stressed mice. However, CSD does not cause extravasation of peripheral monocytes into brain.

**Conclusions:** CSD-S microglia are more phagocytic and secrete molecules that break down the BBB. These kinds of activities represent a CNS-centric inflammatory state that may contribute to the susceptible phenotype.

**Supported By:** NIH IRP

**Keywords:** Microglia, psychoneuroimmunology, Blood brain barrier, social defeat stress, macrophage

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296. Correlating Peripheral and Central Markers of Neuroinflammation to PET Imaging of Translocator Protein (TSPO)

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**Background:** Neuroinflammation is a predisposing factor for major depressive disorder (MDD). We recently showed differences in translocator protein 18 kDa (TSPO), an indirect marker of neuroinflammation, in patients with MDD. Specifically, TSPO binding was increased in unmedicated but not medicated MDD subjects compared to healthy controls (HCs). The aim of this study is to determine if central and peripheral inflammatory biomarkers correlate with these TSPO differences.

**Methods:** Unmedicated (n = 12), medicated MDD (n = 16) and HC (n = 20) subjects who previously underwent PET imaging were included. We obtained peripheral blood samples on all subjects and cerebral spinal fluid (CSF) collection was elective. We utilized Enzyme-Linked Immunosorbent Assay (ELISA) to measure peripheral levels of various pro- and anti-inflammatory proteins.

**Results:** Interim results show that in plasma, TNF-alpha and quinolinic acid levels are significantly elevated in medicated MDD subjects compared to unmedicated subjects and HCs. In CSF, vascular endothelial growth factor levels are increased in medicated MDD subjects compared to HCs and interferon-gamma levels are higher in unmedicated MDD subjects compared to HCs. All differences are significant at a p<0.05 level. There was no correlation of plasma or CSF inflammatory markers to TSPO binding.

**Conclusions:** These preliminary results indicate significant differences in peripheral and central markers of inflammation depending on mood state and treatment status but how this relates to TSPO binding, and neuroinflammation, must be better characterized. These findings are important to help with understanding the heterogeneity of MDD and for development of novel therapeutic agents.

**Supported By:** IRP-NIMH-NIMH-DHHS; Janssen Pharmaceuticals, Inc.

**Keywords:** Inflammation, Neuroinflammation, Translocator Protein (TSPO), Kynurenic acid, VEGF

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297. Neopterin and Zinc Differentially Predict Mood Severity in Men and Women with Bipolar Disorder

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**Background:** Symptomatic mood states in bipolar disorder (BD) may be associated with elevated inflammatory markers, however this may differ in men and women. The aim of the current work was to examine the association of zinc, a neural modulator, and neopterin, an inflammatory marker, with mood severity in BD men and women.

**Methods:** Subjects with DSM IV bipolar disorder I and II (BD, N=27) were recruited through the Pennsylvania Psychiatric Institute (PPI) during an acute mood episode. Participants were fasting for at least 6 hours when blood was drawn for biomarkers. The second serum sample was collected when the subject was asymptomatic, or after 3 months had elapsed.

**Results:** Serum zinc concentration was significantly lower in the BD group than in the healthy control (HC) group at baseline (p=0.04). Plasma neopterin concentrations at baseline were not different between HC and BD participants, on average. We found a significant interaction between gender and neopterin concentrations associated with mania at baseline (p=0.013). We also found a significant interaction of gender and serum zinc associated with depression severity at baseline (p=0.03). Follow-up analysis revealed a significant increase in serum zinc between baseline and follow up (p=0.02).

**Conclusions:** We report that severity of mania may be associated with neopterin in men, while depression severity may be associated with zinc in women. Our report also highlights the importance of analyzing gender in human studies of BD and the potential for differences in the underlying pathophysiology between men and women.

**Supported By:** NIH KL2

**Keywords:** Mood disorders, Bipolar Disorder, Inflammation, Inflammatory Markers, Biomarkers

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298. Peripheral inflammation, Physical Activity and Cognition in Bipolar Disorder

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**Background:** Alterations in peripheral inflammation, physical activity (PA), and cognition have been reported in bipolar disorder (BD), yet little is known about the relationships between these factors. We examined associations among pro-inflammatory cytokines, objectively measured PA, and executive functioning.
to examine the interrelations between inflammation (IL-6) and anhedonia in depressed youth. Methods: Forty-four psychotropic medication-free youth with adolescent major depressive disorder (MDD) and anhedonia in depressed youth, and 36 healthy controls (HC; 12–21 years old) underwent administered cognitive tests and health questionnaires, and wore an actigraphy watch measuring degree of movement for two weeks. Blood samples were obtained from a subsample of participants (15 BD and 23 HC) and were assayed for interleukin-6 (IL-6) and C-reactive protein (CRP). PS and EF composite scores were derived from averaging z-scores of relevant tasks.

Results: Groups were comparable on age, gender, ethnicity, body mass index (BMI) and stroke risk. The BD group had significantly higher levels of IL-6 and exhibited worse EF and PS performance than the HC group. While there were no group differences in PA or CRP, higher average PA across the two-week period was associated with lower CRP in the BD group only. This relationship remained significant after accounting for stroke risk and BMI.

Conclusions: This preliminary investigation suggests that pro-inflammatory cytokines linked to vascular risk, particularly CRP, may be sensitive to levels of PA. Further, BD patients may be particularly responsive to the beneficial effects of PA on inflammation. Future studies will examine the impact of mood on PA.

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Keywords: Bipolar Disorder, Inflammation, physical activity, cognition

299. Inflammation, \( \gamma \)-Aminobutyric Acid Deficits, and Anhedonia in Depressed Youth

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Background: Inflammatory processes and \( \gamma \)-aminobutyric acid (GABA) deficits have both been separately implicated in reward dysfunction in adolescent major depressive disorder (MDD), resulting in the clinical outcome of anhedonia. Here, we sought to examine the interrelations between inflammation, GABA levels, and anhedonia in depressed youth.

Methods: Forty-four psychotropic medication-free youth with MDD and 36 healthy controls (HC; 12–21 years old) underwent a proton magnetic resonance spectroscopy scan; plasma levels of 13 cytokines were measured in a subset of this sample (MDD = 33, HC = 26). Anhedonia was evaluated both dimensionally and categorically.

Results: GABA levels were reduced in depressed youth compared to HC [F(1, 77) = 8.08, p = .006]. When patients were classified based on the presence of anhedonia, only the anhedonic MDD subgroup had lower GABA levels compared to HC [p = .002]. Dimensional analyses further showed that GABA levels correlated with anhedonia severity in MDD \( \tau = -.33, p = .03 \). Additionally, both interleukin 7 (IL7) \( \rho = -.36, p = .04 \) and IL6 \( \rho = -.35, p = .04 \) correlated with GABA levels in MDD, and IL4 \( \rho = .38, p = .03 \) was related to anhedonia severity. However, Sobel’s test of mediation did not show that alterations in GABA mediated the relationship between inflammation (IL4) and anhedonia in MDD [CI: -.04, .05].

Conclusions: While both inflammation and alterations in GABA are independently related to anhedonia severity, the complete mechanism underlying these complex relationships is still unclear in adolescent MDD and warrants further investigation.

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Keywords: Inflammation, GABA, Adolescence, Anhedonia, brain reward circuit

300. Improvement in Measures of Depressed Mood and Anhedonia in Two Randomized, Placebo-Controlled Phase III Studies of Sirukumab, a Human Anti-Interleukin-6 Antibody, in Patients with Rheumatoid Arthritis

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Background: Interleukin-6 (IL-6) is involved in neural plasticity, stress coping and depression. Depressive symptoms are prevalent in patients with rheumatoid arthritis (RA), a disease with high peripheral IL-6. Previous analysis of a phase II study showed that anti-IL-6 treatment can alleviate depressive symptoms in RA patients.

Methods: Here we analyzed 2 Phase III, double-blind, placebo-controlled trials of sirukumab, an anti-IL-6 monoclonal antibody, in patients with active RA and serum CRP >8mg/L or ESR >28mm/h despite disease-modifying anti-rheumatic drugs (DMARDs) or anti-TNF therapy. Patients were grouped by presence/absence of prevalent depressed mood and anhedonia (PDMA), based on two core depressive symptoms was evaluated directly and with adjustment for RA severity using the DAS28-CR. RA response was defined by achieving ACR50.

Results: At baseline, 19%-22% of patients were classified as PDMA. Sirukumab treatment, compared to placebo, significantly improved depressive symptoms by week 8 among PDMA patients in both studies (p = 0.0216, p = 0.0458). The within-treated-group mood effects remained significant after co-varying for changes in RA severity (p < 0.0001) and in patients designated as RA non-responders (p < 0.0001) while between-group effects reduced to trends. Meta-analysis of 4 anti-IL-6 studies (1 siltuximab and 3 sirukumab) revealed that anti-IL-6 treatment may help alleviate depressive symptoms (Standardized Mean Difference = 0.25, p = 0.03).

Conclusions: Consistent with previous result, our findings showed that peripheral anti-IL-6 treatment is associated with improvement in depressive symptoms in RA patients, supporting a role for IL-6 dysfunction in depression.

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Keywords: Major Depressive Disorder (MDD), IL-6, Neuroimmunology