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Research paper

Inflammatory cytokines influence measures of white matter integrity in Bipolar Disorder

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ABSTRACT

Background: Bipolar Disorder (BD) is associated with elevated biomarkers of cell-mediated immune activation and inflammation and with signs of widespread disruption of white matter (WM) integrity in adult life. Consistent findings in animal models link WM damage in inflammatory diseases of the brain and serum levels of cytokines.

Methods: With an exploratory approach, we tested the effects of 22 serum analytes, including pro- and anti-inflammatory cytokines and neurotrophic/hematopoietic factors, on DTI measures of WM microstructure in a sample of 31 patients with a major depressive episode in course of BD. We used whole brain tract-based spatial statistics in the WM skeleton with threshold-free cluster enhancement of DTI measures of WM microstructure: axial (AD), radial (RD), and mean diffusivity (MD), and fractional anisotropy (FA).

Results: The inflammation-related cytokines TNF-α, IL-8, IFN-γ and IL-10, and the growth factors IGFBP2 and PDGF-BB, shared the same significant associations with lower FA, and higher MD and RD, in large overlapping networks of WM fibers mostly located in the anterior part of the brain and including corpus callosum, cingulum, superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate, forceps, corona radiata, thalamic radiation, internal capsule.

Conclusions: Higher RD is thought to signify increased space between fibers, suggesting demyelination or dysmyelination. The pattern of higher RD and MD with lower FA suggests that inflammation-related cytokine and growth factor levels inversely associate with integrity of myelin sheaths. The activated inflammatory response system might contribute to BD pathophysiology by hampering structural connectivity in critical cortico-limbic networks.

1. Introduction

Changes of white matter (WM) microstructure and oligodendroglia have been associated with Bipolar Disorder (BD). *Post mortem*, brains of patients with BD showed a substantial reduction of the numerical density of oligodendroglial cells (Manji et al., 2000; Ongur et al., 2014; Rajkowska and Miguel-Hidalgo, 2007; Uranova et al., 2004). *In vivo*, diffusion tensor imaging (DTI) studies consistently documented a pattern of higher mean diffusivity of water (MD), with higher diffusivity perpendicular to the main axis of brain WM tracts, although coated by myelin sheaths (radial diffusivity, RD), and lower diffusivity along the main axis of the WM fiber (axial diffusivity), altogether resulting in a lower preferential diffusivity along WM tracts (fractional anisotropy, FA). These measures reflect the myelination, orientational coherence, and microtubular axonal structure of fibers (Benedetti and Bollettini, 2014; Heng et al., 2010; Marlinge et al., 2014), and their changes have been associated both, with the genetic risk for BD (Chaddock et al., 2009; Whalley et al., 2013), and with environmental stressors increasing the risk (Benedetti et al., 2014b), and are counteracted by lithium salts, the mainstay for the treatment of BD (Benedetti et al., 2013). Changes of WM microstructure also associate with core clinical features of BD including impulsivity and suicide (Matsuo et al., 2010), cognitive performance (Oertel-Knochel et al., 2014; Poletti et al., 2015a), and response to

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treatment (Bollettini et al., 2015). Altogether, DTI studies support the hypothesis that changes of WM microstructure in circuitries critical for emotional and cognitive processing could be linked with BD psychopathology (Benedetti et al., 2011b), and that WM alterations in BD are a potential target for drug discovery and development (Marlinge et al., 2014).

Elevated biomarkers of cell-mediated immune activation and inflammation, in the absence of active somatic immune diseases, have been consistently reported in mood disorders (see reviews in (Bergink et al. (2014), Dantzer (2012) and Leonard and Maes (2012)), including BD (Anderson and Maes, 2015). Pivotal studies associated the activation of the inflammatory response system with vulnerability for mood disorders (Mesman et al., 2015; Padmos et al., 2009), diagnosis of BD (Padmos et al., 2008), and core clinical features including depressive cognition (Alesci et al., 2005; Steiner et al., 2013), course of illness (Haarman et al., 2014), and response to treatment (Benedetti et al., 2002; Lanquillon et al., 2000; Maes et al., 1997). Peripheral cytokines can enter the brain by volume diffusion, or via active cytokine transporters at the blood–brain barrier (Dantzer et al., 2008). According to the inflammation theory of mood disorders, the deregulation of the immune system involves both, elevated peripheral markers of macrophage/monocyte inflammatory activation patterns, and activation of microglia into the brain (Beumer et al., 2012; Drexhage et al., 2010). Microglia participates in neurogenesis, axon remodeling, synaptogenesis, synaptic pruning, synaptic remodeling, and developmental cell death, and its inflammatory activation disrupts these processes by lack of provision of neuronal growth factors or by producing neurotoxic factors and cytokines (Beumer et al., 2012; Drexhage et al., 2010).

Cytokines can influence the cell fate of oligodendrocytes, and even moderate systemic inflammation alters WM development, also including production of serum cytokines which in the periphery induce, in a bystander fashion, activation of monocytes and T cells (Favrais et al., 2011; Martino et al., 2000). It can be surmised that the detrimental effects of the pro-inflammatory state might involve WM microstructure in BD. Oligodendrocytes have immune functions, express innate immune receptors, produce and respond to chemokines and cytokines that modulate immune responses, and maintain a cross-talk with microglia (Peferoen et al., 2014; Zeis et al., 2015). Microglia modulate the wiring of the embryonic forebrain (Squarzoni et al., 2014), and in a model of maternal inflammation, activation of the immune system altered microglial activity resulting in the de-fasciculation of dorsal callosal axons (Pont-Lezica et al., 2014). Microglia also promotes re-myelination by secreting several growth factors, and the oligodendrocyte damage observed in inflammatory disorders of the brain may also be immune mediated (Peferoen et al., 2014). The toxic inflammatory potential of activated microglia (Beumer et al., 2012) could extend to oligodendrocytes, thus contributing to explain the changes of WM microstructure associated with BD (Benedetti et al., 2011b).

Existing literature provides no evidence of concurrent WM abnormality and elevated pro-inflammatory cytokines in patients with BD. Indeed, few studies addressed this issue and reported no association between WM structure and IL-1RA (Lotrich et al., 2014), and higher levels of ICAM-1 in *post-mortem* WM and GM of patients with BD compared to unipolar depression, schizophrenia and healthy controls, consistent with the presence of an inflammatory response in BD WM (Thomas et al., 2004). With an exploratory approach, here we studied the relationship between a panel of inflammation related cytokines and growth factors with WM microstructure in a sample of patients with a major depressive episode in course of BD.

2. Methods

2.1. Participants and clinical measures

We studied 31 consecutively admitted inpatients affected by a major depressive episode, without psychotic features, in course of Bipolar Disorder type I, Given the proposed relationship between lifetime stress, inflammation, and depression (Raison et al., 2006), we rated the exposure to early (between age 5 and 15) and recent (last 3 years) stressful life events using instruments validated in patients with BD: Risky Family Questionnaire (RFQ) (Benedetti et al., 2014a), Social Readjustment Rating Scale (SRRS) (Benedetti et al., 2014b), Childhood Trauma Questionnaire (CTQ) (Janiri et al., 2015), and Perceived Stress Scale (PSS) (Cohen et al., 1983).

To be included in the study the patients had to meet the following criteria: to be willing to participate; a baseline Hamilton Depression Rating Scale (HDRS) score of 18 or higher; absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, major medical and neurological disorders; no treatment with long-acting neuroleptic drugs in the last three months before admission; absence of a history of drug or alcohol dependency or abuse within the last six months. The study was performed within the frame of the MOODINFLAME and PSYCHAID study (http://moodinflame.eu/), two large-scale European medical scientific projects aiming to advance early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system. Additional MOODINFLAME exclusion criteria were inflammation related symptoms, including fever and infectious or inflammatory disease; uncontrolled systemic disease; uncontrolled metabolic disease or other significant uncontrolled somatic disorder known to affect mood; somatic medications known to affect mood or the immune system, such as corticosteroids, non-steroid anti-inflammatory drugs and statins. Physical examinations, laboratory tests and electrocardiograms were performed at admission. Blood sampling was performed in the morning for all patients. After complete description of the study to the subjects, a written informed consent was obtained. All the research activities were approved by the local ethical committee. All patients were recruited and underwent MRI scanning in Milano, while immunological determinations were made in Rotterdam and in Münster.

2.2. Laboratory determinations

We studied a panel of 22 molecules, known to interact with oligodendrocytes (Peferoen et al., 2014; Zeis et al., 2015) and with BD (Bergink et al., 2014; Dantzer, 2012; Leonard and Maes, 2012). Cytokines: Tumor necrosis factors α (TNF-α), Interferon γ (IFN-γ), Interleukin 5 (IL-5), Interleukin 6 (IL-6), Interleukin 7 (IL-7), Interleukin 8 (IL-8), Interleukin 10 (IL-10), monocyte chemotactic protein 1 (MCP1), C-X-C motif chemokine 10 (CXCL10), Pentraxin-related protein (PTX3), Granulocyte-colony stimulating factor (G-CSF), vascular cell adhesion molecule 1 (VCAM-1), Intercellular Adhesion Molecule 1 (ICAM-1), interleukin-1 receptor antagonist (IL-1RA), interleukin 2 receptor alpha (IL-2RA); Neurotrophic/hematopoietic growth factors: brain derived neurotrophic factor (BDNF), S100 calcium binding protein B (S100B), Stem Cell Factor (SCF), Insulin-like Growth Factor-Binding Protein 2 (IFGBP-2), Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor-BB (PDGF-BB) and Vascular Endothelial Growth Factor (VEGF). Serum concentrations of all these molecules were measured using the bead-based Luminex system. These multiplexed sandwich immunoassays were developed from commercially available capture and detection antibodies and standard proteins, validated and approved at EDI-GMBH according to methods described previously (Schmohl et al., 2012). Assays were measured on either the