Title

Associations Between Inflammatory Marker Profiles and Cognitive Functioning in Adults With Schizophrenia and Non-Psychiatric Comparison Subjects

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Background: Posttraumatic Stress Disorder (PTSD) is characterized by various symptom profiles and high comorbidities with other conditions, including Major Depressive Disorder (MDD). A dissociative subtype of PTSD (PTSD-DST) has been specified by additional symptoms of depersonalization and derealisation. However, the underlying neurobiology of PTSD-DST is poorly understood. This study examined neuroendocrine and inflammatory biomarkers in relation to symptom profiles of PTSD.
Methods: Participants included combat-exposed Canadian Armed Forces veterans (N=35, Mage=47.7, 68.6% males, 31.4% females) who had a diagnosis of PTSD-DST (n=10), PTSD non-DST (n=17), or MDD (n=8). Depression symptoms were assessed with the Beck Depression Inventory (BDI) and PTSD severity with PTSD Checklist (PCL-5). Saliva and blood samples were used to determine levels of cortisol and inflammatory marker, C-Reactive Protein (CRP), through radioimmunoassay and ELISA, respectively.
Results: PTSD symptom severity was greater in the PTSD-DST group compared to the non-DST group, p=0.034. In contrast, BDI scores did not significantly differ across all three groups, p=0.90, reflecting the high degree of depressive symptoms among individuals with PTSD. Levels of CRP were higher in the PTSD-DST group compared to the non-DST group, p=0.023. While cortisol tended to be blunted in the PTSD groups compared to the MDD group, this difference was not statistically significant, p=0.10.
Conclusions: While preliminary, there data suggest that PTSD-DST can potentially be differentiated from other subtypes or symptom profiles of PTSD through inflammatory biomarkers. Identifying biomarker profiles to characterize the heterogeneity of PTSD could lead to more personalized and targeted treatments of PTSD.
Supported By: Department of National Defense
Keywords: PTSD Symptom Severity, MDD, PTSD, Inflammatory Markers, Trauma Exposure

Research Method: Neuroimmunology

Association of Astrocyte Derived Exosomal Cytokines and PTSD Symptoms in Veterans

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Background: Growing evidence suggests inflammation plays a role in trauma-related psychiatric disorders. Studies suggest PTSD is associated with altered immune protein levels. Little is known, however, about the relationship between central and peripheral inflammation in driving PTSD.
Methods: To specifically probe the relationship between the central nervous system (CNS) and peripheral inflammation, we isolated astrocyte-derived exosomes (ADEs) from peripheral blood plasma samples from subjects with and without PTSD (N=32). After exosomal lysis, cargo protein cytokines were quantified using multiplex enzyme-linked immunosorbent assay plates. These cytokines were compared to clinical measures of PTSD using the PCL-5 and PHQ9.
Results: We found modest detection of some but not all cytokines as exosome cargo in ADEs, including IL-2, IL-6, IL-1b, TNFa, and IFNg. Most cytokines from ADEs did not correlate significantly with plasma cytokine levels (ρ ranging from 0.059 - 0.570), except for IL-2 measured from both plasma and ADEs (ρ= 0.498, R^2=0.170, p = .004). Notably, we detected a significant relationship between anhedonia as measured and ADE IL-1b and IL-2 levels (ρ=0.493, p<0.01; ρ=0.489, p<0.01).
Conclusions: Our findings that few plasma cytokines appear to correlate with cytokines isolated from ADEs, suggests that ADE cytokines may represent a tissue-specific signature of CNS immune dysregulation. These exploratory findings highlighting the association between ADE cytokine levels and anhedonia underscore that ADE's may hold promise to identify immune dysfunction in neuropsychiatric disorders.
Supported By: CESAMH; VA Merit Award BX002558-01
Keywords: PTSD, Inflammation, Cytokine, Exosomes, Veterans

Associations Between Inflammatory Marker Profiles and Cognitive Functioning in Adults With Schizophrenia and Non-Psychiatric Comparison Subjects

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Background: Cognitive dysfunction in schizophrenia is the key predictor of functional disability and drives the economic burden, though its etiology remains unclear. This study explores the role of inflammation in cognitive functioning in schizophrenia using a data-driven approach.
Methods: Participants included 143 persons with schizophrenia and 139 healthy controls, from an ongoing longitudinal study of aging. Cognitive assessments included executive functioning and visuospatial skills. Plasma levels for 24 biomarkers associated with inflammation were quantified using commercially available assays. We used Spearman's correlations to develop a focused "inflammatory profile," and partial least squares regression to determine associations with the cognitive outcomes via the creation of biomarker composites. We then constructed a best-fit model using these composites and their interactions with diagnosis and sex as the predictors, controlling for covariates.
Results: High sensitivity C-reactive protein, serum amyloid A, intercellular adhesion molecule 1, and fractalkine showed a significant main effect of group when stratified by diagnosis and sex. Post hoc comparisons showed that interleukin-6 was only higher in women with schizophrenia, while serum amyloid A was only higher in men with schizophrenia. A number of biomarkers displayed a negative correlation with scores on cognitive assessments, notably in controls, and more so in women. The best-fit model showed a significant three-way

biomarker composite by diagnosis by sex interaction, for both executive function and visuospatial skill.
Conclusions: This data-driven approach to building an "inflammatory profile" may provide insight into inflammatory pathways affecting brain function, and potentially target anti-inflammatory interventions to improve cognition in schizophrenia.
Supported By: NIMH R25, R01, and K23 grants, NIH UL1TR001442, and the Stein Institute for Research on Aging at UCSD
Keywords: Inflammatory Markers, Cognitive Functioning, Schizophrenia

Interleukin-1 Family Signaling Related to Agitation in Severe Mental Disorders

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Background: Exacerbations of the clinical picture in severe mental disorders have been linked to activation of certain members of the interleukin-1 family immune pathway. Here we investigated if disturbances in neuroimmunologically relevant elements of this pathway are associated with agitation, a challenging clinical feature that contributes to symptom severity across several symptom dimensions in severe mental disorders.
Methods: Individuals with schizophrenia- or bipolar spectrum disorders (N=788) underwent blood sampling and thorough clinical characterization. Circulating levels of interleukin-1 receptor antagonist (IL-1RA), interleukin-18, and interleukin-18 binding protein (IL-18BP) were measured. Level of agitation was characterized by the Positive and Negative Syndrome Scale Excited Component. Multiple linear regression was used to investigate the associations between immune markers and agitation, while controlling for sex, age, body mass index, and smoking.
Results: Agitation was positively associated with circulating IL-18BP levels (p=0.009). There were no significant associations between agitation and IL-1RA nor interleukin-18.
Conclusions: Our findings of the association between agitation and IL-18BP combined with no significant association between agitation and interleukin-18 may suggest a compensatory dysregulation of interleukin-18 pathway related to agitated clinical picture in severe mental disorders.
Supported By: Research Council of Norway (223273); The South-Eastern Norway Health Authorities (2020100); Ostfold Hospital (AB3461)
Keywords: Interleukin-18, Interleukin-18 Binding Protein, Interleukin-1 Receptor Antagonist, Agitation, Symptom Severity

The Kynurenine Pathway in Major Depressive Disorder, Bipolar Disorder, and Schizophrenia: A Large Meta-Analysis

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Background: The importance of tryptophan as a precursor for neuroactive compounds has long been acknowledged. The metabolism of tryptophan along the kynurenine pathway and its involvement in mental disorders is an emerging area in psychiatry. We performed a meta-analysis to examine the differences in kynurenine metabolites in major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ).
Methods: Electronic databases were searched for studies that assessed metabolites involved in the kynurenine pathway (tryptophan, kynurenine, kynurenic acid, quinolinic acid, 3-hydroxykynurenine, and their associate ratios) in people with MDD, SZ, or BD, compared to controls. We computed the difference in metabolite concentrations between people with MDD, BD, or SZ, and controls, presented as Hedges' g with 95% confidence intervals.
Results: 101 studies with 10,912 participants were included. Tryptophan and kynurenine are decreased across MDD, BD, and SZ; kynurenic acid and the kynurenic acid to quinolinic acid ratio are decreased in mood disorders (i.e., MDD and BD), whereas kynurenic acid is not altered in SZ; kynurenic acid to 3-hydroxykynurenine ratio is decreased in MDD but not SZ. Kynurenic acid to kynurenine ratio is decreased in MDD and SZ, and the kynurenine to tryptophan ratio is increased in MDD and SZ.
Conclusions: Our results suggest a shift in the tryptophan metabolism from serotonin to the kynurenine pathway, across these psychiatric disorders. In addition, a differential pattern exists between mood disorders and SZ, with a preferential metabolism of kynurenine to the potentially neurotoxic quinolinic acid instead of the neuroprotective kynurenic acid in mood disorders but not in SZ.
Supported By: None
Keywords: Kynurenine, Tryptophan Metabolism, Bipolar Disorder, Mood Disorders, Meta-Analysis

Transcriptomic Signatures of Inflammation and Metabolic Reprogramming in Peripheral Blood Immune Cells are Implicated in Psychomotor Retardation in Depression

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