., 2011; Modabbernia et al., 2013; Barbosa et al., 2014a). More specifically, serum levels of pro-inflammatory molecules interleukin-4 (IL-4), tumor necrosis factor alpha (TNF-α), soluble interleukin-2 receptor (sIL-2R), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), soluble receptor of TNF-alpha type 1 (STNFR1) and C-reactive protein (CRP) are elevated in BD patients compared to healthy controls (Barbosa et al., 2014a). Of note, several studies suggest that cytokine levels may vary depending on mood state. During periods of euthymia, sTNFR1 is the only consistently elevated inflammatory marker (Brietzke et al., 2009a; Barbosa et al., 2013, 2014a). During manic episodes, serum levels of IL-6, TNF-α, sTNFR1, IL-RA, CXCL10, CXCL11, and IL-4 have been shown to be elevated (Liu et al., 2004; Barbosa et al., 2013, 2014a, 2014b). During depressive episodes, serum levels of sTNFR1 and CXCL10 are elevated (Barbosa et al., 2014a, 2014b). Only a limited number of studies have investigated cytokine levels of BD during depressive episodes; however, more robust cytokine studies investigating major depressive episodes (MDEs) in major depressive disorder (MDD) have demonstrated elevation in serum levels of TNF-α, IL-6 and IL-1β (Dantzer et al., 2008; Eller et al., 2009; Felger and Lotrich, 2013; Rosenblat et al., 2014). Taken together, serum cytokine levels in BD patients are suggestive of a chronic low-grade inflammatory state (Barbosa et al., 2014b). Further, peripheral serum cytokines may traverse the blood-brain-barrier through leaky regions leading to elevated cerebral spinal fluid (CSF) cytokine levels with resultant neuro-inflammation propagation (Weller et al., 1996; Miller et al., 2013; Rosenblat et al., 2014). In addition, a recent study showed functional lymphatic vessels lining the dural sinuses in an animal model (Louveau et al., 2015). This breakthrough discovery contradicted the conventional thinking that the central nervous system (CNS) was devoid of a classical lymphatic drainage system. The presence of lymphatic vessels in the CNS thus provides an additional potential avenue for cytokines to be transported to and from the brain.

Several pathophysiological mechanisms have been proposed and investigated to understand the interaction between inflammation and mood symptomatology in BD; however, significantly less investigation has been conducted to elucidate the effect of inflammation on the domain of cognition in BD (Stewart et al., 2009; Barbosa et al., 2014a; Khandaker et al., 2014; Rosenblat and McIntyre, 2015). Given the significant functional impairment caused by cognitive dysfunction in BD, an improved understanding of its pathophysiology may be of great interest with the potential for significant therapeutic implications (Green, 2006; Tse et al., 2014). Therefore, the objective of the current systematic review is to summarize and synthesize the extant literature describing the relationship of inflammation (as identified by changes in inflammatory markers) with cognitive impairment in BD. To provide further context to this topic, a narrative review of potential mechanisms facilitating this interaction was conducted. Additionally, a discussion of potential therapeutic implications and