Published in final edited form as:

Brain Behav Immun. 2020 August ; 88: 403–410. doi:10.1016/j.bbi.2020.04.003.

TNF- α and its soluble receptors mediate the relationship between prior severe mood episodes and cognitive dysfunction in euthymic bipolar disorder

C.E. Millett^{1,2,*}, J. Harder^{1,2,*}, J.J. Locascio⁴, M. Shanahan^{1,4}, G. Santone³, R. Fichorova³, A. Corrigan¹, C. Baecher-Allan^{5,6}, K.E. Burdick^{1,2}

¹Mood and Psychosis Research Program, Department of Psychiatry, Brigham and Women's Hospital, Boston, MA

²Department of Psychiatry, Harvard Medical School, Boston, MA

³Laboratory of Genital Tract Biology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁴Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital and Harvard Medical School

⁵Ann Romney Center for Neurologic Disease, Harvard Medical School, Boston, MA 02115 USA

⁶Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115 USA

Abstract

Background: Bipolar disorder (BD) is one of the most disabling mental health conditions in the world. Symptoms of cognitive impairment in BD contribute directly to occupational and social deficiencies and are very difficult to treat. Converging evidence suggests that BD patients have increased peripheral markers of inflammation. The hypothesis of neuroprogression in BD postulates that cognitive deficits develop over the course of the illness and are influenced by prior severe mood episodes, leading to wear-and-tear on the brain— however, there exists a paucity of data statistically testing a mediating role of immune molecules in cognitive dysfunction in BD.

Methods: This is a cross-sectional study. We measured serum levels of tumor necrosis factor alpha (TNF- α), and soluble (s) TNF receptors one and two (sTNF-R1 and sTNF-R2) in 219 euthymic BD patients and 52 Healthy Controls (HCs). Structural equation modeling (SEM) was used for the primary purpose of assessing whether TNF markers (measured by the multiple

Corresponding author contact: Katherine E Burdick, PhD, Brigham and Women's Hospital, 221 Longwood Ave, Suite 4-42, Boston, MA, 02115, Phone: 617-732-5789, kburdick1@bwh.harvard.edu.

* authors contributed equally to this work.

Disclosures:

Dr. Burdick has served as an advisory board member to Dainippon Sumitomo Pharmaceutical Neuralstem, and Takeda-Lundbeck. All other authors have nothing to disclose.

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indicators TNF- α , sTNF-R1 and sTNF-R2) mediate the effect of number of prior severe mood episodes (number of prior psychiatric hospitalizations) on cognitive performance.

Results: BD and HC groups did not differ on circulating levels of TNF molecules in the present study. However, we found higher sTNF-R1 concentration in ‘late-stage’ BD illness (>1 prior psychiatric hospitalization) compared to those in early stage illness. In the subsequent SEM, we found that the model fits the data acceptably (Chi-square= 49.2, $p=0.3$), and had a ‘close fit’ (RMSEA= 0.02, PCLOSE= 0.9). Holding covariates constant (age, sex, premorbid IQ, education, and race), we found that the standardized indirect effect was significant, $p=0.015$, 90% CI [-0.07, -0.01], indicating that the estimated model was consistent with peripheral TNF markers partially mediating a causal effect of severe mood episodes on executive function.

Conclusions: Our results indicate that circulating levels of TNF molecules partially mediate the relationship between prior severe mood episodes and executive function in BD. These results may implicate TNF variables in the neuroprogressive course of BD and could point to novel interventions for cognition.

Keywords

cognition; mood disorder; euthymia; inflammation

1. Introduction

Bipolar disorder (BD) is a chronic mental illness associated with functional decline, mortality, and significant health care costs (Ferrari et al., 2013). Significant cognitive impairment has been found in 40–60% of people with BD (Burdick et al., 2011), and such impairments are thought to underlie functional deficits seen in this disorder (Depp et al., 2016). Thus far cognitive impairment has not been successfully targeted by treatment. In recent decades, the immune system has emerged as an important candidate mechanism underlying the onset and progression of BD. BD has been categorized as a multisystem inflammatory disease due to the high rate of inflammatory illnesses associated with the disorder (Leboyer et al., 2012). Yet much is still unknown about the potential for inflammatory molecules as treatment targets in this debilitating mental illness. Elucidating the immunological markers underlying the disease that are associated with BD’s clinical features, may hold answers in the future for such understanding.

The term *neuroprogression* has been used to describe the pathological brain changes that occur over time in BD (F. Kapczinski et al., 2014a). Evidence suggests that BD is a neuroprogressive condition, with declines in baseline functioning observable in a large proportion of patients (López-Villarreal et al., 2019; Rosa et al., 2010). Cognitive and functional decline have been associated with course of illness (including number of mood episodes, duration of illness, and number of prior psychiatric hospitalizations) (Bourne et al., 2013; Martinez-Aran et al., 2007; Torrent et al., 2012) which is thought to reflect a stepwise cumulative effect, tied directly to the ‘wear and tear’ on the brain (F. Kapczinski et al., 2014b; Lewandowski et al., 2011). The biological mechanisms that drive this declining course are unknown, but recent evidence suggests a key role for inflammation.

Many peripheral inflammatory cytokines are upregulated during acute manic and depressive states in BD. These acute elevations typically return to “normal” levels (similar to those of HCs) during euthymic periods (Berk et al., 2011). Acutely elevated inflammatory markers rise to a level that is intermediate between the healthy state and the highly inflamed state of sepsis (Kauer-Sant’Anna et al., 2009; Panizzutti et al., 2015; Siwek et al., 2017a; Tatay-Manteiga et al., 2017), with attenuated recovery in later stages of the illness, resulting in low-grade chronic inflammation.

One marker that has been consistently implicated in *late-stage* BD is the pro-inflammatory cytokine tumor necrosis factor- α (TNF- α), which increases as the illness progresses (Kauer-Sant’Anna et al., 2009). TNF- α soluble receptors— sTNF-R1 and sTNF-R2— have also been linked to the pathophysiology of BD (Siwek et al., 2017b). A recent meta-analysis found that levels of TNF- α are significantly increased in mania and bipolar depression but not in euthymic periods (Rowland and Marwaha, 2018). Another study suggests that TNF- α levels may drop after an acute episode is treated, whereas sTNF-R1 and sTNF-R2 levels may be persistently elevated in the euthymic period (Doganavsargil-Baysal et al., 2013). Importantly, an inverse association between TNF family molecules and cognition in BD has been suggested (Hope et al., 2015a; Hoseth et al., 2016). TNF family molecules are found at higher concentrations in later stages of BD, which are marked by persistent cognitive impairment in euthymia (Kauer-Sant’Anna et al., 2009).

There remains a gap in our understanding as to *whether and how* TNF family molecules propagate cognitive deterioration in BD. Few studies have directly tested the mediating properties of the TNF family of molecules on the neuroprogressive pathway in BD. To directly test this question, we developed a structural equation model (SEM) to examine whether TNF family molecules exhibit a mediating effect on prior severe mood episodes and cognitive outcomes in BD.

2. Methods

2.1 Participants

Participants with BD-I and BD-II based on DSM-IV criteria (n=219, ages 18–65) were euthymic and recruited as outpatients from the Icahn School of Medicine at Mount Sinai Hospital (ISMMS). Criteria for exclusion for the BD participants included the inability to consent, current affective instability indicated by a score of >8 on the Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960), and/or on the Young Mania Rating Scale (YMRS)(Young et al., 1978). Further exclusionary criteria included current diagnosis of mild cognitive impairment (MCI) or dementia, a history of CNS trauma, an active and unstable medical condition that interferes with cognition, neurological disorder, known learning disability or childhood onset ADHD, substance abuse or dependence within 3 months of study visit, medications that are known to reduce (i.e., topiramate, tricyclics, anticholinergics), or enhance cognition (e.g., dopamine agonists or amphetamine), and electroconvulsive therapy (ECT) in the last year.

The Healthy Control (HC) participants (n=52, ages 20–70) were recruited through advertisements. Exclusionary criteria were the same as those for the BD group, with the

exception that the presence of an Axis-I disorder was exclusionary. The study was approved by the Institutional Review Board (IRB) at ISMMS, and all participants gave written informed consent prior to participating in the study.

Approximately 386 individuals were screened for the BD group. From this group, 149 were excluded for various reasons (consented but deemed ineligible (n=66), 'no show' for the study appointment (n=75), did not complete the study (n=6) or had compromised data (n=4)). Of the remaining participants, 224 had available cytokine data. 5 individuals were further excluded due to key missing clinical or neurocognitive data (final n=219).

2.2 Clinical Measures

The BD and HC participants were assessed for diagnostic eligibility using the Structured Clinical Interview for the DSM-IV (SCID-IV). Depressive and manic mood states were assessed with the HDRS and YMRS, respectively, and were administered within one week of neurocognitive testing. For those with a BD diagnosis, a trained staff member assessed and recorded illness features (derived from the SCID), including age at onset, number and type of prior episodes and prior psychiatric hospitalizations, BD and psychotic subtype, rapid cycling and comorbid axis I diagnoses (current and lifetime).

2.3 Neurocognitive Measures

We administered tests to assess executive function including the Controlled Oral Word Association Task (COWAT)(Benton et al., 1994), the Stroop color and word test (Golden, 1978) and the Wisconsin Card Sorting Task (WCST)(Grant and Berg, 1948). Z-scores were calculated for cognitive data in the BD group (normalized using the HC group), for subsequent analyses. We also assessed neurocognition for all participants using the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). All neurocognitive scores from the MCCB were standardized on a T scale score (mean=50, SD=10), and age and sex adjusted using published MCCB normative data.

2.4 Blood Biomarker Analysis

Samples were drawn via venous blood draw, in a serum separator tube by a trained staff member. Samples were stored at -80°C until used. Concentrations of TNF α , sTNF-R1 and sTNF-R2 were quantified at the Genital Tract Biology Laboratory at Brigham and Women's Hospital (under accreditation by the College of American Pathologists) using an electrochemiluminescence (ECL) multiplex-based assay platform with a S600 Meso Scale Discovery (MSD) reader (MSD, Gaithersburg, MD). The ECL platform is highly sensitive with a 5-log scale of linearity, with lowest level of detection (LLD) for TNF 3.96 pg/ml, sTNF-R1 2.6 pg/ml and sTNF-R2 – 0.226 pg/ml. Samples were run undiluted for TNF α , and diluted to fit the linearity range of the soluble receptors – 4-fold for the sTNF-R1 and 10-fold and 50-fold for the sTNF-R2 assay. Two split quality control samples were run on each ECL assay plate to ascertain reproducibility of measurement across the linearity range of each analyte showing acceptable 10 % inter-assay coefficient of variation (4.59% and 8.69% for TNF α , 9.3 and 10% for sTNF-R1 and 9.16% and 9.99% for sTNF-R2).

2.5 Statistical Analysis

All analyses were performed using the statistical program SPSS (IBM SPSS Statistics version 24, 2016), SPSS Amos Graphics (version 26, 2019, IBM Corp), and R Studio (Version 1.1.442, 2008–2018). Normality of data was assessed using the Kolmogorov-Smirnov test. Demographic differences between groups were assessed using Student's *t* tests and Chi-square tests for continuous and categorical variables, respectively. For non-normally distributed cytokine data, we used the non-parametric Mann-Whitney U test to compare groups. The Box-Cox power transformation approach was used to transform biomarker concentrations into normal distributions for structural equation modeling analyses (Box and Cox, 1964). The Box-Cox lambda for each TNF variable was determined in R software, and variable transformation was performed in SPSS software. For TNF- α , transformation did not result in normalization on the first try. Based on this, one extreme outlier was removed. Subsequent transformation successfully resulted in normality for each marker; Kolmogorov-Smirnov test: TNF- α , $D(219)=0.06$, $p=0.06$; sTNF-R1, $D(219)=0.05$, $p=0.2$; sTNF-R2, $D(219)=0.04$, $p=0.2$. We used the Box-Cox transformed concentrations in subsequent analyses.

2.5.1 Structural Equation Model (SEM)—The SEM was performed using SPSS Amos Graphics (version 26, 2019, IBM Corp). The SEM was used for the primary purpose of assessing whether TNF markers mediate the effect of clinical variables related to neuroprogression on executive function in BD (Bollen, 1989). Our final model was informed by an initial non-significant model which tested for the mediation effect of TNF variables in a simplistic way (using single variables) between clinical variables of disease progression (total number of mood episodes and prior psychiatric hospitalizations) and executive function (initial evaluation of correlations among variables partly suggested the initial model). Based on the lack of fit of our initial model, changes were made based on statistical criteria (“modification indices”) and substantive reasonableness.

A subsequent SEM with both latent and manifest variables was then tested using maximum likelihood estimation. *P*-values were obtained through bootstrapping. The latent variables are shown in ovals and the observed variables are in rectangles in Figure 3. A latent variable, “Peripheral TNF” measured by the multiple indicators TNF- α , sTNF-R1 and sTNF-R2, was hypothesized to mediate the effect of number of prior psychiatric hospitalizations on the latent variable “Executive Function” assessed by a set of observed variables, namely, the neurocognitive tests: COWAT, WCST and Stroop. A separate direct effect of prior psychiatric hospitalization on executive function, apart from the mediation of TNF, was also allowed for in the model. We included five exogenous covariates in the model, namely, sex, age, education, race and premorbid IQ. Incorporation of correlations among exogenous covariates into the model was determined by their statistical significance. Non-significant path coefficients were removed from the model in an iterative process. One non-significant association was retained in the model, between race and executive function, because it reached trend level significance ($p=0.06$). Statistical identification of latent variables was achieved by setting the path coefficient for one of the multiple indicators of each of the latent variables to one (see Figure 3).

2.5.2 Assessment of Model Fit —Goodness of fit of the path model was assessed by examining the Chi-square test (which assesses the fit between the empirical and predicted correlation matrices), and the Root Mean Square of Error Estimation (RMSEA) and PCLOSE measure. A good model was defined by a non-significant p value in the Chi-square test ($p > 0.05$), and a RMSEA value of < 0.06 .

3. Results

3.1 Clinical and demographic data –

Table 1 shows the clinical and demographic data for the participants with BD. The sample was almost half female (47%) and Caucasian (47%), and mostly non-Hispanic (~77%). On average BD participants had 14 years of education (equivalent to some college) and were overweight (BMI > 25). Most participants were taking at least one psychotropic medication (~78%); the average number of meds being taken was 1.7 (± 1.3). The average participant had been ill for about 22.0 (± 11.5) years and had experienced about 24.0 (± 21.2) mood episodes in their lifetime.

In a series of Mann Whitney U Tests, we found no significant main effect of diagnosis (BD and HC) in TNF family molecule concentrations (reported as mean and standard deviation): TNF- α (HC: 3.6 ± 1.7 pg/mL; BD: 3.6 ± 1.6 pg/mL; $p = 0.9$), sTNF-R1 (HC: 3991.0 ± 1193.9 pg/mL; BD: 4174.8 ± 2406.0 pg/mL; $p = 0.9$), and sTNF-R2 (HC: 4540.9 ± 2092.3 pg/mL; BD: 4796.2 ± 2414.0 pg/mL; $p = 0.4$).

3.2 Peripheral TNF in early and late stage BD–

Peripheral TNF concentrations (TNF- α , sTNF-R1, and sTNF-R2) were compared between early vs. late-stage BD (Figure 1). We used psychiatric hospitalizations as a proxy for “severe mood episodes” for three reasons: 1) inpatient hospitalizations for affective mood symptoms are markers for a more severe course of illness and have been shown to predict cognitive function in BD (Levy and Weiss, 2009); 2) Our SCID-based interview is inherently retrospective, the analysis of “total mood episodes” is limited based on patients’ memories. We propose that hospitalizations are a more reliable measure than total mood episodes alone; 3) An episode for which a patient is hospitalized is inherently severe in nature and may therefore contribute more directly to cognitive decline (and therefore be a more reliable estimate of prior course/stage).

Early stage BD was defined as having one or fewer prior psychiatric hospitalizations for either mania or depression; late stage BD was defined as having greater than one prior severe mood episodes. It should be noted that validation of staging for people with BD is still a work in progress, and there is no single accepted clinical cutoff to define early or late stage of illness (F Kapczinski et al., 2014). However, we chose this cutoff based on prior literature which indicated that early or late stage of illness can be defined based on the presence of psychiatric hospitalizations (Cao et al., 2016; Lavagnino et al., 2015; Magalhães et al., 2012). Early and late stage groups did not differ by sex: Chi-square (1, 219) = 2.6 $p = 0.1$, race (dichotomized): Chi-square (1, 219) = 0.35, $p = 0.6$, education: $t(217) = 1.5$ $p = 0.1$, age: $t(217) = -1.2$, $p = 0.2$, or BMI: $t(35) = -1.7$, $p = 0.09$. The groups did not differ on duration

of illness, $t(217)=-1.5$, $p=0.1$, nor number of psychotropic medications $t(217)=-1.8$, $p=0.06$. A series of non-parametric Mann Whitney U tests revealed that sTNF-R1 was significantly higher in late-stage BD ($N=130$, 4440.0 ± 2967.1 pg/mL) relative to early-stage BD ($N=89$, 3787.5 ± 1086.1 pg/mL), $p=0.047$. We did not find a significant difference between early and late stage groups for TNF- α ($p=0.5$) or sTNF-R2 ($p=0.09$).

3.3a Partial correlations between peripheral TNF variables and cognitive tests –

A series of partial correlational analyses (controlled for age and sex), performed prior to the design of the SEM, revealed significant negative associations between TNF- α and executive function measures, including Stroop (Pearson $r=-0.2$, $p=0.005$) and WCST (Pearson $r=-0.2$, $p=0.03$). sTNF-R2 was also significantly associated with Stroop (Pearson $r=-0.2$, $p=0.005$) (Figure 2). The relationship seemed to be specific to executive functioning, as we did not find a significant correlation between TNF variables and the MCCB composite: TNF- α ($r=-0.006$, $p=0.9$), sTNF-R1 ($r=0.1$, $p=0.2$), sTNF-R2 ($r=-0.03$, $p=0.6$).

3.3b Relationship between TNF family molecule, psychiatric hospitalizations, and cognitive function –

The results of the SEM with estimated path coefficients (standardized partial regression coefficients) are shown in Figure 3. The Chi-Square value of 49.2 had a non-significant p -value of 0.3, indicating acceptable model fit. Further, the Root Mean Squared Error Approximation (RMSEA) of 0.02 and PCLOSE of .9 further supported that the model had a 'close fit' (Browne and Cudeck, 1989).

Holding covariates constant (age, sex, premorbid IQ, education, and race), the direct effect (c' path) of prior psychiatric hospitalizations on executive function (EF) is -0.14 (standardized path coefficient), and the direct effect of soluble TNF receptor levels on EF in this model is -0.19 (b path). The indirect effect ($a*b$ paths) of prior psychiatric hospitalizations on EF (using the tracing rule) mediated by TNF is $(0.15 \times -0.19) = -0.03$; thus, the total effect (c path) of hospitalizations on EF is $(-0.14 + (-0.03)) = -0.17$. The path coefficients above are individually significant per the path diagram, and thus by inference the direct (c') effect [std $\beta = -0.138$ (90% CI $[-.26, -.03]$, $p=0.025$)], indirect ($a*b$) effect [std $\beta = -0.028$ (90% CI $[-.07, -.01]$, $p=0.015$)] and total (c) effect [std $\beta = -0.166$ (90% CI $[-.28, -.07]$, $p=0.01$)] are each statistically significant. Thus, this estimated model is consistent with peripheral TNF variables partially (though not completely) mediating a causal effect of psychiatric hospitalizations on executive cognitive function.

4. Discussion

Here we have shown that although TNF family molecules (TNF- α , sTNF-R1, sTNF-R2) are not elevated in euthymic BD compared to HCs, sTNF-R1 is elevated in late-stage BD patients, and these molecules mediate the relationship between the number of severe mood episodes and cognition in BD, with executive function being particularly affected. These results suggest that TNF family molecules may play an important role in the pathophysiology of neuroprogression in BD.

We did not find group differences in soluble TNF family molecules between BDs and HCs. TNF family molecules have previously been reported to be altered in euthymic BD, yet the literature is mixed (Barbosa et al., 2014). Results from several studies suggests that sTNF-R1 is elevated in euthymic BD groups compared to HCs (Modabbernia et al., 2013; Munkholm et al., 2013) with one study also noting elevated sTNF-R2 (Teixeira et al., 2015). Notably, two recent meta-analyses reported either no significant elevation of TNF- α in euthymic BD compared to HCs, or a “normalization” of TNF- α in the euthymic phase of illness. Although meta-analyses indicate an *overall* increase in sTNF-R1 in euthymic BD, a few individual findings are consistent with our results, reporting no significant difference between BD and HC groups in TNF family molecule concentrations.

Few studies have statistically tested for mediating properties of TNF in the neuroprogressive pathway using outcomes such as cognition as markers of progression; however, some have shown that TNF family molecules represent independent markers of illness stage in BD. A few studies have found sTNF-Rs to be positively associated with duration of illness (Barbosa et al., 2011) and number of psychiatric hospitalizations in BD groups (Hope et al., 2013), in line with our present findings. A study comparing levels of TNF- α in 30 early-stage BD (recent first manic episode) and 30 late-stage BD patients (minimum of 10 years after diagnosis), found significantly higher TNF- α in the late-stage group (Kauer-Sant’Anna et al., 2009). Another study of inflammatory biomarkers in 133 BD patients found increased sTNF-R (80kDa) in later-stage illness (Siwek et al., 2017b) suggesting it may represent a staging biomarker. Of note, these later stages of illness are characterized by persistent cognitive impairment in the inter-episode period (Kapczinski et al., 2009).

Our work fits into a burgeoning body of literature suggesting TNF-family molecules are associated with cognitive dysfunction in major psychiatric illnesses; however, results are mixed. In one study in non-euthymic BD (N=117) and patients with schizophrenia (SZ N=109), sTNF-R1 was negatively associated with performance on verbal memory and working memory learning and recall tests (Hoseth et al., 2016), a domain that has been shown to be affected by executive function (Chang et al., 2010). In another study, in which levels of sTNF-R1 were higher in non-euthymic patients (BD, N=111, SZ, N=121) than controls, sTNF-R1 was observed to be negatively associated with general cognitive functioning based on the WASI IQ test (Hope et al., 2015b). However, in subgroup analyses, sTNF-R1 was only associated with general cognitive ability in the SZ group, and the authors did not observe a significant association in the BD group, in contrast to our findings. Another group found that TNF- α was negatively correlated with delayed recall in 54 euthymic BD patients (Doganaşargil-Baysal et al., 2013). In contrast, one study of euthymic BD patients (N=25) found that TNF- α was positively correlated with inhibitory control, and sTNF-R2 levels were inversely correlated with motor programming (Guimarães Barbosa et al., 2012). It is worth noting that our sample of BD participants is twice as large as the largest study reporting these relationships to date, thereby allowing for enhanced power to detect these relationships.

Our results suggest that executive function is particularly influenced by TNF molecules, which is consistent with reports implicating TNF in BD-related changes in the lateral and medial prefrontal cortex (PFC). The relationship between TNF family molecules and

cognitive performance observed in our study and others is in keeping with findings that there are regional variations in mood disorder patients in this family of molecules in the frontal cortex (Dean et al, 2013), the volume and thickness of which has been associated with executive functioning (Yuan & Raz, 2014). Further, in vivo studies in mood disorder patients have shown that increased peripheral TNF levels correlate with the presence of white matter hyperintensities, which are in turn associated with executive function impairment (Smagula et al., 2017). TNF levels also impact functional connectivity within the PFC in MDD (Liu et al., 2019).

The TNF family system, reflected in literature examining transcript levels (mRNA) and soluble and membrane-bound protein forms of TNF and its receptors, is a highly complex interplay of ligand and receptor molecules. Soluble TNF-Rs compete with the transmembrane receptors for TNF- α , and regulate TNF- α signaling (Aderka et al., 1992; Moelants et al., 2013). The manner in which sTNF receptors affect TNF activity depends on their concentration as well as on the concentration of TNF itself, such that these soluble receptors can either inhibit or augment the effects of TNF (Aderka et al, 1992). As such, elevation in sTNF-Rs may be insufficient to completely neutralize TNF- α activity in sites where transmembrane TNF-Rs are markedly increased (Cope et al., 1992). In diseases such as rheumatoid arthritis (RA) there is a correlation between elevated sTNF-R concentrations and clinical indicators of inflammatory disease activity (Cope et al., 1992). Further, levels of sTNF-Rs have been found to be indicative of disease activity in other inflammatory conditions, including Guillain-Barré syndrome (Créange et al., 1996) and juvenile chronic arthritis (Rooney et al., 2000). The story of this system is complicated further by tissue and cell type examined. Future work should aim to develop conceptual models which integrate this complex network of molecules.

There were a few limitations to the current study. One is the potential confounding factors that may impact TNF-family molecule levels which we did not measure in our participants, including level of physical activity, diet, and infections or low-grade inflammatory conditions that were not identified. TNF-family molecules are altered in various chronic health conditions such as cardiovascular disease (Ferrari, 1999) and autoimmune disorders like rheumatoid arthritis (Cope et al., 1992) and multiple sclerosis; however, beyond patient self-report of medical conditions we did not collect this information. Further, TNF-family molecules are known to fluctuate based on the time of day (Keller et al., 2009) and we did not standardize collection times nor systematically collect information related to the time of blood collection.

Based on current evidence, it stands to reason that chronic elevation in pro-inflammatory pathways may affect cognitive function in some people. TNF- α may directly affect the brain at the level of the blood-brain-barrier (BBB) where it binds to its receptors (TNF-R1 and TNF-R2) and is translocated to the basal side of the endothelium (Pan and Kastin, 2007). Subsequent pro-inflammatory cascades in the parenchyma may result in activation of resident immune cells in the brain, including microglia, which can also secrete TNF- α (Giridharan et al., 2019). It has been proposed that disruptions in the BBB in BD render the central nervous system more vulnerable to the heightened pro-inflammatory profile observed in the periphery (Patel and Frey, 2015). Further, TNF- α is known to activate endothelium,

cause white blood cell recruitment and vascular leakage (Brietzke and Kapczinski, 2008); It can also activate apoptotic pathways, leading to cell death (Brietzke and Kapczinski, 2008). Further, TNF- α is expressed by macrophages, endothelial cells, neurons, astrocytes and microglia (Giridharan et al., 2019). In the brain, TNF- α can influence synaptic transport, synaptic pruning, neurogenesis and long-term potentiation (Giridharan et al., 2019).

TNF- α has already been identified as a target for clinical intervention in BD. Early trials have begun to use anti-inflammatory agents targeting TNF (infliximab) to treat aspects of BD (depression) (McIntyre et al., 2019; C. L. Raison et al., 2013). Infliximab reduces circulating TNF- α by mimicking sTNF-Rs, and is a medication typically used for treatment of RA (Moss et al., 2008). Early evidence suggests that the effectiveness of anti-inflammatory treatments is greatest within a subgroup of BD patients, i.e., those with an “inflammatory” illness type versus those without (Fillman et al., 2014). High baseline levels of CRP (>3 – 5 mg/L) have been shown to predict antidepressant response to both lurasidone and infliximab in mood disorders (Raison et al., 2013; Raison et al., 2018). These results point toward inflammation as a primary treatment target, at least in a subgroup of BD patients. Our data suggests that if anti-TNF α treatment is to be tested in BD, measuring changes in cognition during the course of treatment may be useful to indicate responder/non-responder status.

Here we have shown evidence that 1) circulating TNF levels do not differ between BD and HC groups in our sample, 2) late-stage BD is marked by increased sTNF-R1 levels, 3) TNF- α and sTNF-R2 are negatively associated with executive function in BD, and 4) TNF family molecules partially mediate the relationship between number of severe mood episodes and executive function in euthymic BD. These results suggest a role for TNF family molecules in the pathophysiology of neuroprogression in affectively stable patients with BD. The partiality of mediation may point to a subgroup of patients (those with higher peripheral inflammation) who may benefit from an anti-inflammatory adjunctive agent during severe mood episodes in an effort to slow or abort cognitive decline. This idea is supported by a recent meta-analysis which indicated that only a subset (27%) of patients present with low-grade inflammation in depression (Osimo et al., 2019). Our prior work also supports the idea of “inflammatory heterogeneity” in BD (as described in our recent work Millett et al., 2019). Although SEM models can be useful to test for a (statistically) causal relationship among key measures; our data are cross-sectional. A true causal relationship cannot be established until longitudinal studies are done to address the exact nature and timing of these brain changes in BD.

Funding Sources:

The work is funded by R01MH100125 to KEB. CEM is partially supported through the Harvard University Sackler Scholars in Psychobiology Program.

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- We found no significant difference between BD and HC groups in circulating TNF family molecule concentrations.
- Circulating soluble TNF receptor one (sTNF-R1) was significantly higher in late-stage BD compared to early-stage illness.
- We found significant negative associations between TNF family molecules and executive function measures in BD.
- TNF variables partially (though not completely) mediate a causal effect of psychiatric hospitalizations on executive cognitive function in BD.

Figure 1.

Non-parametric Mann Whitney U tests on early versus late TNF family molecules. Early stage illness is defined as ≤ 1 psychiatric hospitalizations and late stage illness is defined as >1 psychiatric hospitalization. $*=p<0.05$.

Figure 2. Partial Pearson correlations between TNF-family molecules and cognitive assessments of executive function (controlled for age and sex). COWAT (Controlled Oral Word Association Test), WCST (Wisconsin Card Sorting Task), Stroop color-word. *= $p < 0.05$, **= $p < 0.01$, #= $p = .13$

Figure 3.

Structural Equation Model (SEM) showing standardized path coefficient estimates and correlations among exogenous covariates. Latent variables are shown as circles and manifest variables are shown as rectangles. Covariates (education, sex, age, premorbid IQ, race) are in grey. $^* = p < 0.05$, $^{**} = p < 0.01$, $^{***} = p < 0.001$, $^{\wedge} p = .06$.

Table 1.

Clinical and demographic variables of BD and HC groups. Data represented as Mean ($\pm$ SD) or N (%) unless otherwise noted.

VARIABLES	BIPOLAR (N=219)	HC (N=52)	p- value
TNF- α (pg/mL) *	3.3 (IQR=1.4)	3.4 (IQR=1.5)	0.91
sTNF-R1 (pg/mL) *	3825.1 (IQR=1461.1)	3806.8 (IQR=1216.4)	0.88
sTNF-R2 (pg/mL) *	4224.9 (IQR=1739.5)	4185.3 (IQR=1842.0)	0.42
Age	43.6 ($\pm$ 11.9)	38.9 (13.4)	0.02
BMI	N=37, 29.9 ($\pm$ 6.3)	N=24, 26.1 ($\pm$ 5.9)	0.02
Education	14.2 ($\pm$ 2.5)	15.6 ($\pm$ 1.7)	<0.001
Sex (female)	103 (47.0%)	30 (57.7%)	0.17
Ethnicity (Hispanic)	50 (22.8%)	10 (19.2%)	0.57
Race (Caucasian)	101 (46.1%)	15 (28.8%)	<0.001
Premorbid IQ (WRAT-3)	100.7 ($\pm$ 15.3)	107.1 ($\pm$ 11.4)	<0.01
BD type I	176 (80.4%)	--	--
Not on medication	49 (22.4%)	--	--
Duration of illness (years)	21.9 ($\pm$ 11.5)	--	--
Manic episodes	N=214, 7.7 ($\pm$ 9.6)	--	--
Depressive episodes	N=214, 13.4 ($\pm$ 14.2)	--	--
# Mood episodes	N=213, 24.1 ($\pm$ 21.2)	--	--
Psychosis history	93 (42.5%)	--	--
Wks since mood episode	N=217, 57.4 ($\pm$ 110)	--	--
# Psych hosps	3.7 ($\pm$ 4.5)	--	--
# Suicide attempts	0.9 ($\pm$ 2.2)	--	--
# Psychotropic meds	1.7 ($\pm$ 1.3)	--	--

* data shown as median and interquartile range (IQR).