The Brain-Immune-Gut Axis, and Psychiatric Disorders: Opportunities for Prevention and Treatment

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Inflammation and Psychiatric Disorders-Converging Evidence

Genetic

Schizophrenia risk from complex variation of complement component 4.

Sekar A1,2,3, Bialas AR4,5, de Rivera H1,2, Davis A1,2, Hammond TR4, Kamitaki N1,2, Tooley K1,2,


The complement system: a gateway to gene-environment interactions in schizophrenia pathogenesis.

Nimgaonkar VL1,2, Prasad KM1, Chowdari KV1, Severance EG3, Yolken RH3.

Neuropathologic

Markers of inflammation in the prefrontal cortex of individuals with schizophrenia

S G Fillman1,2,3, N Cloonan4, L C Miller5 and C S Weickert1,2,3

Molecular Psychiatry (2013) 18, 133; doi:10.1038/mp.2012.199

Systemic

A combined marker of inflammation in individuals with mania.

Dickerson F1, Stallings C, Origoni A, Vaughan C, Katsafanas E, Khushalani S, Yolken R

Pharmacologic

Anti-inflammatory treatment in schizophrenia

Norbert Müller, Aye-Mu Myint, Daniela Krause, Elif Weidinger, Markus J. Schwarz
Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Munich, Germany
The Origin of Immune Activation in Psychiatric Disorders

• Inflammation is a major component of schizophrenia and mood disorders
• The immune response of the periphery and central nervous system are interrelated
• Crucial Questions:
  – What is the source of the inflammatory process?
  – How can the inflammatory response be modulated to benefit patients?
The Brain-Immune-Gut (BIG) Interactome in Psychiatric Disorders

A substantial portion of the body’s serotonin receptors are in the GI tract

Adapted from Emily Severance, 2014, Schizophrenia Res
Gastroenterology Issues in Schizophrenia: Why the Gut Matters

Emily G. Severance • Emese Prandovszky • James Castiglione • Robert H. Yolken

Ilya Mechnikov
1845-1916

A Treatise
on
INSANITY,

OF WHICH ARE CONTAINED
THE PRINCIPLES OF A NEW AND MORE PRACTICAL MORPHOLOGY
OF MENTAL DISORDERS.

TRANSLATED FROM THE FRENCH,

BY PH. PINEL,

PROFESSOR OF THE HOSPITAL OF BICLARETTE AT PARIS;

BY D. D. DAVIS, M.D.

PHYSICIAN TO THE HOSPITAL GENERAL INFIRMARY;

SHEFFIELD:

PRINTED BY W. YODD,

FOR NICHOLAS GILBERT AND DAVID, STRAND, LONDON.

1805
Could schizophrenia be reasonably explained by Dohan's hypothesis on genetic interaction with a dietary peptide overload?

Reichelt KL¹, Seim AR, Reichelt WH.

The Gut Microbiota and the Emergence of Autoimmunity: Relevance to Major Psychiatric Disorders.

Severance EG¹, Tveiten D, Lindström LH, Yolken RH, Reichelt KL.
What Environmental Factors Affect Intestinal Inflammation? How might these be modulated?

Gliadin
Other Food Antigens
Food Chemicals

Immune-modulatory Microbes
Sheppard Pratt Study Cohort

• Collected starting 2002. As of March 1, 2019
  – Total of 2114 individuals
    • Schizophrenia       N=766
    • Recent Onset Psychosis N=119
    • Mania              N=251
    • Other Mood Disorders N=398
    • Non-Psychiatric Controls N=580
  – Multiple samples from many individuals (N=3369 total sample)

• Clinical Measures
  – Clinical symptom scores
  – Suicide attempts
  – Cognitive functioning (RBANS)
  – Medications (Conventional and Clinical Trials)
  – Environmental and dietary exposures (Cigarette smoking)

• Biological Samples
  – Blood
  – Throat/skin swabs
  – Urine

• Laboratory Measures
  – Antibodies to infectious agents
  – Antibodies to food antigens
  – Markers of Inflammation
  – Genetic analyses
Gliadin Antibodies by Clinical Diagnosis

*** p<.001, ** p<.05
adjusted for age, gender, race and native birth
Have you ever…
Worked or lived on a farm?
Worked in a garden with your hands in the soil?
Eaten raw meat?
Eaten undercooked meat?
Prompt for/circle all that apply: Beef; pork; poultry chicken, turkey, duck; lamb
Tasted raw meat while cooking?
Eaten raw clams or oysters?
Eaten raw fish such as sushi or sashimi?
Eaten undercooked fish such as rare tuna?
Eaten cooked crabs or other shellfish?
Eaten salami?
Eaten cooked meat including pork?
Eaten procured dry cured meat?
Prompt specifically for: Beef jerky; turkey jerky; prosciutto; salami
Drunk unpasteurized milk?
Drunk water from a well?
Drunk bottled water?
Consumed water from a lake or stream on a camping trip?
Eaten unwashed vegetables?
Eaten unwashed fruits?
Eating Cured Meat By Diagnostic Group

- p<.05, **p<.01, *** p<.001
- Adjusted for age, gender, race, maternal education

- **P<5 \times 10^{-7}**

- Ctr N=303, Scz N=218, Rec Onset N=80, Bp Unsel N=136, Bp Depr N=44, Uni Depr N=22, Mania N=62
Food Exposures by Diagnostic Group

Khambadkone et al., Molecular Psychiatry 2018

*** p<5x10^-7, * p<.05 adjusted for age, gender, SES, multiple comparisons

Adjusted Odds Ratio (Mean +/- 95% CI)

- Cured Meat
- Undckd Meat
- Raw Meat
- Undckd Fish
- Raw Fish

Control: N=341
Mania: N=215
Bp Depr: N=96
Unip Depr: N=74
Scz: N=360
Nitrated Cured Meats

• Created by adding nitric acid to meat as a preservative in place of smoking
• Developed during the industrial revolution as nutrition for factory workers
• Popular in modern culture due to availability and convenience
• Potential interaction with biological pathways utilizing nitrates
Rat model of nitrated meat exposure

- Rats fed diets containing chow, commercial nitrated meat (beef jerky) and meat with defined amounts of added sodium nitrate
- 14 days of diet before beginning of behavioral testing
- Diet continued through duration of experiment
- Dietary intake, animal weight, fecal samples collected every 2 days through duration of experiment
- Performance of behavioral tests directed at activity.
- Analysis of gene expression in the hippocampus
- Comparison with human post-mortem samples from individuals with mania and controls
Eating Beef Jerky and Nitrated Meats Result in Increased Activity in Rats

Beef Jerky

Chow with added sodium nitrate

Effect not seen in “Jerky” product without added nitrate
Dietary Nitrate Alters the Intestinal Microbiome and Brain Serotonin Receptor Signaling
Probiotics for the Elderly
Windlove Senior

Probiotics: One of The Best Supplements for Women

Helps Support Healthy DIGESTIVE & IMMUNE SYSTEMS in Kids!

#1 Pediatrician Recommended Brand!

How to Choose the Best Probiotic Supplements for Bodybuilding

Probiotic For Newborns

New

PETUltimates™ PROBIOTICS for Cats
20 Species
5 Billion CFUs/Scoop
120 Servings
Made in USA, 44 grams

PETUltimates™ PROBIOTICS for Dogs
22 Species
2 Billion CFUs/scoop

Life space
A Double-Blind Placebo-Controlled Trial of a Probiotic Supplement for Schizophrenia: 

**Design**

- Target enrollment: 66 patients hospitalized for mania
- Study compound added to existing medications
- 6 month administration of a tablet containing $>10^9 \text{L. rhamnosus GG}$ and *Bifidobacterium animalis* subsp. *lactis* BB12 or identical-appearing placebo (provided by Ferrosan)

**Outcomes**
- Improvement in psychiatric symptoms
- Improvement in gastrointestinal symptoms
Clinical Trial of Probiotics in Individuals with Established Schizophrenia

No effect on psychiatric symptoms

Effective at preventing serious gastrointestinal symptoms

P = 0.003
Cardinal Rule of Immune Therapy - Prevention is potentially much more effective than treatment

**A Combined Marker of Inflammation in Individuals with Mania**

**Faith Dickerson**, **Cassie Stallings**, **Andrea Origoni**, **Crystal Vaughan**, **Emily Katsafanas**, **Sunil Khushalani**, **Robert Yolken**

1 Stanley Research Program, Sheppard Pratt Health System, Baltimore, Maryland, United States of America, 2 Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America

- **Antibody Markers**
  - Gliadin
  - Toxoplasma gondii
  - NMDA Receptor
  - Endogenous Retroviruses

![Kaplan-Meier survival estimates graph](image)
A Trial of Adjunctive Probiotic Microorganisms to Prevent Relapse in Patients with Acute Mania

- Reasons for targeting patients hospitalized with mania
  - Defined period of relapse risk
  - Association of acute mania episodes with recent antibiotics
  - Association of relapse risk with markers of inflammation
    - Dickerson et al Plos One 2013 Sep 3;8(9):e73520

- Study Design
  - Study compound added to existing medications
  - N=66 participants
  - 6 month administration of a tablet containing Lactobacillus GG and Bifidobacterium lactis strain Bb12 (>10⁸ colony forming units) or identical-appearing placebo provided by Chr Hansen

- Outcomes
  - Relapse, defined as re-hospitalization
  - Changes in social functioning
  - Changes in psychiatric symptom severity; mood states, and cognitive functioning
Survival Time to Readmission in Placebo Group

Days in Study-Placebo

Fraction Not Rehospitalized

Survival Time to Readmission in Placebo Group
Survival Time to Readmission in Probiotic and Placebo Groups

HR=.37; 95% CI 0.15, 0.91, p=.029
Adjusted for age, gender, race, maternal education

Cumulative Hazard of Re-hospitalization for Individuals with Inflammation Score $\geq 50^{th}$ %tile by Treatment Group

HR 0.09, 95% CI 0.01, 0.66, p = 0.017
(25 events in N=25 individuals)

Gliadin, NR2, MPMV P24, Toxo

Bipolar Disord. 2018 Nov;20(7):614-621
Serious Psychiatric Disorders and The Gut Brain Axis

- Food exposures can increase risk of mania, recent onset psychosis and suicide attempts
- Probiotics can prevent relapses in mania
- Ongoing/Proposed studies
  - Confirmatory studies in mania
  - Additional target disorders
    - Bipolar Depression/Major depression
    - Suicide and suicide Attempts
  - Additional probiotic preparations
    - Lactobacilli, Bifidobacteria and other anaerobes
    - E coli and other aerobic bacteria
  - Prebiotics (Food for “good” bacteria)
  - Enteric bacteria (fecal transplantation)
- Animal models to evaluate safety and potential efficacy of therapeutic preparations
Inflammation and Psychiatric Disorders

Intestinal Tract

Immune Cells

Systemic/Portal Circulation

Intestinal Tract

Toxoplasma gondii

Infection

GI epithelium

LPS

LBP

Liver

Neutralization & Clearance

HDL

Monocyte/Macrophage

sCD14

mCD14, TLR4

Immune Signaling

Microbiome

Gene x Environment
Faith Dickerson
Sheppard Pratt Hospital

Wayne Campbell
Christian Wright

Seva Khambadkone
Kellie Tamashiro
Tim Moran
Mikhail Pletnikov
Zachary Cordner
C Conover Talbot, Jr
Gretha Boersma

Maree Webster
Sanghyeon Kim
E Fuller Torrey

CHR HANSEN
(Diet and Cognitive)
AP-=Antipsychotic Naive

Gliadin and Psychiatric disorders

- Gliadin is the major antigen of gluten, a widely prevalent food glycoprotein.
- Gliadin antibodies are on average increased in individuals with schizophrenia and other psychiatric disorders.
- These antibodies are generally not associated with celiac disease.
- There is a significant amount of individual variation in antibody levels, subclasses, and immune specificity.
- Modulators include:
  - Diet/Source of Gluten
  - Microbiome
  - Medications
  - Genetics
- Controlled trials of gluten restriction
  - Participants selected by biomarkers
  - Strict gluten free diets
  - Gluten modifiers