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Research paper

Inflammation associated with volume reduction in the gray matter and hippocampus of older patients with bipolar disorder

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A B S T R A C T

Background: Bipolar disorder (BD) and aging appear to be associated with inflammatory activation. Inflammatory processes might affect hippocampal function, neurogenesis, and gray matter loss. This study investigated the relationship between BD-specific brain regions and the total gray matter volume, peripheral inflammatory markers, and clinical features in older patients with BD.

Methods: We recruited euthymic patients with bipolar I disorder aged ≥50 years to undergo whole-brain magnetic resonance imaging. Each brain region was divided by an individual's total intracranial volume to obtain that brain region's volume in percentage relative to the total intracranial volume. We measured the plasma levels of soluble tumor necrosis factor receptor-1 (sTNF-R1), soluble interleukin (IL)-2 receptor (sIL-2R), sIL-6R, IL-1β, and IL-1 receptor antagonist when patients were euthymic. Clinical data were obtained by reviewing available medical records and interviewing patients along with their reliable others.

Results: There were 32 patients with a mean age of 61.2 ± 8.3 years and a mean age at illness onset of 33.4 ± 13.8 years in this study. Stepwise regression showed that the right hippocampal volume was negatively associated with the levels of sIL-2R and sTNF-R1. The left hippocampal volume were negatively associated with the sIL-2R level and body mass index. The total gray matter volume had an inverse relationship with sTNF-R1 and IL-1β levels. The duration of bipolar illness, lithium treatment, and antipsychotic use were not associated with hippocampal and total gray matter volumes.

Conclusions: It is suggested that persistent inflammation is associated with reduction of hippocampal and gray matter volumes in older patients with BD. This phenomenon is supported by increases in sTNF-R1, sIL-2R, and IL-1β levels. Neuroinflammation due to aging, obesity, and BD pathophysiology may play a role in BD neuroprogression across the life span.

1. Introduction

Studies on bipolar disorder (BD) have suggested the involvement of immune system dysfunctions in the disease activity of BD (Goldsmith et al., 2016). Furthermore, progressive neuropathological processes (Berk et al., 2011) and various mood phases (Tsai et al., 1999; 2012; 2014) in BD may be linked to alterations in inflammatory cytokines. Microglia, the concentration of which is particularly high in the hippocampus, primarily mediate innate immunity and are involved in most inflammatory processes in the central nervous system (CNS) (Badoer, 2010; Perry et al., 1993). In addition, microglia are activated in response to peripheral inflammation (Carson 2002). Chronic microglial activation can result in neuronal apoptosis, neurogenesis inhibition, and hippocampal volume reduction (Ascoli et al., 2016). There is growing evidence that BD may involve microglial activation in the hippocampus and alterations in peripheral cytokines. Therefore, the neuron–glia interaction is considered a pathophysiological mechanism underlying BD with a potential link between neuroinflammation and peripheral toxicity (Pinto et al., 2018).

The hippocampus plays a key role in BD pathophysiology (Small et al., 2011). Current BD models conceptualize the hippocampus as a crucial node in the prefrontal–hippocampal–amygdala emotion-processing circuit, which is underactive in BD (Phillips et al., 2014). The neuroanatomic abnormalities of BD include ventricular enlargement, gray matter loss in the hippocampus, and variations in the size of the amygdala (Hallahan et al., 2016; Otten et al., 2015; Rimol et al., 2010; Roda et al., 2015). Impaired adult hippocampal neurogenesis and increased levels of circulating cytokines (e.g., IL-2, IL-6, and TNF-a) have been consistently reported in major depression (Miller et al., 2009) and schizophrenia (Na et al., 2014). Higher peripheral inflammatory marker levels are associated with a more severe deficit in brain structural and connectivity abnormalities implicated in BD

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(Chung et al., 2013; Tu et al., 2017). A link was observed between peripheral inflammatory markers and volumetric anomalies in the brains of elderly individuals (Frodl et al., 2014). Aging results in exaggerated immune responsiveness typified by increased proinflammatory cytokine production and signaling (Sierra et al., 2007; Ye and Johnson 2001). Brain microglia become dysregulated with age and cause chronic neuroinflammation. This age-related microglial activity may be specific to the hippocampus and hypothalamus (Ojo et al., 2015; Tang et al., 2015). An elevated sIL-2R level, as an in vitro marker of cell-mediated immunity, has been commonly observed in acute affective episodes and euthymia of BD (Tsai et al., 1999; Maes and Carvalho 2018). The increase in sIL-2R production is linked to the activation of Th1 lymphocytes that triggers the activation of microglia in response to peripheral inflammation (Carson 2002; Cherry et al., 2014). Therefore, inflammation involves in brain volume reductions in psychiatric disorders and normal aging (Tu et al., 2017; Frodl et al., 2014). Furthermore, abnormal amygdala neurodevelopment is noted in adolescent onset BD and possible changes in hippocampus require further evaluation (Lim et al., 2013). Studying patients with BD in old age can help identify neuroprogressive changes caused by aging and inflammation that occur during a longstanding illness (Cao et al., 2016; Lim et al., 2013; Gildengers et al., 2014). However, relatively few studies have focused on the association between peripheral inflammatory markers and the hippocampus and amygdala, in patients with BD after middle age.

A high level of interleukin (IL)-1β, a key inflammatory mediator synthesized and released mainly by microglia and astrocytes, is expressed in the brain, particularly in the hippocampus (Lechan et al., 1990). The IL-1 family may contribute to cognitive impairments in elderly patients with BD (Lotrich et al., 2014). Among older adults, increased circulating inflammatory biomarkers were associated with smaller brain volume and cortical thickness. Therefore, that peripheral inflammatory processes may be involved in the brain atrophy in the elderly (Gu et al., 2017). Since peripheral IL-6 and TNFα are considered to be mainly macrophage-derived cytokines, the over-activity of monocytes are capable of transmigrating into tissue differentiating as macrophages and phagocytosing cellular and subcellular substrates in tissues, possibly the brain, in people with psychotic disorders (Boerrigter et al., 2017). It is unclear how well the most frequently used method of assessing inflammation, i.e. peripheral (blood) inflammation, reflects or maps on to the central nervous system (CNS) immune milieu. However, a recent meta-analysis found support for elevated cerebrospinal fluid IL-6 correlating with plasma IL-6 levels in recent-onset schizophrenia (Radhakrishnan et al., 2017). On the basis of these findings, we hypothesized that some circulating levels of inflammatory markers can be negatively associated with gray matter and hippocampal volumes in older patients with BD. Therefore, because of the literature evidence we focused on the soluble tumor necrosis factor receptor-1 (sTNF-R1), IL-1β, soluble IL-2 receptor (sIL-2R), sIL-6R, and IL-1receptor antagonist (IL-1Ra), rather than other inflammatory markers (Munkholm et al., 2013). The present exploratory study examined relationships among the clinical characteristics of BD, various parameters of inflammation, and volumes of specific brain regions in older patients with BD.

2. Methods

2.1. Participants

Patients were enrolled from Taipei Medical University Hospital (TMUH), Taiwan. Using the computer data of hospital, we recruited all patients who met the following criteria: (1) age ≥ 50 years; (2) a final diagnosis of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) bipolar I disorder; and (3) at least one psychiatric admission to TMUH before the start of the study. Exclusion criteria were (1) any type of dementia (DSM-IV), (2) mental disorders associated with general medical conditions, (3) active substance abuse, or (4) inability to undergo brain imaging. Written informed consent, as approved by the Institutional Review Board of TMUH, was required from all patients participating in this study.

2.2. Clinical data collection

We obtained patients' data by reviewing their medical records and by directly interviewing them and their reliable family members. Patients were interviewed by two experienced psychiatrists using the Chinese version of the Structured Clinical Interview for DSM-IV, patient edition, to confirm the diagnosis of bipolar I disorder as well as the history of any psychiatric disorder. The Young Mania Rating Scale (YMRS) (Young et al., 1978) scores and 21-item version Hamilton Depression Rating Scale (HAMD-21) (Hamilton 1967) scores were used to assess the severity of affective symptoms. All data extracted from medical records were subsequently rechecked to eliminate any potential errors. The obtained information included demographic data, clinical features, physical illness, family history, and laboratory examination results collected during the last acute psychiatric admission.

2.3. Magnetic resonance imaging (MRI) acquisition image collection

Brain MRI of each patient was performed using a 1.5-T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with three pulse sequences: (1) 124 contiguous, 1.2-mm-thick axial planes of 3-dimensional, T1-weighted images (spoiled gradient recalled acquisition in the steady state, repetition time [TR] = 40 ms, echo time [TE] = 7 ms, flip angle = 90°, and voxel size = 0.86 mm × 0.86 mm × 1.2 mm); (2) 58 contiguous, 3-mm-thick axial planes of proton density images (spin echo [SE], TR = 2860 ms, TE = 15 ms, and voxel size = 0.86 mm × 0.86 mm × 3 mm); and (3) 58 contiguous, 3-mm-thick axial planes of T2-weighted images (SE, TR = 2860 ms, TE = 120 ms, and voxel size = 0.86 mm × 0.86 mm × 3 mm). Before further computation, all magnetic resonance images were converted into the ANALYZE format by using MRIcro software (1.40 build 1; www.mccauslandcenter.sc.edu/CRNL/).

2.4. Image analysis

Image analysis was performed using the FMRIB software library (FSL 3.3). After acquisition, T2-weighted images and Proton density (PD) images were coregistered and resliced into T1 native spaces by using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002). Subsequently, multi-channel image segmentation using T1-weighted, PD, and T2-weighted images was performed using the fast tool to generate different tissue probability map images (e.g., gray matter image, white matter image, and cerebrospinal fluid [CSF] image) (FMRIB's Automated Segmentation Tool) (Zhang et al., 2001). The underlying method of image segmentation was based on a hidden Markov random field model and an associated expectation-maximization algorithm. The whole process was automated and could produce different segmented probabilistic tissue volume images. After the segmentation procedure, the brain tissue was classified into different tissue types (e.g., gray matter, white matter, and CSF) while correcting for spatial intensity variations (also known as a bias field). Finally, the individually segmented gray matter mask was automated and labeled into 116 different cortical regions, and the volume of each region was calculated using the Individual Brain Atlases by using the Statistical Parametric Mapping Software toolbox. The Statistical Parameteric Mapping program package is one popular method to measure the intracranial volume (ICV). The total intracranial volume calculated by the summation of the gray matter, white matter, and CSF volumes was also recorded. For further interindividual comparison of different brain regions, each brain region was divided by an individual's total intracranial volume to obtain the brain region volume in percentage