Autoimmune phenotypes in psychiatric disorders

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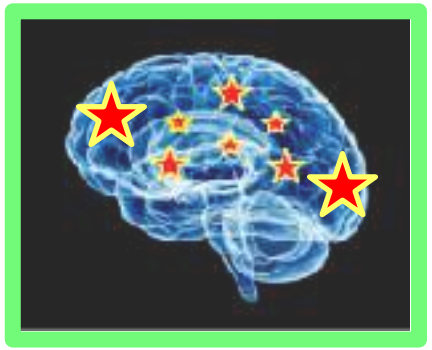


I have no disclosures to report.

Learning Objectives

- Overall, to understand how autoimmunity might contribute to psychiatric disorder diagnoses and/or symptoms
- Specifically, to review the evidence that imbalances of the gut-brain axis cause these autoimmune phenotypes in individuals with psychiatric disorders
- To identify gut and/or brain autoimmune triggers that might lead to the discovery of treatable therapeutic targets

Overview of the current state of schizophrenia & psychosis research

- The development of dopamine-centric antipsychotics has been followed by a stagnant phase of little progress in terms of finding new types of treatments for people with schizophrenia.
- The most promising research theme in schizophrenia involves the immune system which reconciles **gene-by-environmental** hypotheses for this disorder.

autoimmune [aw-toh-i-moon]

adjective

1. of or relating to the immune response of an organism against any of its own tissues, cells, or cell components
2. reflects the inability of a host to differentiate self from non-self
3. usually due to insufficient establishment or loss of immune tolerance

Common features of autoimmune disorders

- Infection is a major trigger of autoimmunity causing:
  - loss of tolerance through polyclonal autoreactive T cells
  - molecular mimicry
  - uncovering cryptic antigens
  - creation of novel self-reactive antigens
- Autoimmune conditions characterized by chronic inflammation, autoantibodies, & tissue injury (from immune complexes & these ICs activate complement)

Autoimmune disorders in schizophrenia

Strong epidemiological associations of autoimmune disorders with psychiatric disorders in large registry-based studies.

Epidemiology Mechanisms

	Autoimmune Disorders	Psychotic Disorders	Low level inflammation	Infection/Pathogen exposures	Autoantibodies (brain-reactive)
Autoimmune Disorders	4%	3.4%	YES	YES	YES
Psychotic Disorders	6-55%	1%	YES	YES	YES

Also associated autoimmune/schizophrenia risk elevated across families (Jeppesen & Benros, 2019)

Autoantibodies & neuropsychiatric problems

Autoimmune Encephalitis

anti-N-methyl-D-aspartate receptor (NMDAR), neuronal surface antibodies

Autoimmune Thyroid Disorders

anti-thyroid antibodies

Celiac disease

anti-gliadin, tissue transglutaminase, endomysial, reticulin IgA antibodies

Crohn's disease

anti-Saccharomyces cerevisiae, flagellin antibodies

Diabetes Type I

anti-glutamic acid decarboxylase (GAD) antibodies

Lupus

anti-GAD, NMDAR antibodies

Multiple sclerosis

(Jeppesen & Benros, 2019)

Pathogen exposures & risk for schizophrenia

Environmental exposures – pathogens & infections

(many decades of evidence; reviewed by Severance & Yolken, 2020)

Associated with diagnosis, symptoms, structural loss

- Viral pathogens
  - herpesviruses
  - coronaviruses
  - influenza viruses
  - endogenous retroviruses
- Toxoplasma gondii
- Candida yeast infections
- Gut microbe dysbiosis

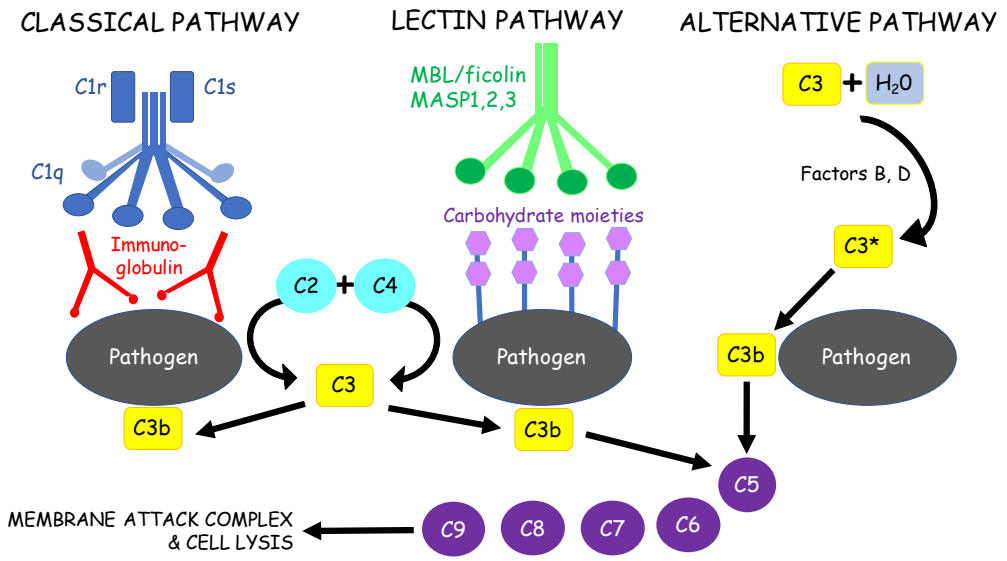
Inflammation, autoimmunity & the complement system

- The best-studied main function of the complement system is to detect & eliminate pathogens.
- When dysregulated, the complement system causes cellular and tissue damage through inflammation.
- Dysregulated complement is a key component of numerous autoimmune disorders including systemic lupus erythematosus, vasculitis, Sjögren's syndrome, and rheumatoid arthritis.
- Complement deficiencies are thought to increase the risk of developing autoimmune disorders.
- These deficiencies may be treatable by inhibiting complement activation components, complement receptors, and membrane attack complex. (Ballanti et al, 2013)

Complement, autoimmunity & the brain

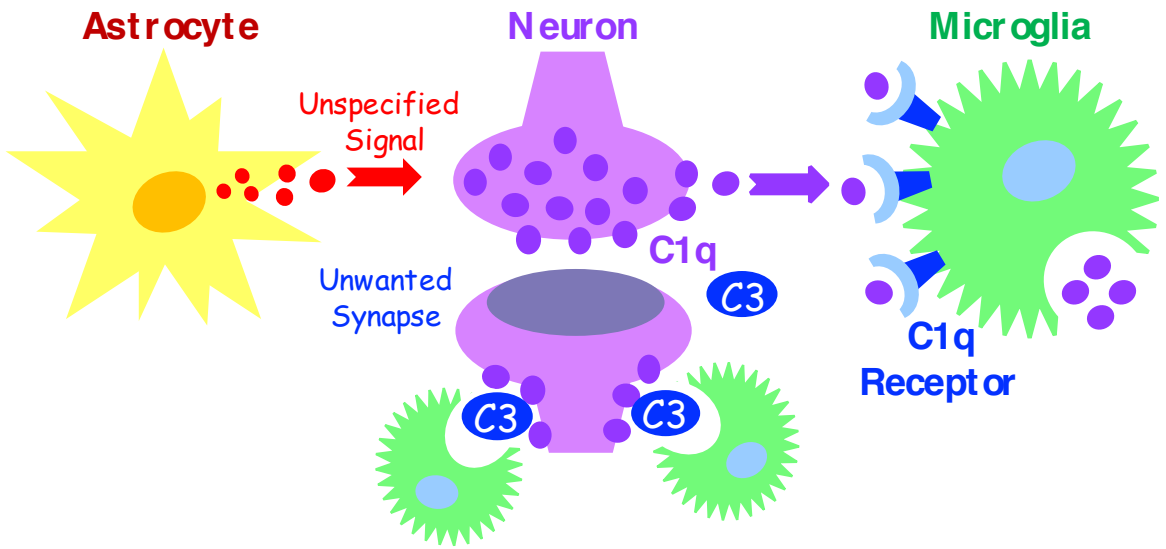
Peripheral Complement

Nimgaonkar et al, 2017



Complement in the CNS

Based on Stevens et al, 2012 & Sekar et al, 2016



Peripherally, complement acts in:

- immune surveillance
- protection of host
- neurogenesis?
- synapse pruning?

In the brain, complement acts in:

- immune surveillance
- protection of host
- synapse pruning

Gene-by-environmental immune interactions in schizophrenia

Environmental exposures - infections (many decades of evidence)

Associated with diagnosis, symptoms, structural loss

- Viral pathogens
  - herpesviruses
  - coronaviruses
  - influenza viruses
  - endogenous retroviruses
- Toxoplasma gondii
- Candida yeast infections

+ Immune gene mutations (last decades)

6p21-6p22 chromosomal region

MHC/HLA & Complement C4 genes

FUNCTION:

- present antigens as self or non-self
- clear invaders & debris
- systemically & in the brain!!!

DYSFUNCTION:

- infectious disease susceptibility
- autoimmunity

What is the source of this autoimmunity in schizophrenia?

Why not check out the largest immune organ in the body - the gastrointestinal (GI) mucosa?

- The GI tract serves as a critical hub regulating self and non-self interactions via the gut-associated lymphoid tissue (GALT).
- The GALT conveys immune tolerance to the complex community of commensal microbes, externally-derived dietary products, and the host's own cellular machinery, while simultaneously protecting the body from destructive pathogens and other dangerous antigens.
- Gut microbes and their products, when functioning correctly, control the immune response and inflammatory status of the GI tract.

The gut-brain axis when dysregulated can generate potent pathological autoimmunity.

Why does the gut matter in schizophrenia & psychoses?

- GI disorders (IBD, IBS, Celiac disease) are prevalent in schizophrenia with estimates ranging from 30 to 90%.
- Psychiatric comorbidities are prevalent in IBD, IBS & Celiac disease with estimates ranging from 20 to 94%.
- GI inflammation, compromised blood-gut & blood-brain barrier, & dysbiotic gut microbiome are all prevalent in schizophrenia.
- Recorded GI conditions in schizophrenia predate DSM, ICD & the 1950's development of antipsychotics.
- Important source of neurotransmitters (serotonin, GABA, tryptophan, norepinephrine, epinephrine, dopamine)
- Provides exchange of other neuroactive molecules (immunomodulatory, antimicrobial neuropeptides)
- Gut bacteria are easily accessed and can be altered through anti-infective agents, anti-inflammatories, gut dysbiosis correction such as probiotics, prebiotics, diet and fecal transplants.

Why does the gut matter in schizophrenia & psychoses?

References for previous slide

Epidemiology & general (Bernstein et al 2019; Buscaino 1953; Gupta et al 1997; Lee et al 2015; Wei & Hemmings 2005; Whitehead et al 2002)

Low-level inflammation (Müller 2018; Bechter 2013; Severance et al 2012)

Leaky gut pathology (Severance et al 2012; 2013; 2019)

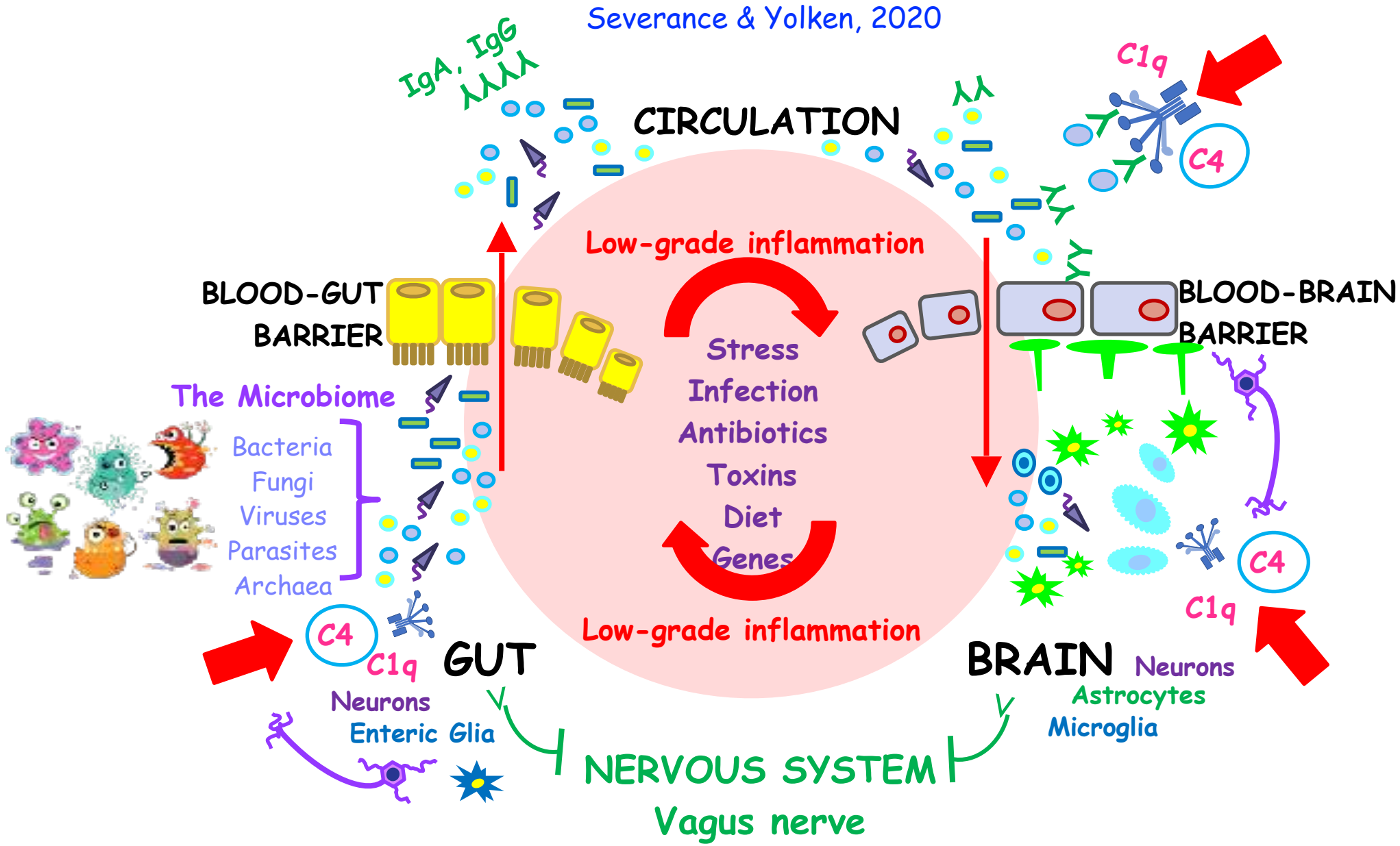
Links to pathogens (esp Toxoplasma gondii, a gut pathogen) (Burgdorf et al 2019; Torrey et al 2012)

Links to food antigens (Cascella et al 2011; Dohan 1966a,b; Severance et al 2010)

Disease-associated shifts in microbial inventories (Castro-Nallar et al 2015; Yolken et al 2015; Schwarz et al 2018; Nguyen et al 20109; Zheng et al 2019)

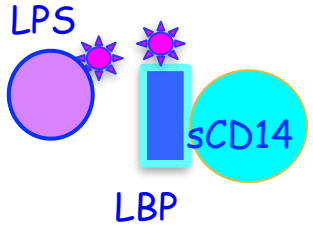
Modest improvements of symptoms with probiotics (Dickerson et al 2014;Tomasik et al 2015; Severance et al 2017; Ng et al 2019; Genedi et al 2019; Okubo et al 2019)

Gut-immune-brain model in schizophrenia



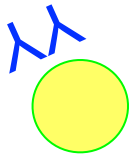
Gut-brain serum/plasma biomarkers in schizophrenia

Bacteria



Pathogens

Viruses
Toxoplasma gondii IgG
Bacteria
Fungi

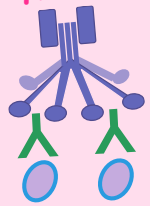


Yeast

Candida albicans IgG
Saccharomyces cerevisiae
IgA, IgG

Complement

C1q, C4



Dietary antigens

Milk casein IgG
Wheat gluten IgG

Autoimmune features

NMDAR autoantibodies
C1q, C4 dysregulation
Wheat gluten IgG

Cellular barriers

S100B
Toxoplasma gondii IgG
Wheat gluten IgG
LBP

Inflammation

General
C-Reactive Protein
Complement
GI
Dietary antigens
Yeast
Bacteria

Severance & Yolken, 2020

Research Stories

1. Biomarkers detect elevated food antigen sensitivities, GI inflammation & complement activation in psychiatric disorders compared to controls

with schizophrenia to a susceptibility to infections and gut dysbiosis

Serum Biomarker Discovery Methods

Patient population: Blood samples from ongoing studies at Sheppard Pratt Health System, Baltimore, MD, U.S.A.

(n=900+ established schizophrenia, n=500+ bipolar disorder, n=500+ controls)

Blood biomarkers:

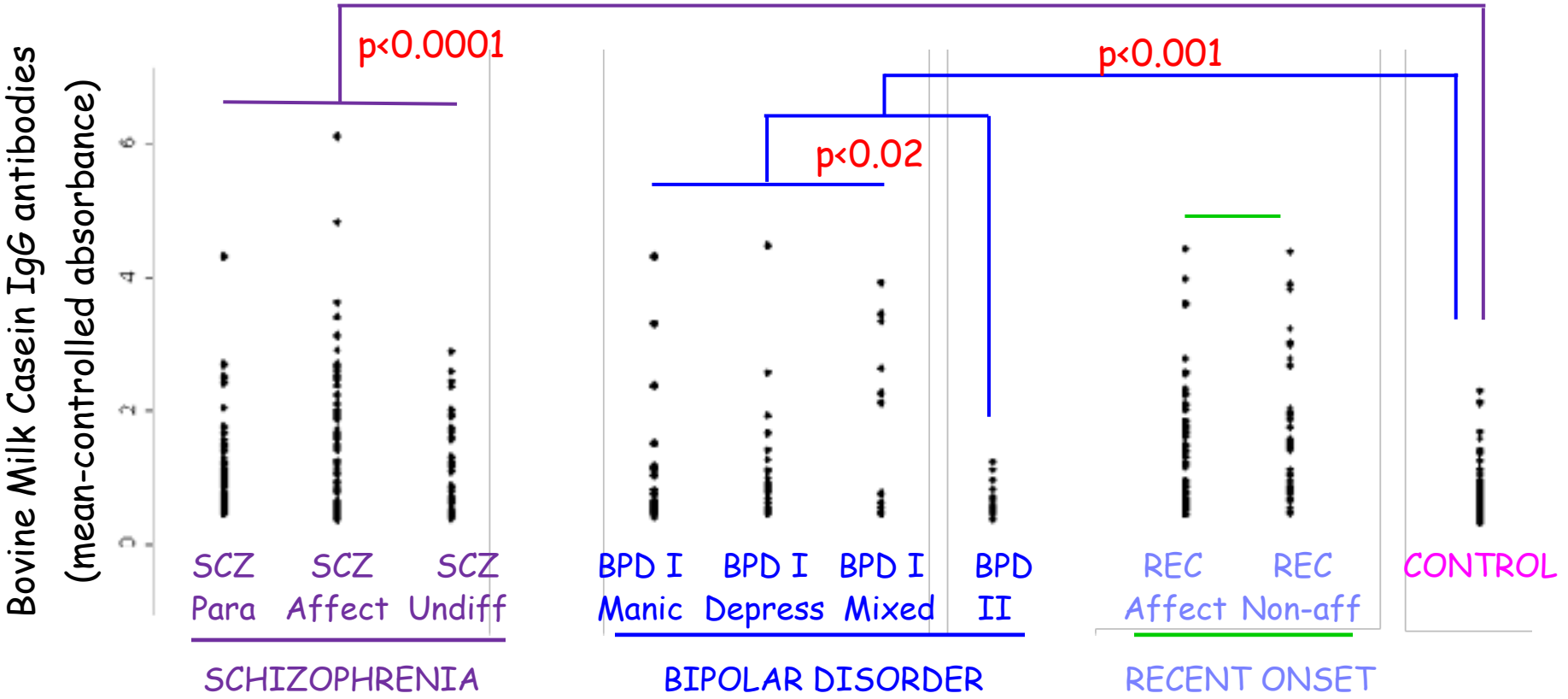
- Complement pathway components
- Dietary antigens
- Yeast translocation
- Bacterial translocation
- Endothelial barrier instability
- Inflammation
- Autoimmune features

Hamilton Depression Rating Scale for depression, psychic anxiety & somatic anxiety

RBANS scores for cognition; PANSS scores for psychiatric symptoms

Dietary antigens, inflammation & the gut

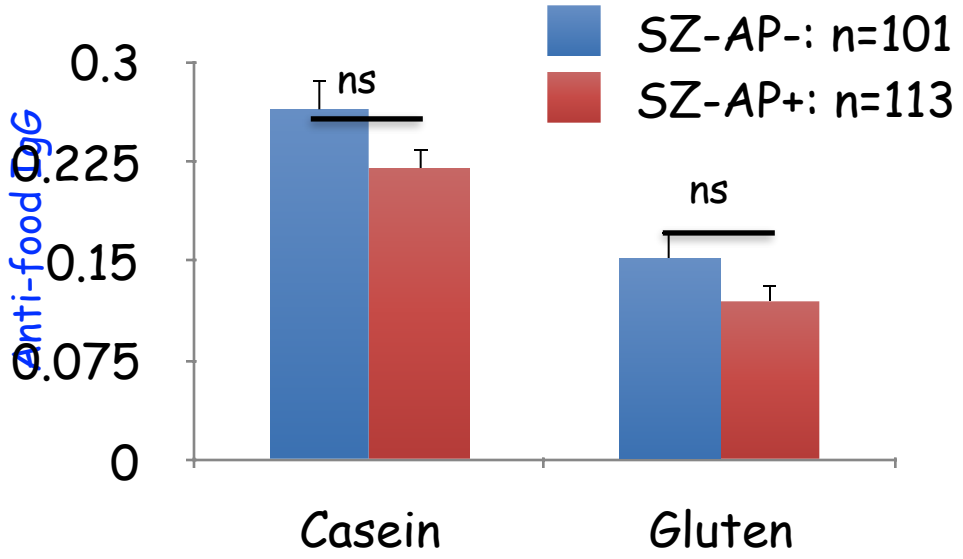
Anti-food antibodies were elevated in SCH & BPD compared to controls and in BPD I subtypes compared to BPD II subtypes.

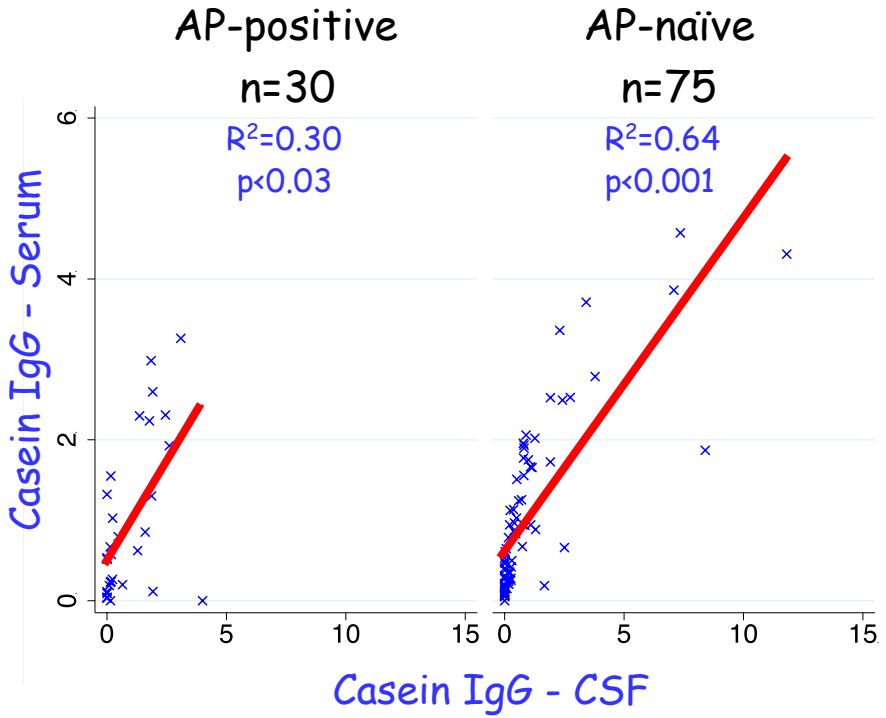


Severance et al, 2010a,b

Medication effects?

Disease associated anti-food antibodies are not a function of medication.





Same patterns for anti-fungal IgG (S. cerevisiae & C. albicans)

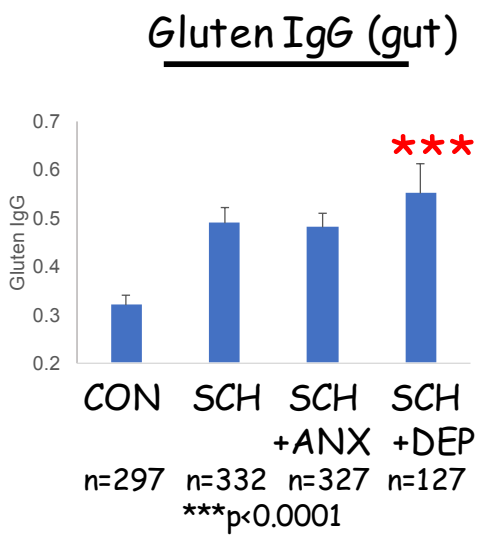
Severance et al, 2010a,b; 2012; 2015; 2016

Refining a responsive phenotype (for clinical trials)

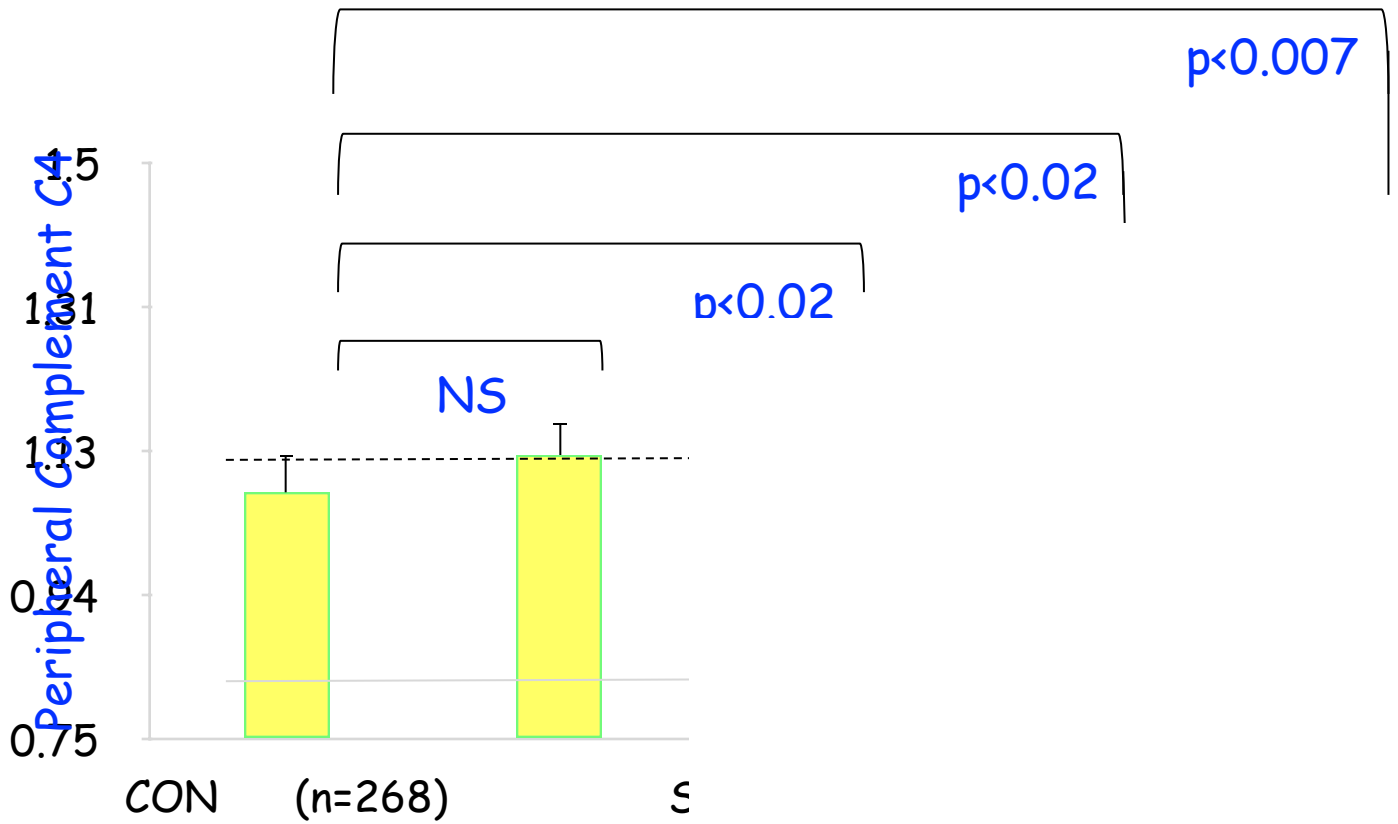
Schizophrenia + Comorbid Anxiety & Depression

Dietary antigens

Wheat gluten IgG



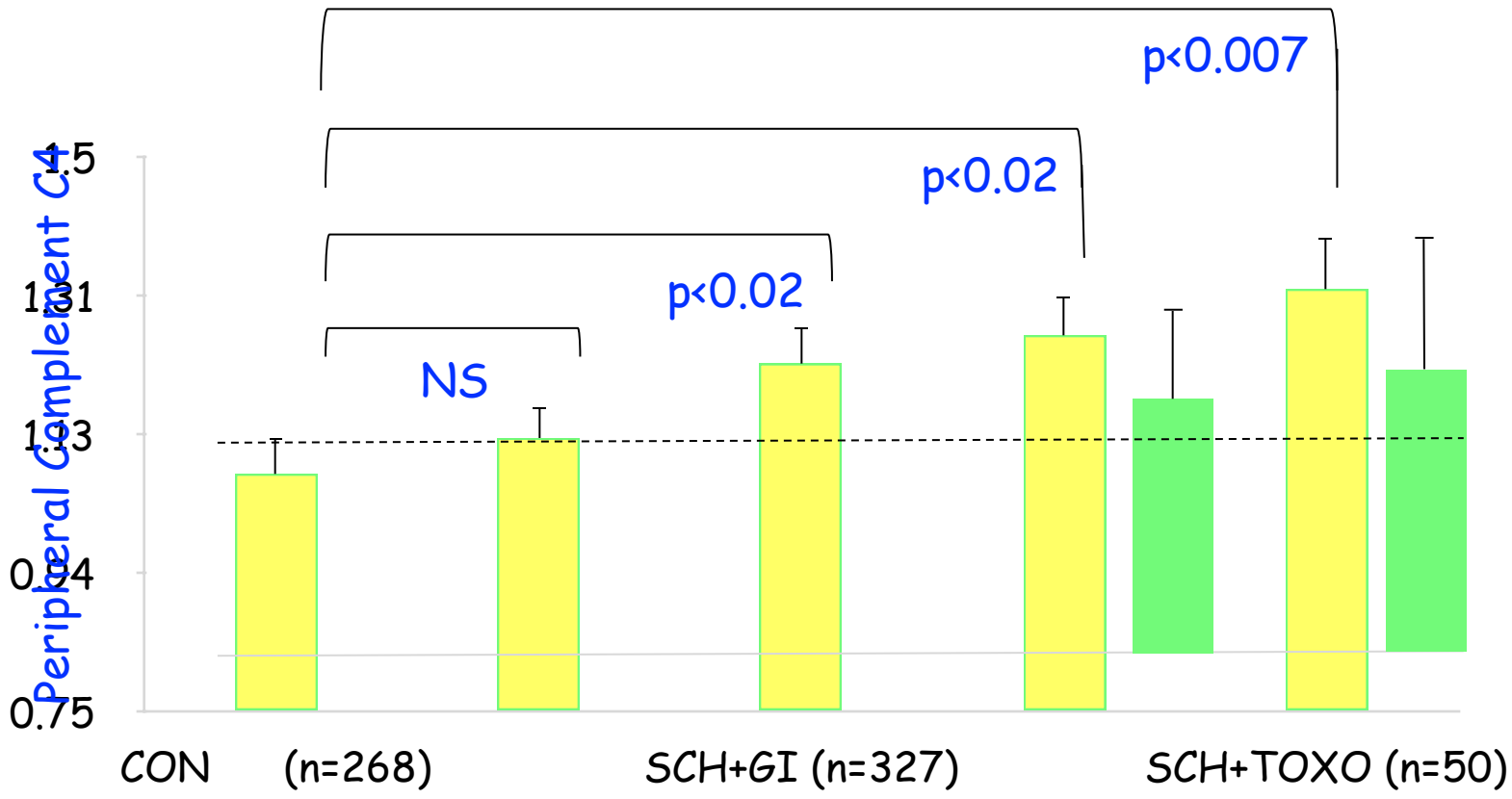
Differences in plasma complement C4 protein in schizophrenia vs non-psychiatric comparison group?



CON = non-psychiatric comparison group

Severance et al., Unpublished

Differences in plasma complement C4 protein in schizophrenia vs non-psychiatric comparison group?

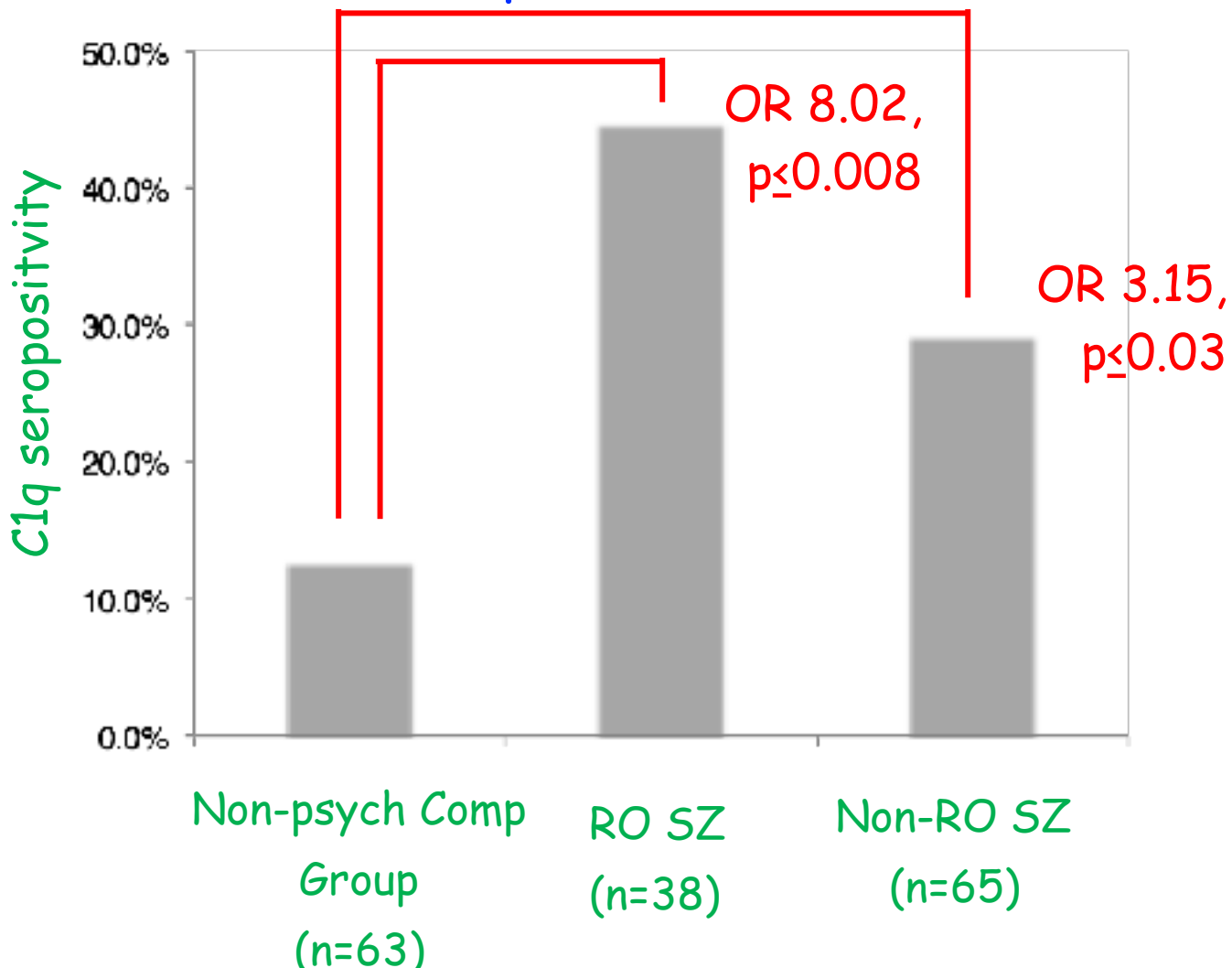


CON = non-psychiatric comparison group

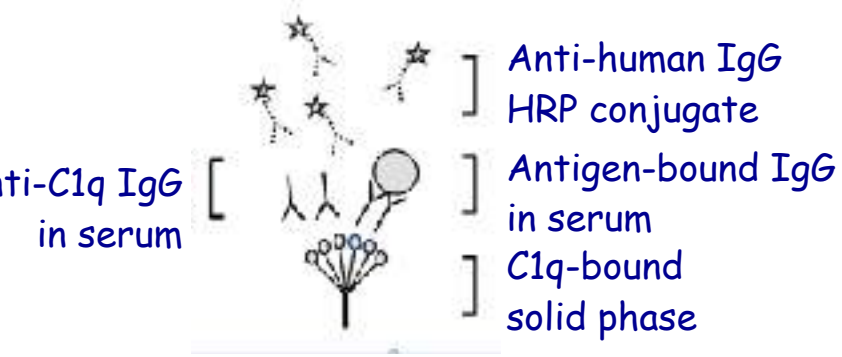
Severance et al., Unpublished

Peripheral C1q-containing immune complexes

Recent-onset & non-recent onset schizophrenia



C1q immune complexes & autoantibodies:

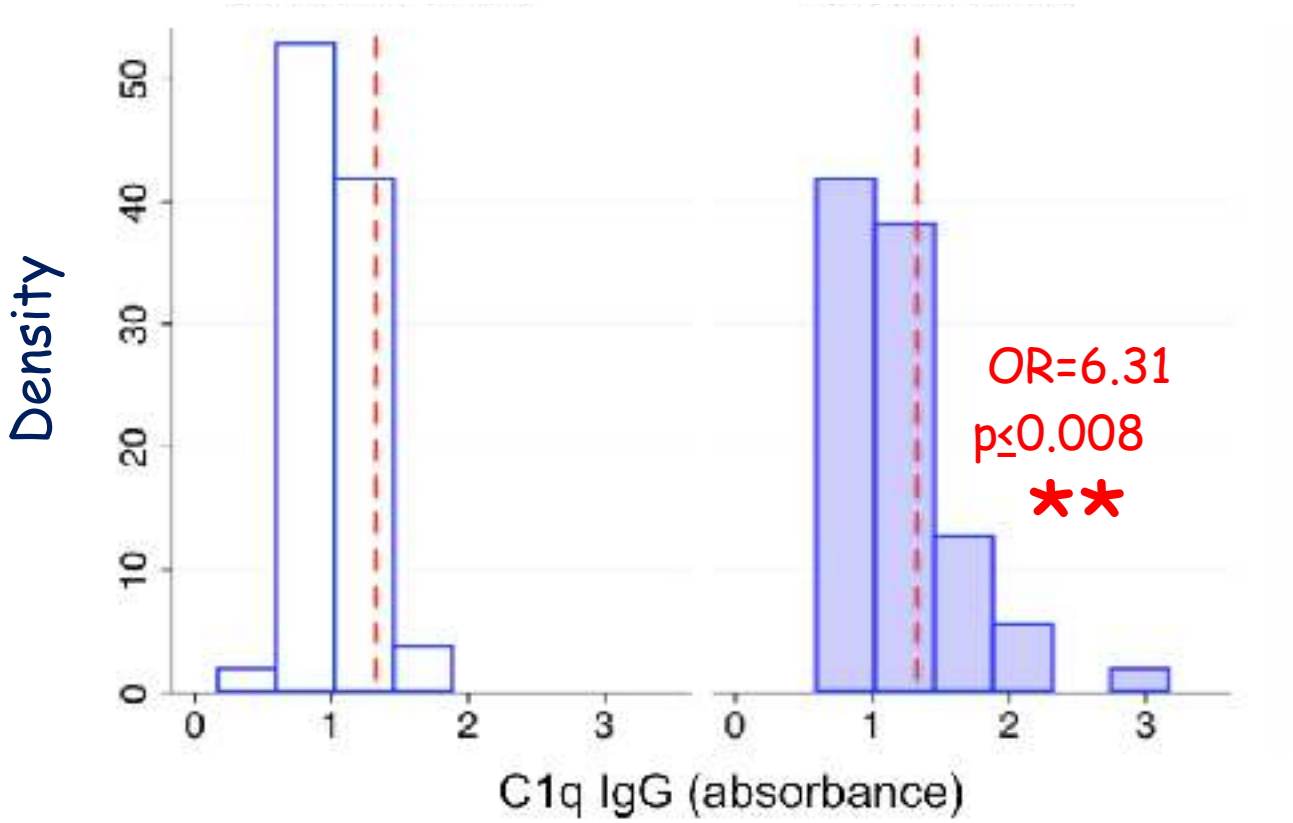


Epstein Barr Virus

Severance et al., 2012b

Maternal complement activation & schizophrenia/psychoses

National Collaborative Perinatal Project



n= 55 matched pairs

Antigens associated with maternal C1q:

- gluten
- HSV2
- adenovirus

Severance et al., 2014

Research Stories

1. Biomarkers detect elevated food antigen sensitivities, GI inflammation & complement activation in psychiatric disorders compared to controls

2. Translational study of infection in mice and schizophrenia reveals unfolding of Gut-immune-brain model:

    - GI inflammation leads to loss of endothelial barrier integrity, and generation of brain-active NMDA receptor autoantibodies
    - GI inflammation leads to activation of the complement pathway peripherally and in the brain.

3. Specific complement C4 genotypes predispose certain individuals with schizophrenia to a susceptibility to infections and gut dysbiosis

Toxoplasma gondii, a common parasite & cellular barrier breaker

- T. gondii is found worldwide, infects warm-blooded animals & transmits via ingestion.
- From the gut, T. gondii causes inflammation & disseminates throughout the body including to the brain.

- Hosts infected with this parasite can display altered behaviors & cognitive deficits.
- Numerous investigations demonstrate that T. gondii infection increases the risk for schizophrenia.

(Burgdorf et al 2019; Severance et al 2018; Torrey et al 2012).

Study Objectives & Design

MICE

Evaluate histochemical & blood biomarker evidence of blood-gut & blood-brain barrier permeability in a T. gondii model of infection

T. gondii model of infection; male BALB/c; n=4-8 per group

Cohort 1: Time series; 2,4,6,8,12,16,20 wpi;T. gondii (PRU, ME49)

Cohort 2: Live parasite vs UV-inactivated; 19 wpi

HUMANS

Validate mouse findings in populations of individuals with schizophrenia & a non-psychiatric comparison group

Identify T. gondii seropositive individuals in:

Cohort 1: n=602 established schizophrenia
n=297 controls
Sheppard Pratt Health System, Baltimore, MD, U.S.A.

Cohort 2: n=66 antipsychotic-naïve schizophrenia
n=57 medicated schizophrenia
Universities of Cologne, Germany & Sydney, Australia

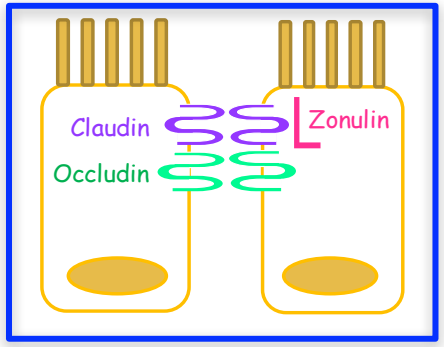
Kannan…Severance, 2017

Part 1

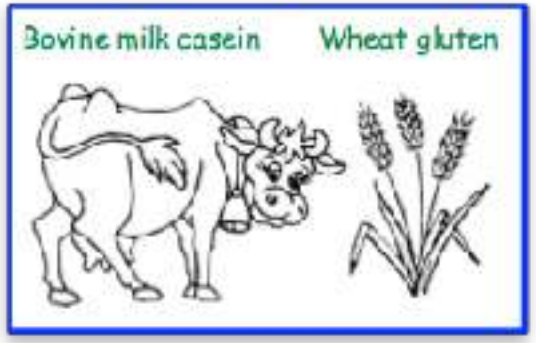
MICE

Evaluate histochemical & blood biomarker evidence of blood-gut & blood-brain barrier permeability in a T. gondii model of infection

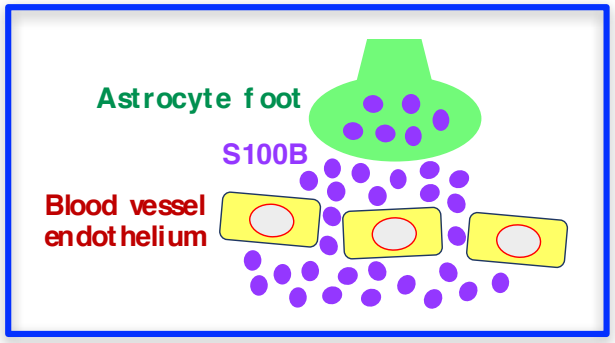
GI permeability
Tight Junction Proteins



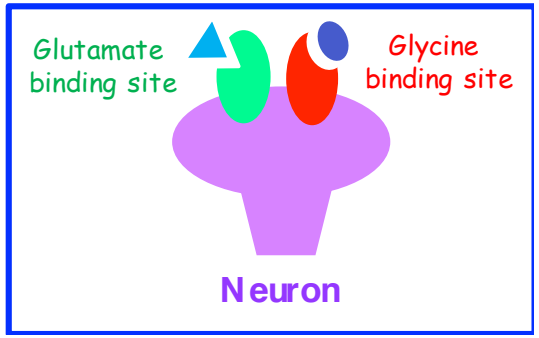
GI inflammation
Anti-gluten grain IgG



BBB permeability
S100B



Autoimmunity
NMDAR IgG

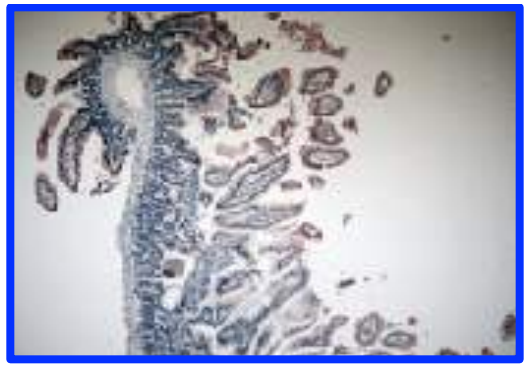


T. gondii infection & gut tight junction protein stability

DAB immunohistochemistry

Uninfected

↑ Claudin-1 expression



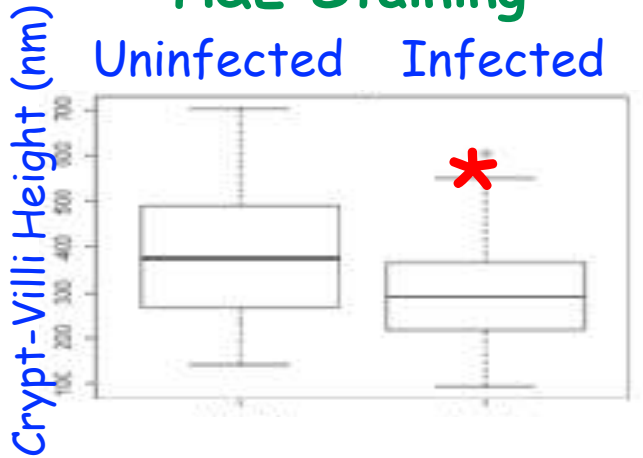
Infected

↓ Claudin-1 expression

↑ Zonulin expression

↓ Zonulin expression

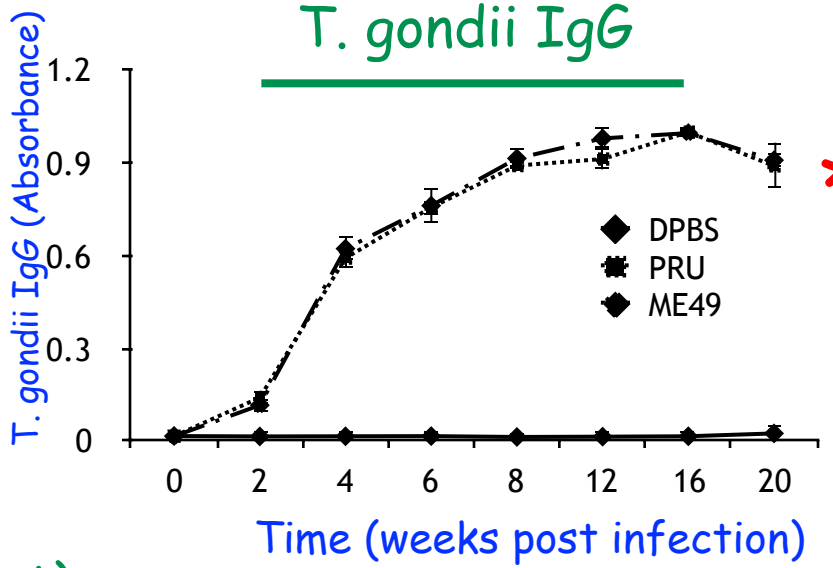
H&E Staining



Severance Unpublished

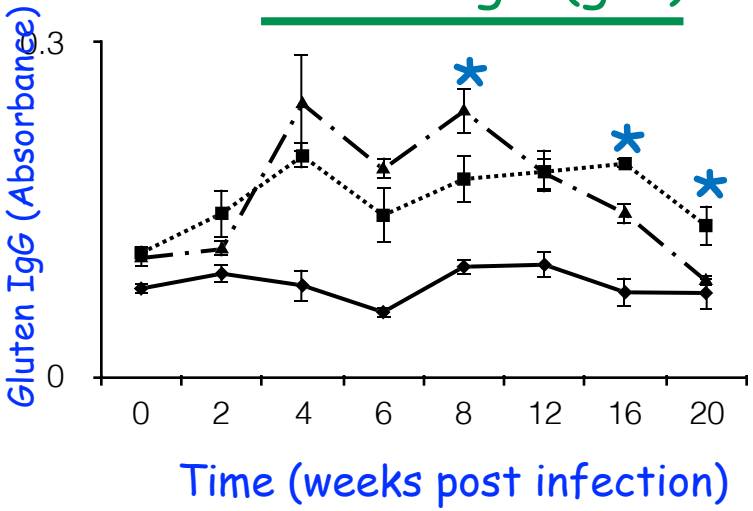
T. gondii infection & blood barrier biomarkers

T. gondii IgG



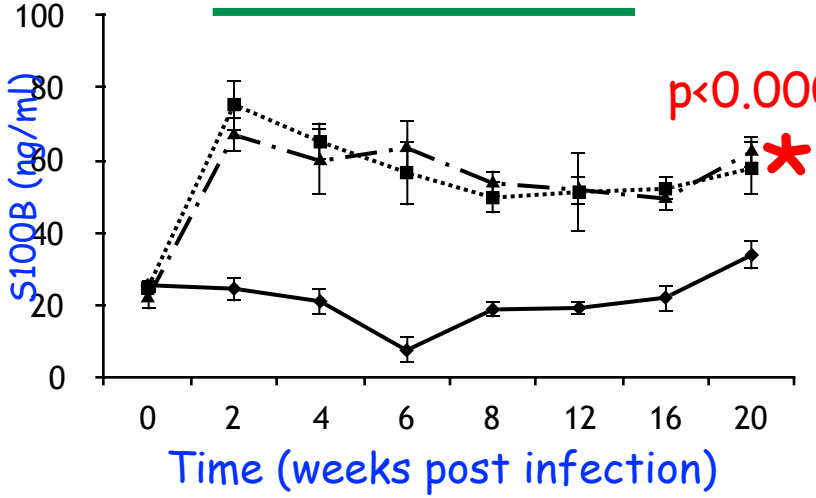
* Interaction Time & Infection
p<0.0001

Gluten IgG (gut)



p<0.0001

S100B (brain)

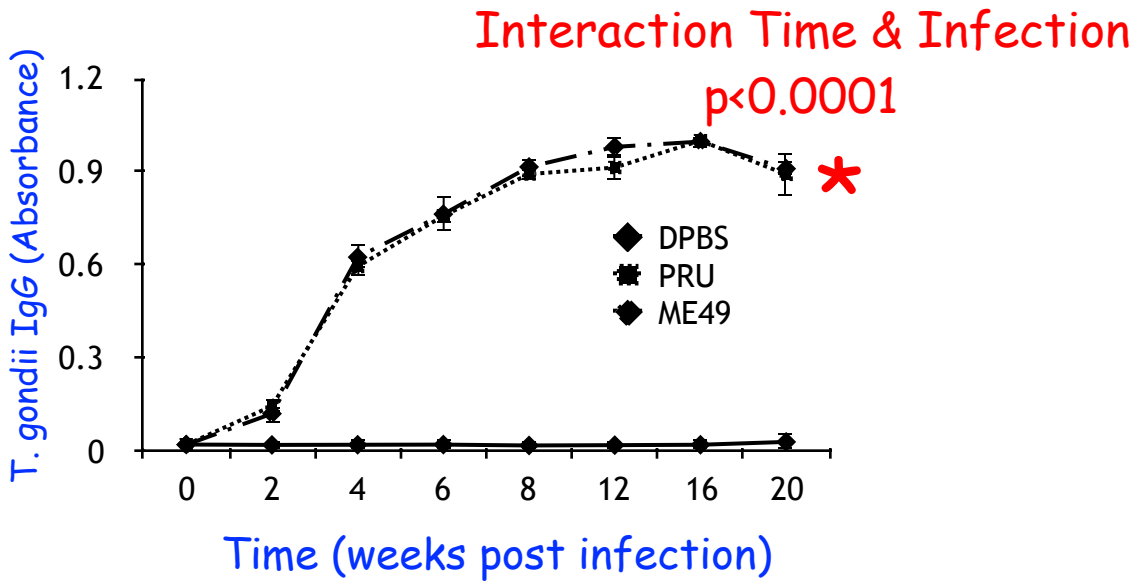


p<0.0002

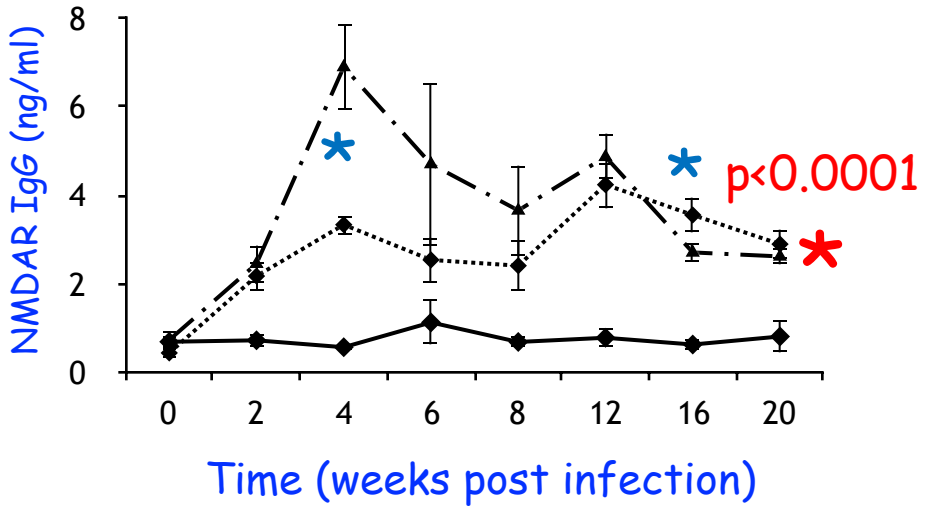
Kannan…Severance, 2017

T. gondii infection & autoimmunity

T. gondii IgG



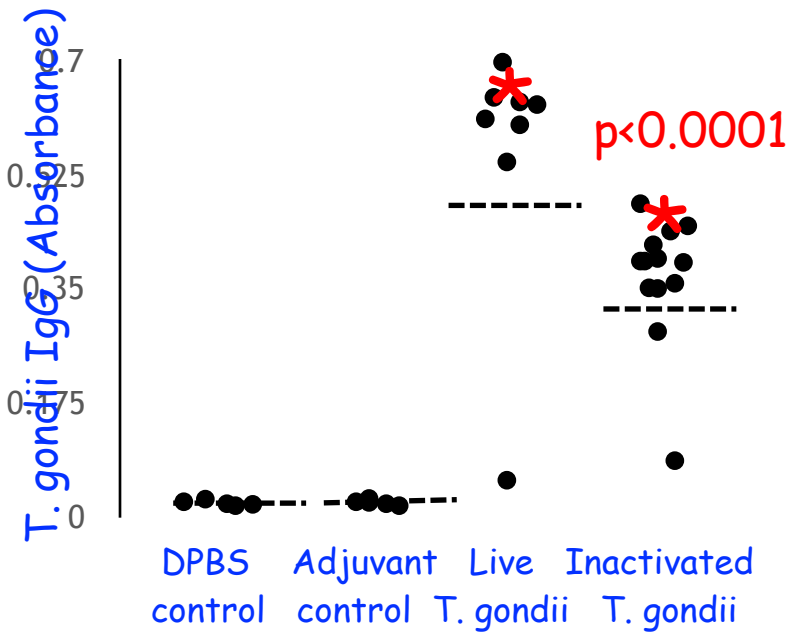
NMDAR IgG



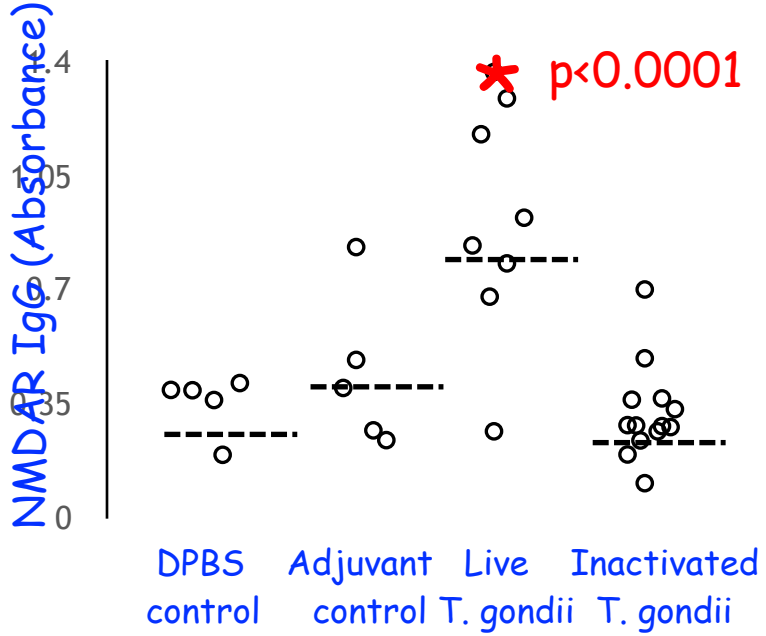
Kannan…Severance, 2017

T. gondii infection, autoimmunity & cross-reactivity

T. gondii IgG



NMDAR IgG



Kannan…Severance, 2017

Part 2

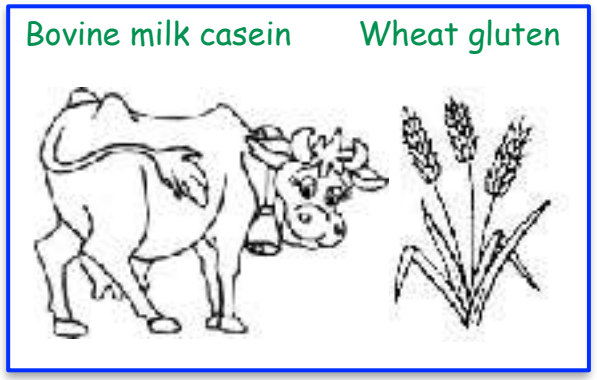
HUMANS

Validate mouse findings in two schizophrenia cohorts stratified by T. gondii seropositivity:

- Cohort 1: Case-control
- Cohort 2: Antipsychotic-naïve vs. medicated

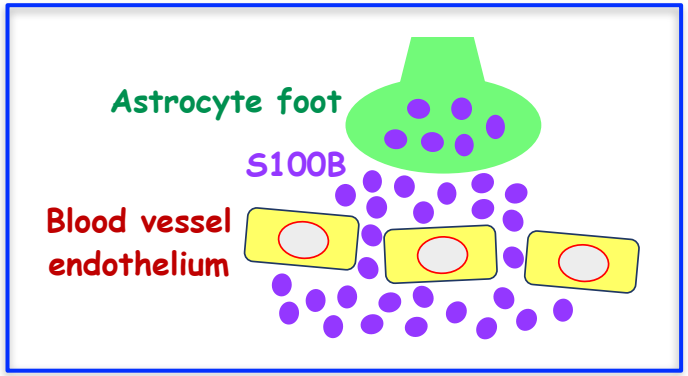
GI inflammation

Anti-gluten grain IgG



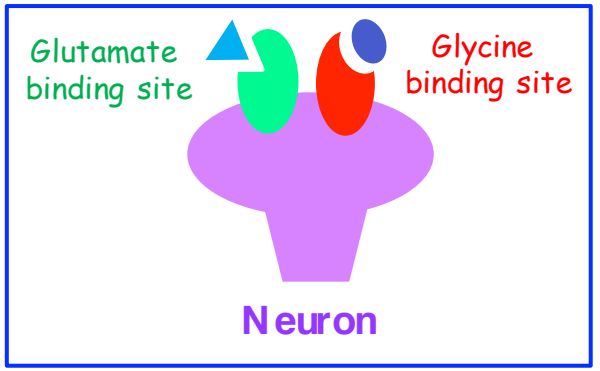
BBB permeability

S100B



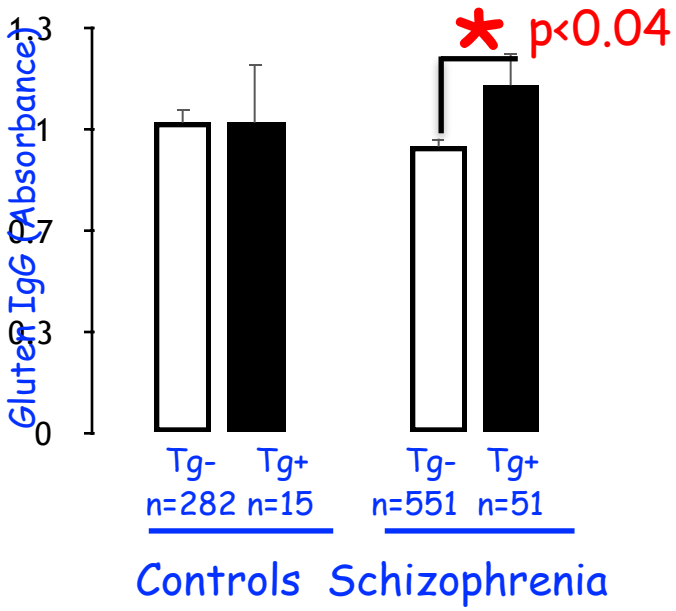
Autoimmunity

NMDAR IgG

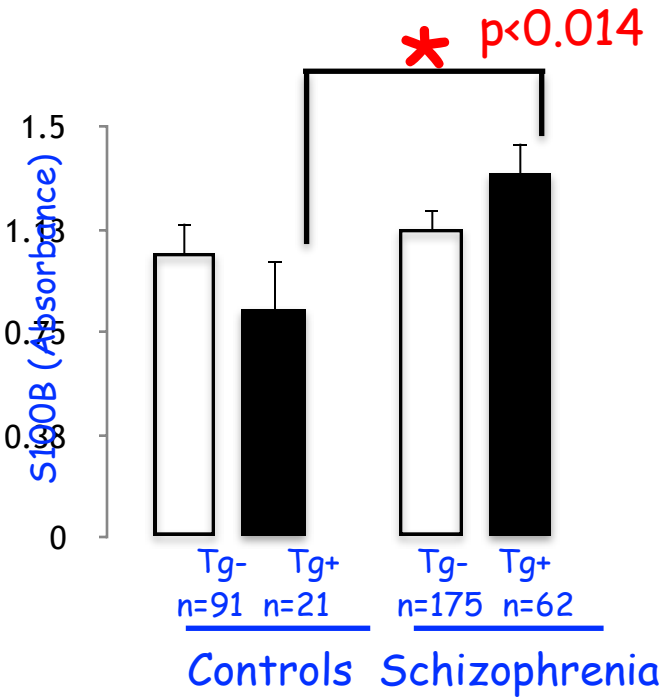


T. gondii infection & blood barrier biomarkers

Gluten IgG (gut)



S100B (brain)

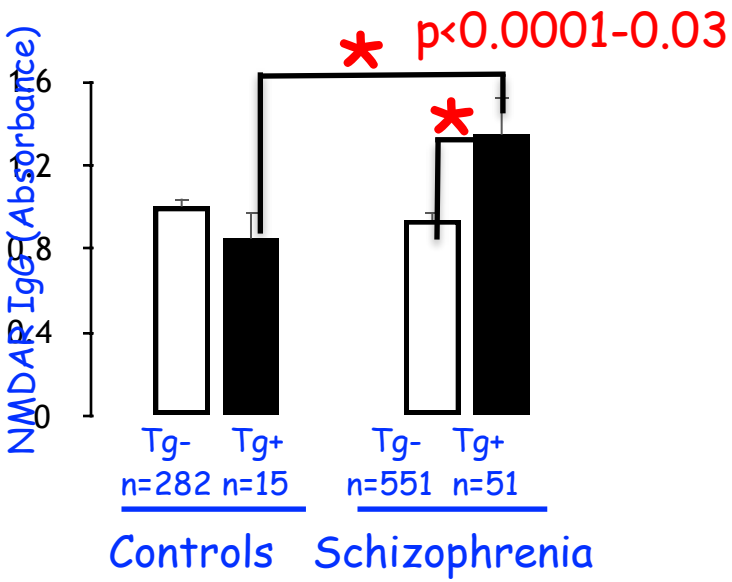


Kannan…Severance, 2017

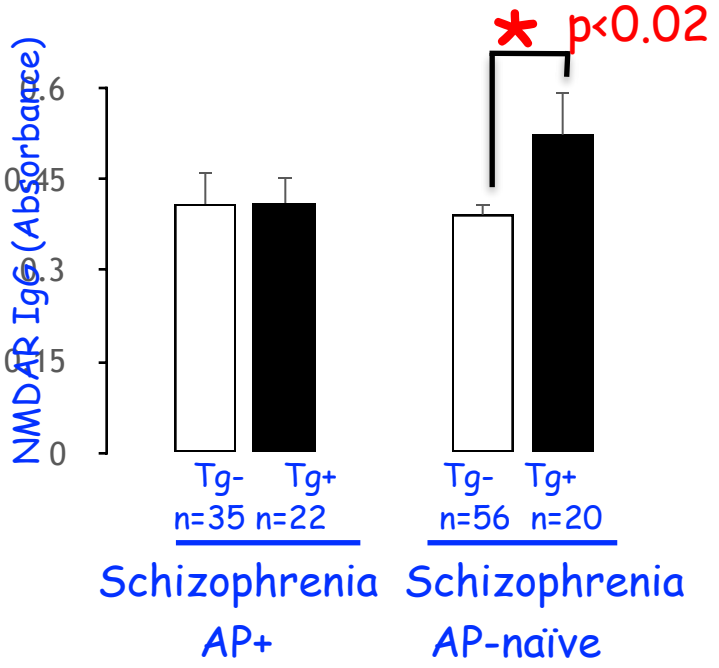
T. gondii infection & autoimmunity

NMDAR IgG

Human 1 cohort: case-control

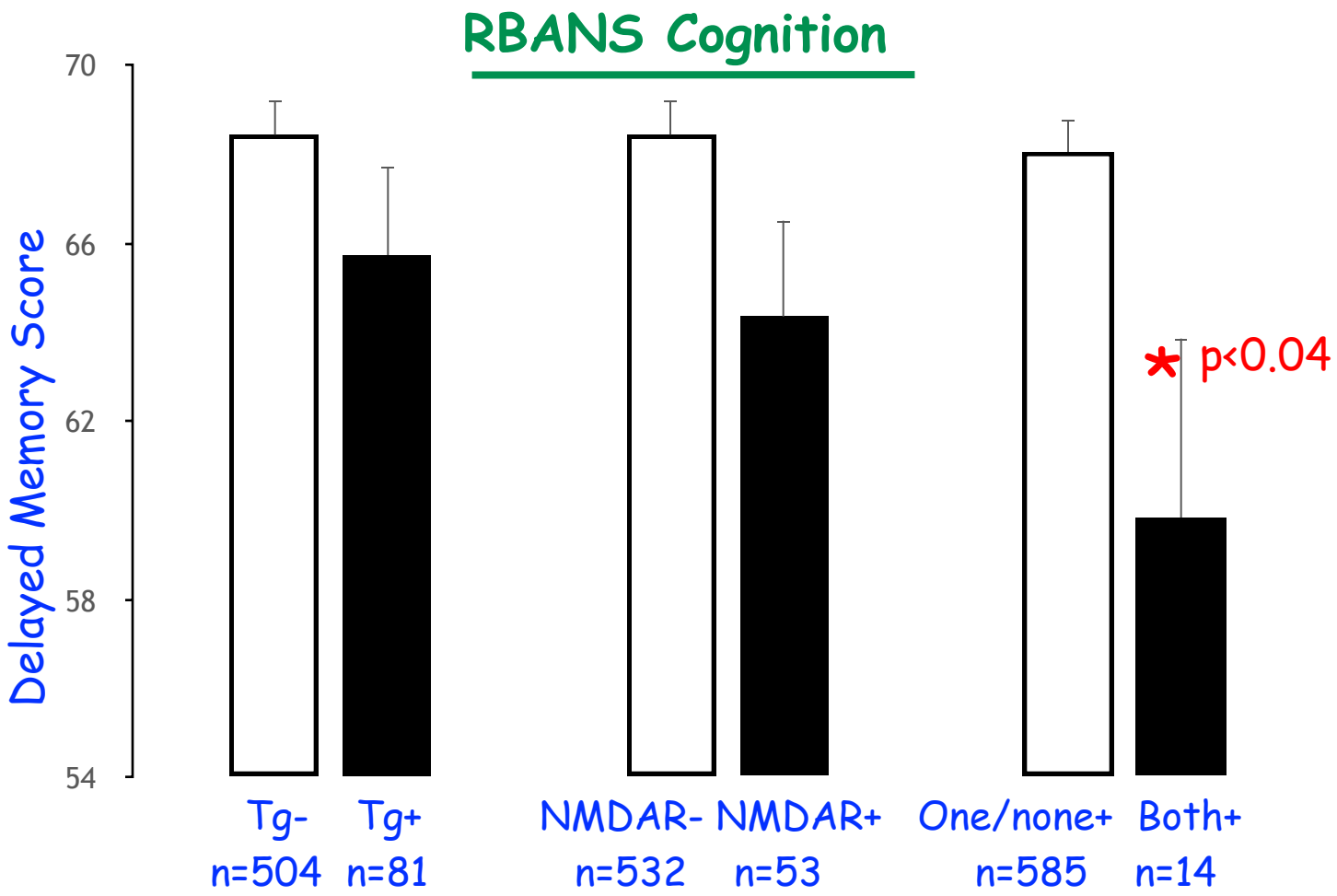


Human 2 cohort: medication



Kannan…Severance, 2017

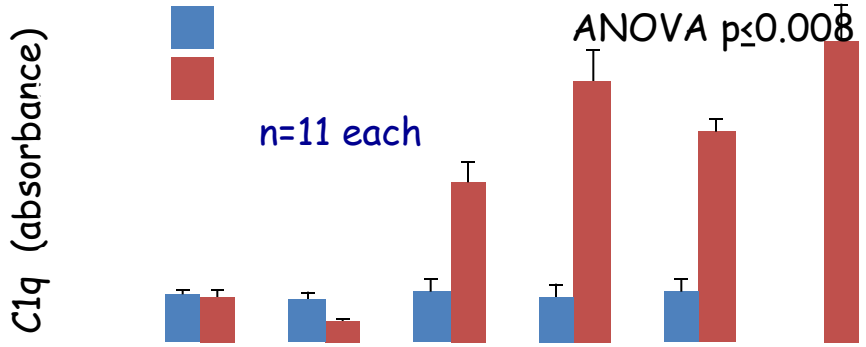
T. gondii & consequences of autoimmunity



Kannan…Severance, 2017

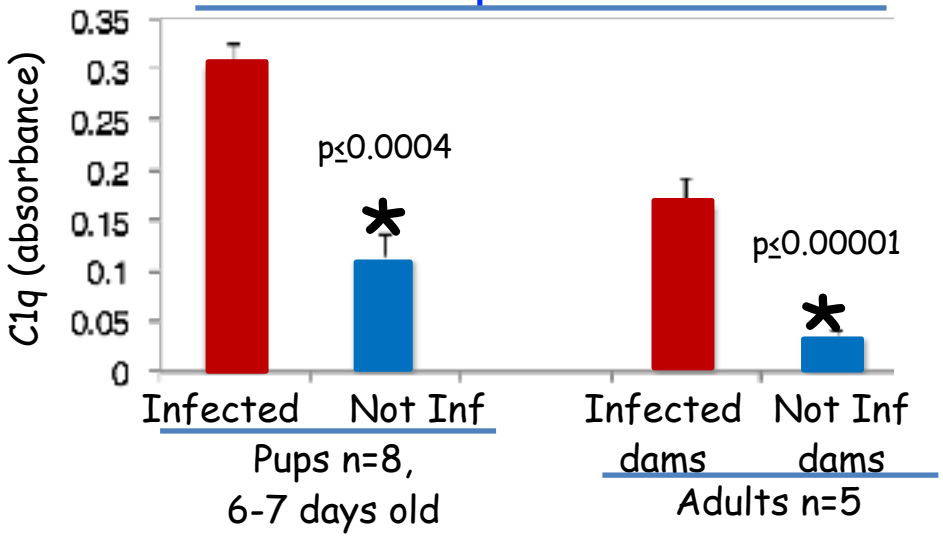
What about complement??? (SERUM - Mice)

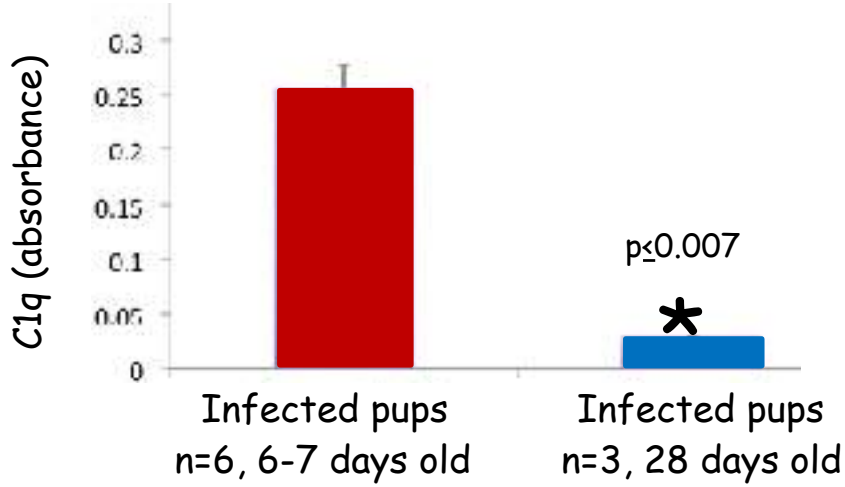
Intraperitoneal infection (n=22)



Peroral infection (n=32)

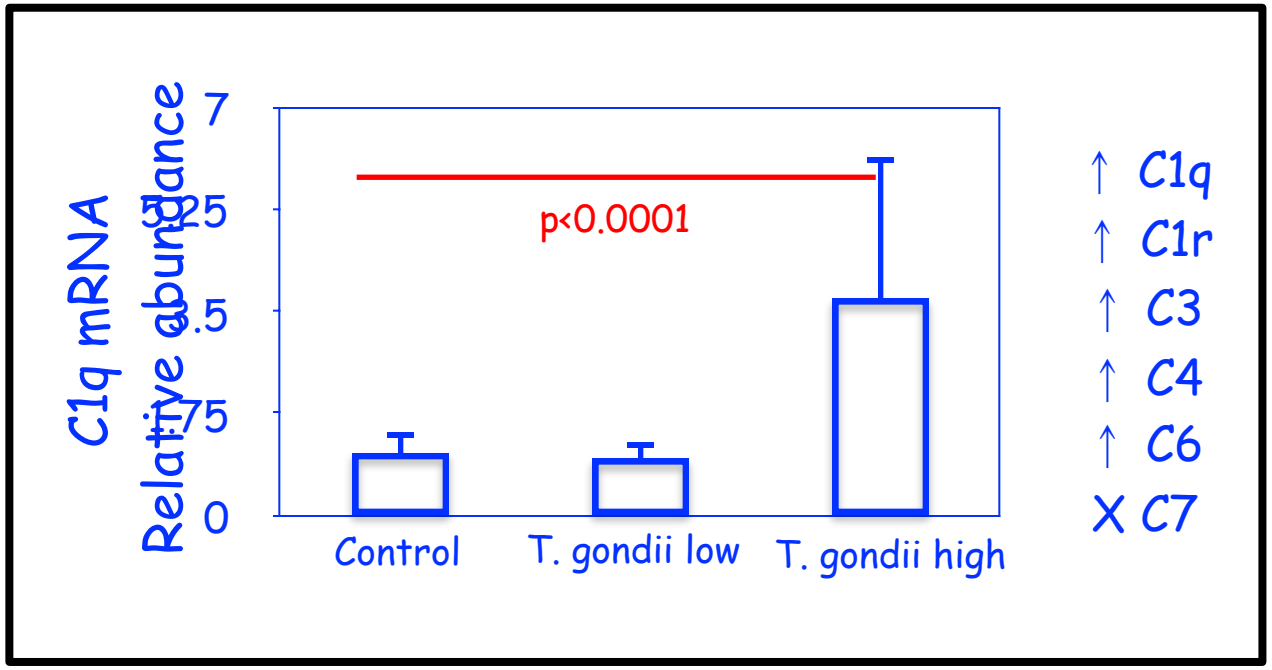
Prenatal exposure



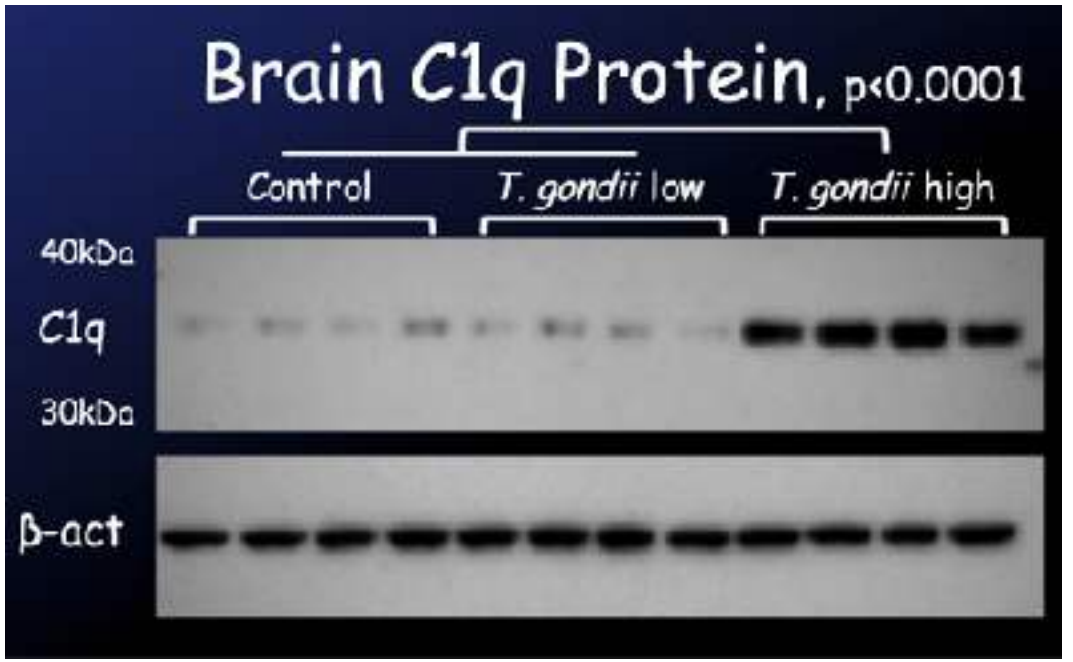


Complement activation in immune-challenged mice - BRAIN

Prefrontal Cortex mRNA



Prefrontal Cortex Protein

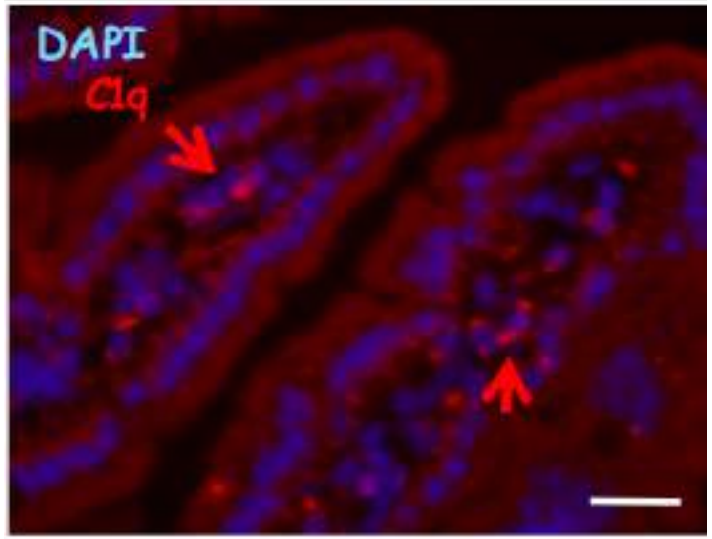


Li et al., 2019; Xiao…Severance, 2016

Multisite-complement activation in immune-challenged mice

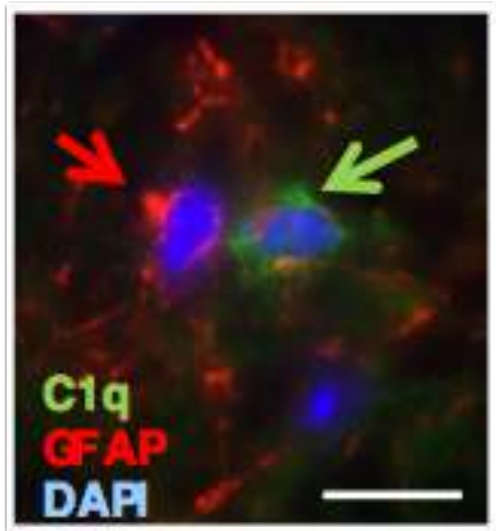
GUT

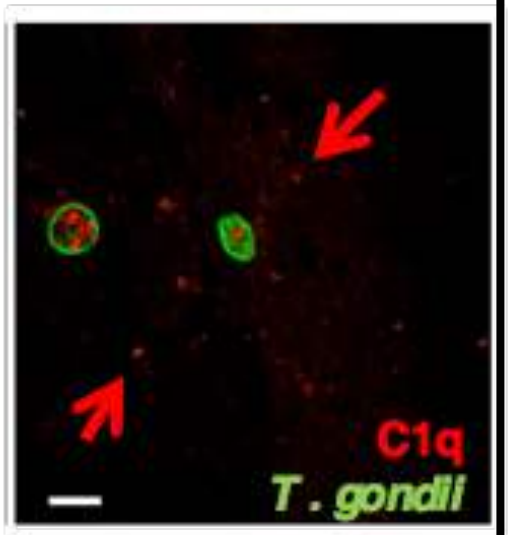
Gut C1q after infection



BRAIN

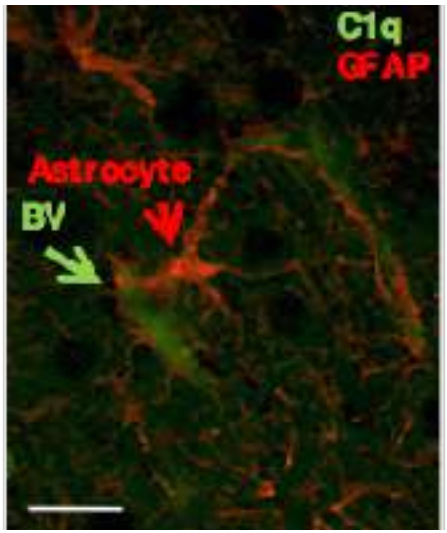
Brain C1q – intracellular & synaptic





BBB

Blood C1q at BBB



Severance et al., Unpub; Xiao…Severance, 2016

Research Stories

1. Biomarkers detect elevated food antigen sensitivities, GI inflammation & complement activation in psychiatric disorders compared to controls

2. Translational study of infection in mice and schizophrenia reveals unfolding of Gut-immune-brain model:

   - GI inflammation leads to loss of endothelial barrier integrity, and generation of brain-active NMDA receptor autoantibodies
   - GI inflammation leads to activation of the complement pathway peripherally and in the brain.

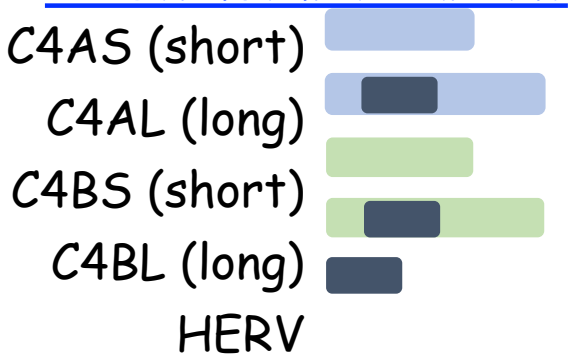
3. Specific complement C4 genotypes predispose certain individuals with schizophrenia to a susceptibility to infections and gut dysbiosis

What about the genes???

Sekar et al, Nature 2016

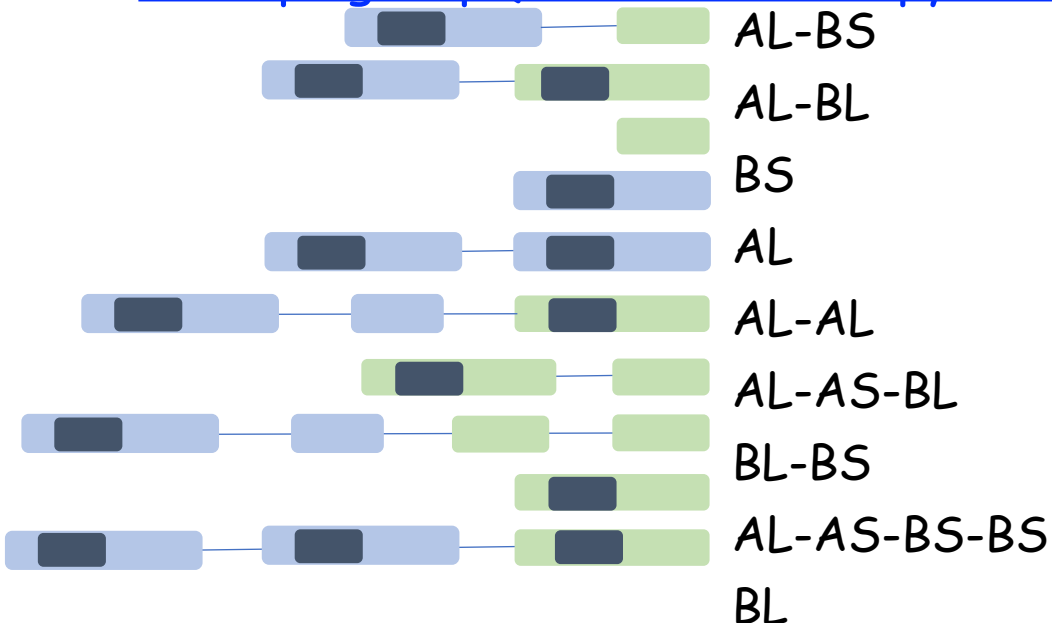
A

C4 structural variant



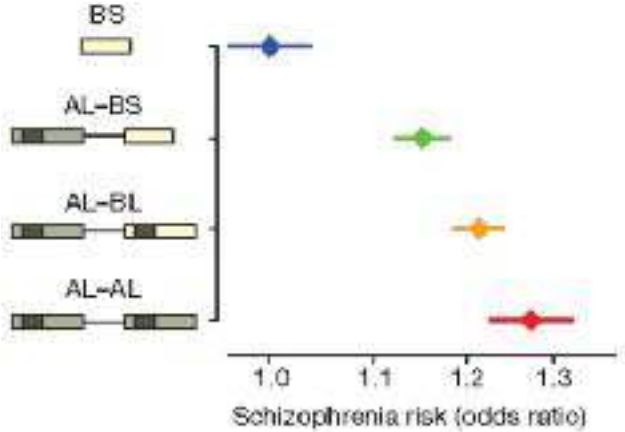
B

C4 haplogroup (structural & copy number)



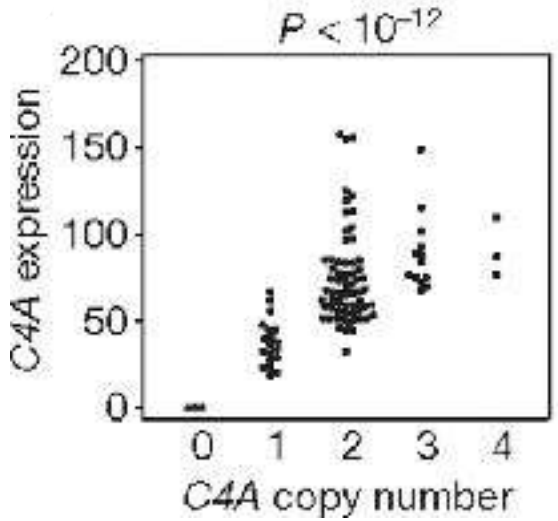
C

C4 haplogroup association with schizophrenia

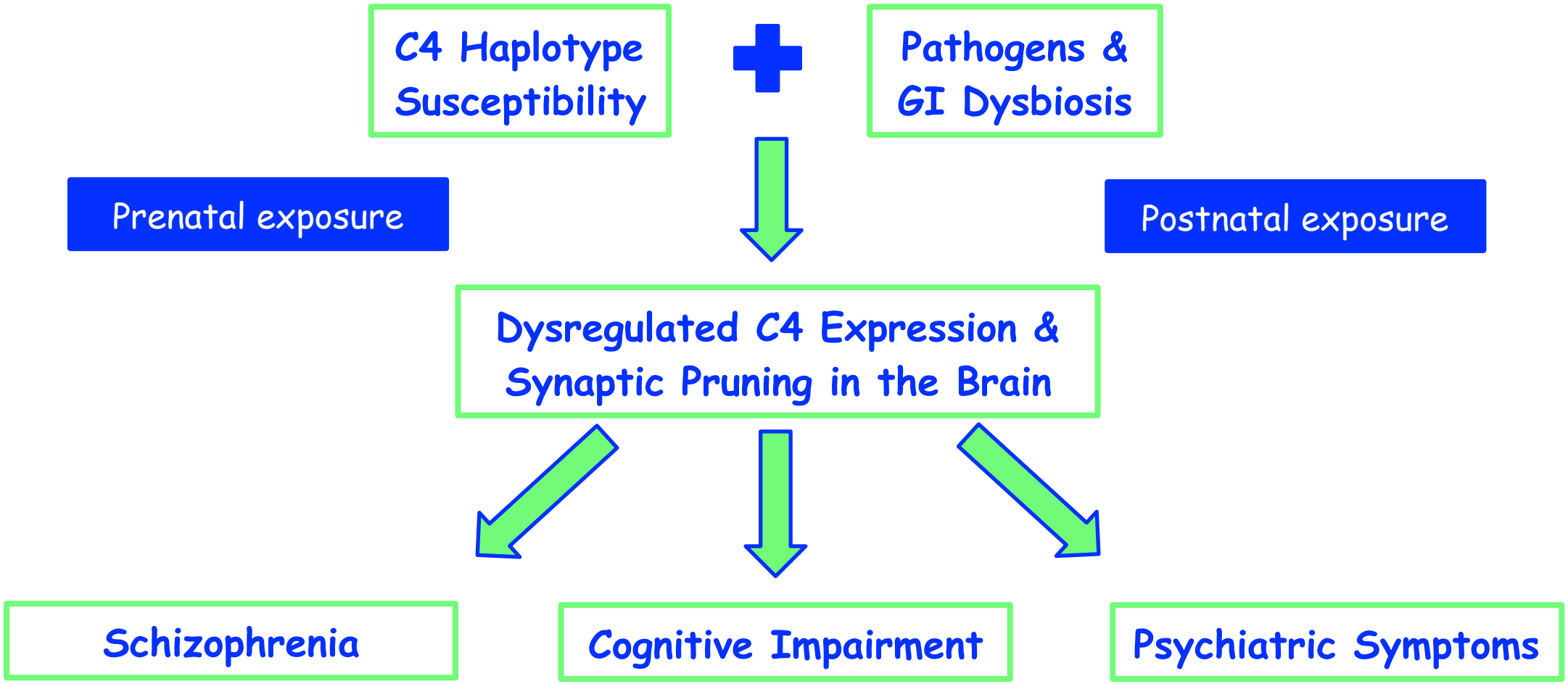


D

↑ C4 copy number = ↑ brain C4 expression



Genes & the Environment



Complement C4 Gene-by-environmental study

Objective

To examine C4 structural & copy number polymorphisms for association with:

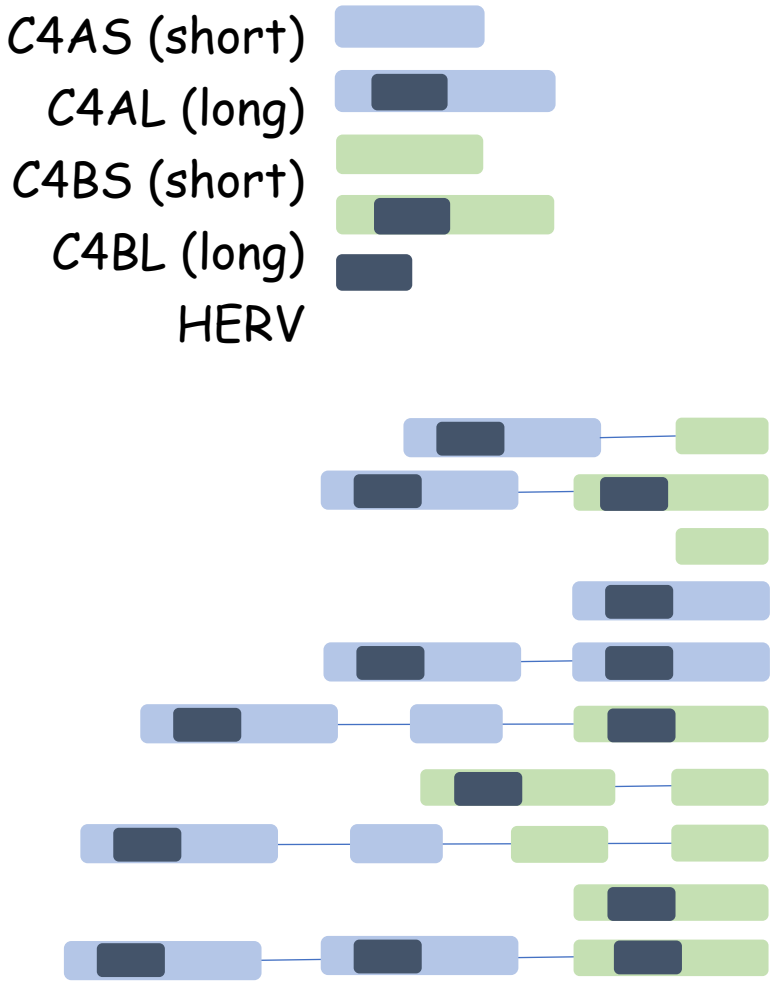
- Diagnosis
- Psychiatric symptoms (PANSS)
- Cognitive impairment (RBANS)
- Environmental exposures (infection & gut dysbioses)
  - Candida albicans
  - Cytomegalovirus
  - LPS-binding protein
  - Toxoplasma gondii

Participants

Sheppard Pratt Health System, Towson, MD:

- n = 238 individuals with schizophrenia
- n= 140 individuals who were part of the non-psychiatric comparison group

C4 copy number haplotype frequencies in schizophrenia & non-psychiatric comparison group



	NPCG (n=140)		Schizophrenia (n=238)		
Haplogroup	Frequency	Percent	Frequency	Percent	Chi2, p-value
AL-BS	132	47.14%	213	44.75%	NS
AL-BL	102	36.43%	174	36.55%	NS
BS	17	6.07%	20	4.20%	NS
AL	11	3.93%	16	3.36%	NS
AL-AL	**7**	**2.50%**	**43**	**9.03%**	13.11, **0.0003**
AL-AS-BL	5	1.79%	1	0.21%	NS
BL-BS	4	1.43%	0	0.00%	NS
AL-AS-BS-BS	1	0.36%	1	0.21%	NS
BL	1	0.36%	7	1.47%	NS
AL-AL-BL	0	0.00%	1	0.21%	NS

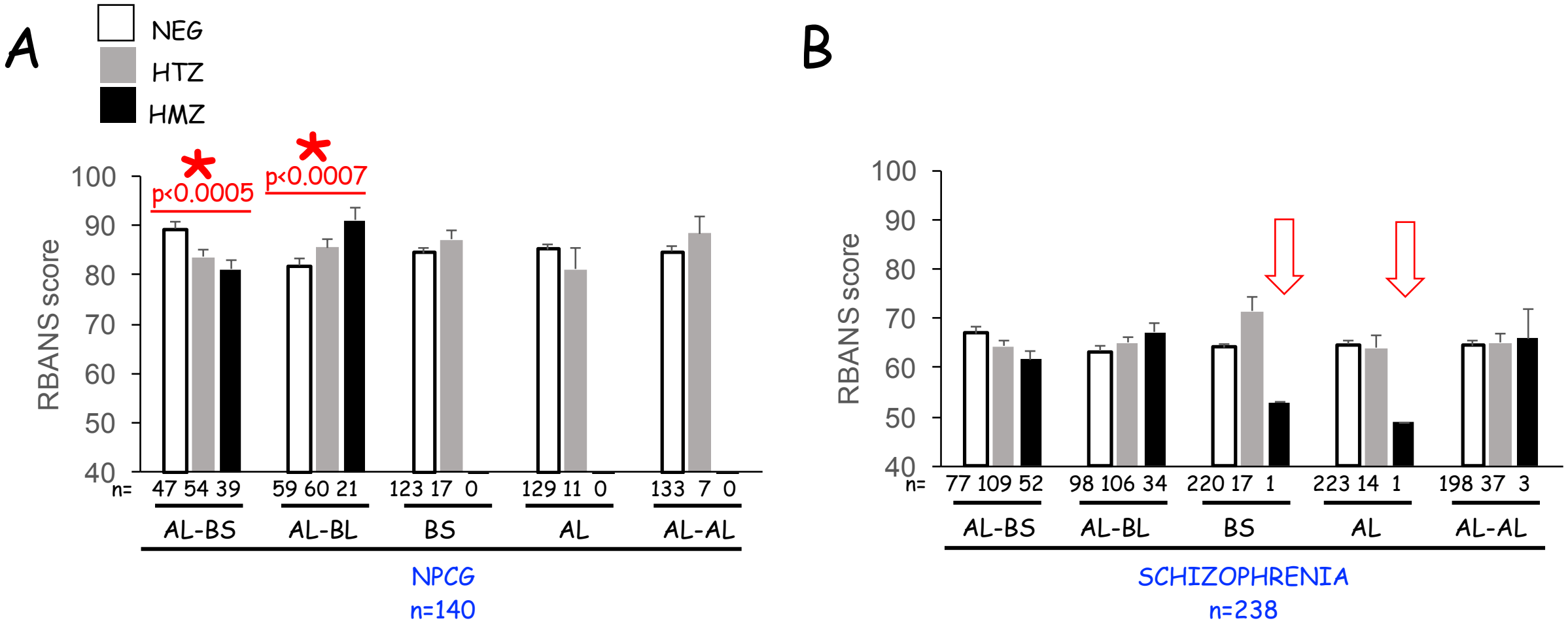
Severance et al., 2021

Odds ratios for C4 copy number & haplotype group association with schizophrenia

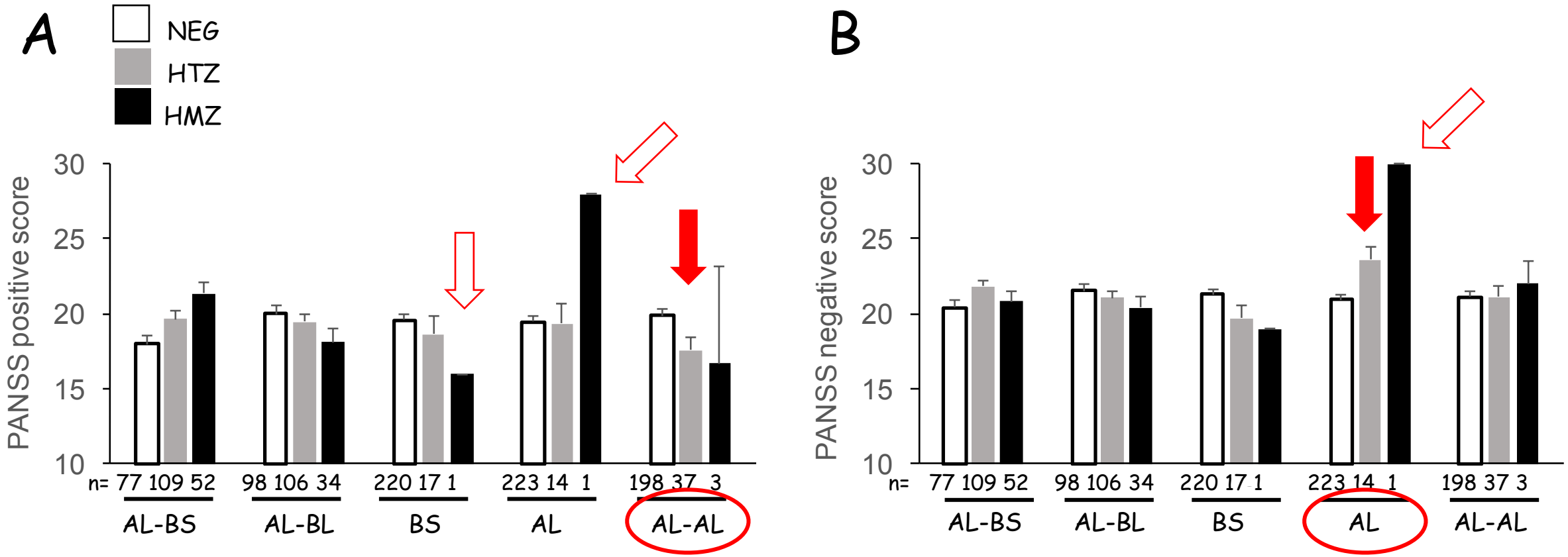
	OR	95th%CI	p
Haplogroup			
AL-BS	1.03	0.76-1.41	NS
AL-BL	0.91	0.66-1.27	NS
BS	0.49	0.24-1.02	NS
AL	0.77	0.33-1.76	NS
AL-AL	**3.53**	**1.51-8.24**	**0.0001**
Copy Number			
C4A	**1.75**	**1.14-2.71**	**0.0001**
C4B	**0.47**	**0.26-0.83**	**0.0001**
C4S	0.84	0.62-1.13	NS
C4L	1.19	0.91-1.55	NS

Mult -corrected.

Haplotype associations with cognitive (RBANS) scores in schizophrenia & controls



Haplotype associations with psychiatric (PANSS) scores in schizophrenia



Pathogen & GI biomarker associations with C4 haplogroups & diagnosis

AL	2.16	NS	1.56	0.20	NS	1.09	NS	0.33

Conclusions

- Converging evidence points to an altered microbiome, immune dysregulation & perturbed gut-brain axis in schizophrenia & mood disorders.
- These data support a unique role of complement as a system that unites multiple risk factors for schizophrenia (inflammation, infection, dietary sensitivity, autoimmunity), participates in each venue of a gut-immune-brain pathway and is consistent with a gene by environment etiology of schizophrenia.
- Complement genotyping and serum monitoring of related biomarkers during and after pregnancy and in prodromal individuals, might be a useful screening tool to identify those who are susceptible to potentially deleterious immune activation from multiple infectious and antigenic sources.
- The current data also indicate that improving gut health and stabilizing endothelial barriers may have important consequences for the brain.

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