Title
Persons With Schizophrenia Exhibit Altered Gut Microbiome Functional Pathways Related to Immune Modulation and Cardiovascular Risk

Permalink
https://escholarship.org/uc/item/6rd3h5v7

Journal
Biological Psychiatry, 89(9)

ISSN
0006-3223

Authors
Nguyen, Tanya
Kosciolek, Tomasz
Daly, Rebecca
et al.

Publication Date
2021-05-01

DOI
10.1016/j.biopsych.2021.02.261

Peer reviewed
**Persons With Schizophrenia Exhibit Altered Gut Microbiome Functional Pathways Related to Immune Modulation and Cardiovascular Risk**

**Tanya Nguyen**, Tomasz Kosciolek, Rebecca Daly, Yoshiki Vázquez-Baeza, Austin Swafford, Rob Knight, and Dilip Jeste

1University of California, San Diego, 2Matopolska Centre of Biotechnology, Jagiellonian University, 3Center for Microbiome Innovation, University of California, San Diego

**Background:** Persons with schizophrenia have higher rates of cardiovascular disease and exhibit inflammatory abnormalities. Emerging evidence has linked the gut microbiome changes to schizophrenia. However, there has been limited research into the functional pathways by which the gut microbiota contributes to the phenotype of persons with chronic schizophrenia.

**Methods:** We characterized the composition and functional potential of the gut microbiota in 48 individuals with chronic schizophrenia and 48 matched non-psychiatric comparison subjects (NCs) using 16S rRNA sequencing. PICRUSt was performed to predict functional potential of microbial communities, based on metagenomes inferred from 16S data.

**Results:** Patients with schizophrenia demonstrated significant beta-diversity differences in microbial composition (p=0.002) and predicted genetic functional potential (p=0.008), compared to NCs. Alpha-diversity of taxa and functional pathways were not different between groups. Random forests analyses revealed that the microbiome predicts differentiation of patients with schizophrenia from NCs using taxa (75% accuracy) and functional profiles (67-70% accuracy). Differential abundance testing revealed that the family Lachnospiraceae was associated with schizophrenia (p=0.005). Functional pathways related to trimethylamine-N-oxide reductase and Kdo2-lipid A biosynthesis were altered in schizophrenia (p<0.001). These metabolic pathways were correlated with higher Framingham Risk Score (p=0.393, p=0.026) and decreased levels of anti-inflammatory cytokine IL-10 (p =0.761, p=0.001), respectively, in patients with schizophrenia.

**Conclusions:** Findings suggest potential mechanisms by which the microbiota may impact the pathophysiology of the disease through modulation of functional pathways related to immune signaling/response and lipid and glucose regulation, which might have implications for accelerated biological aging in schizophrenia.

**Funding Source:** K23 MH118435; R01 MH094151; T32 MH019934; UC San Diego Sam and Rose Stein Institute for Research on Aging; IBM Research through the AI Horizons Network, UC San Diego AI for Healthy Living program in partnership with the UC San Diego Center for Microbiome Innovation

**Keywords:** Microbiome-Gut-Brain Axis, Schizophrenia, Accelerated Aging, Cardiovascular Disease, Inflammation

**mGluR5 Availability in Chronic Pain: An in Vivo Study With [18F]FPEB PET Study**

**Margaret Davis**, Sarah DeBonee, Ryan Cool, Robert Gereau, and Irina Esterlis

1Yale University, 2Washington University School of Medicine

**Background:** Chronic pain (CP) is frequently treated with opioid-based analgesics leading to high rates of addiction. Identification of novel targets to rapidly reduce pain in CP without leading to substance misuse must be prioritized. Using positron emission tomography (PET) we conducted a novel examination of the role of mGluR5 - a potential treatment target for CP with low abuse-potential - in chronic pain and cognitive deficits in individuals reporting CP and those with no pain (NCP).

**Methods:** Participants (n=25 CP [MAge=36.76, 13 female, 16 MDD or PTSD]; n=25 NCP [MAge=38.08, 13 female, 16 MDD or PTSD]) were matched for age, gender, diagnostic and smoking status. Participants completed 1 MRI and 18F-FPEB PET scan, psychiatric and cognitive assessments.

**Results:** MANOVA analysis showed significant group differences in mGluR5 availability (VT; F=4.91, p=0.001). CP individuals had significantly higher mGluR5 availability in frontal (p's=.001-.004, 16-21% difference) regions. Results remained significant when mood symptoms and psychiatric diagnosis were controlled for (p's=.001). ACC mGluR5 availability was higher in females (p=.04, 13% difference) with CP compared to NCP. mGluR5 availability was negatively correlated with attention (r's=-.45-.50; p's=.02-.03), and working memory (r's=-.48-.57; p's=.007-.04) in CP.

**Conclusions:** Individuals with CP had higher mGluR5 availability in frontal regions, with ACC mGluR5 particularly high in females. This gives support to animal work showing dysregulation of novel targets to rapidly reduce pain in CP may provide some cognitive restoration. Further evaluation of mGluR5 targets for the treatment of chronic pain is warranted.

**Funding Source:** R01MH104459 ; 1K08MH117351-01 ; DANA Foundation

**Keywords:** Chronic Pain, mGluR5, PET Imaging, Sex Differences

**Shared Genetic Effects may Partially Explain Higher Depression and PTSD Prevalence Among Women Using Hormone Therapy (HT)**

**Laramie Duncan**, Joeri Meijisen, Hanyang Shen, Mytilée Vemuri, Natalie Rasgon, and Karestan Koenen

1Stanford University, 2Stanford University & Mental Health Center Sct. Hans, Mental Health Services Copenhagen, 3Harvard School of Public Health

**Background:** Fluctuating gonadal hormone levels are thought to contribute to the higher prevalence of major mood disorders. Depression and PTSD are more prevalent in women than men. It is not clear if this is due to differences in sex steroid exposure or genetic factors. The population attributable fraction (PAF) for genes in the human sex steroid receptor family that vary between testosterone and estradiol in women and may contribute to the increased risk of depression and PTSD in women is unknown. We examined whether shared genetic effects between sex hormones and depression and PTSD are the source of increased prevalence in women using hormone therapy (HT). We performed a genome-wide association study (GWAS) and analyzed whether shared genetic effects were driving the association between depression and PTSD and sex steroid hormones in women using HT.

**Methods:** We performed a GWAS of depression and PTSD in 2,371 women using HT. We tested for evidence of shared genetic effects with hormones by fitting conditional models to the GWAS results with and without controls for hormone exposure, adjusting for age, and age at HT initiation. We estimated PAF for sex steroid receptors in HT indicating genes that drive the association between depression and PTSD and hormone exposure.

**Results:** Shared genetic effects may partially explain higher depression and PTSD prevalence among women using HT.

**Conclusion:** Shared genetic effects may partially explain higher depression and PTSD prevalence among women using HT.

**Funding Source:** DANA Foundation