The immune system its role in brain development and neurocircuiritry

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Disclosures

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Perspective

*We are all interconnected in our ever changing world*

- Neural Circuits
- Cosmic Dark Matter & Energy
- Social Networks
An emerging area of science

- **August 2015**
  - *Special Issue*: What Does Immunology have to do with Brain Development and Neuropsychiatric Disorders?

- **August 2016**
  - *Special Issue*: Immune Cells & the Brain

- **March 2017**
  - *Special Issue*: Neuroimmune Mechanisms in Autism

- **October 2018**
  - *Special Issue*: Brain Development

- **January 2019**
  - *Special Issue*: Prenatal Programming of Neuropsychiatric Disorders Across the Lifespan
Key Points

• Neural development is an enormously complex and dynamic process.

• From very early in brain development ‘immune cells’ play a key role in a number of processes including the formation and refinement of neural circuits.

• There is a growing body of evidence that the immune system plays an important role in the pathobiology of neurodevelopmental and neuropsychiatric disorders.
Neural-Immune Cross-Talk

Key Points

• In this complex, interconnected world, the more we learn, the more we realize how little we truly understand.

• As we gain a deeper understanding of the role of immune system plays in neuropsychiatric disorders, novel forms of treatment and preventative interventions will likely emerge.
Emerging Evidence

Disorders in which the immune system plays a role:

• Autism
• Schizophrenia
• Mood disorders
• Tourette syndrome
• Obsessive-compulsive disorder
• Sydenham’s chorea, Pediatric autoimmune disorder associated with streptococcal infections (PANDAS), Pediatric acute-onset neuropsychiatric syndrome (PANS)
• Sleep disorders
• Parkinson’s disease, Alzheimer’s, epilepsy
• Many somatic disorders
## What Is the Immune System?

<table>
<thead>
<tr>
<th>Innate immune system</th>
<th>Adaptive immune system</th>
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<tbody>
<tr>
<td>Response is non-specific</td>
<td>Pathogen and antigen specific response</td>
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<tr>
<td>Exposure leads to immediate maximal response</td>
<td>Lag time between exposure and maximal response</td>
</tr>
<tr>
<td>Cell-mediated and humoral components</td>
<td>Cell-mediated and humoral components</td>
</tr>
<tr>
<td>No immunological memory</td>
<td>Exposure leads to immunological memory</td>
</tr>
<tr>
<td>Found in nearly all forms of life</td>
<td>Found only in vertebrates</td>
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Innate Immune System

Innate immune system: The first line of defense against invading pathogens. It distinguishes between the "self" and "non-self" by recognizing molecules called pathogen associated molecular patterns (PAMPs).

Protective mechanisms include phagocytosis (e.g., neutrophils as well as organ specific phagocytes – microglia in the brain), fever, and the release of interferons and other cytokines in response to pathogens.
Microglia

*Microglia* are the resident macrophages of the CNS. They also eliminate excess functional connections between neurons to sculpt neuronal circuits during development and throughout life.

*Understanding how microglia recognize and prune synapses during development is providing insight into synapse loss and dysfunction in disease.*
Microglia

In addition to sculpting synaptic connectivity. Emerging data show that microglia normally perform a variety of functions in the developing brain. They include: (i) regulating the number and maturation of neural precursors and other resident CNS cell types, and (ii) regulating axon outgrowth, and vascular branching.

Brown & Neher, 2014

Frost & Schafer, 2016
When do Microglia enter the brain?

When do Microglia enter the brain?

Arnold & Betsholtz, 2013

Vascular Cell
Microglia

Microglia and early brain development: An intimate journey

Morgane S. Thion¹*, Florent Ginhoux²,³, Sonia Garel¹*

Glia as architects of central nervous system formation and function

Nicola J. Allen¹* and David A. Lyons²*

October 2018
Microglia

Sex-Specific Features of Microglia from Adult Mice

Villa et al., Cell Reports, 2018
Brain based studies of microglia

Microglia in the Cerebral Cortex in Autism
Nicole A. Tetreault, Atiya Y. Hakeem, Sue Jiang, Brian A. Williams, Elizabeth Allman, Barbara J. Wold, John M. Allman
Journal of Autism Developmental Disorders 2012

Review Article
Microglial Dysregulation in OCD, Tourette Syndrome, and PANDAS
Luciana Frick and Christopher Pittenger
Journal of Immunology Research 2016

Imaging microglia activity in schizophrenia
Microglia and schizophrenia: where next?
T Notter and U Meyer
Molecular Psychiatry 2017

Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder
Sophia Attwell, HSc; Elaine Setiawan, PhD; Alan A. Wilson, PhD; Pablo M. Ruizan, PhD;
Romina Mizuki, MD, PhD; IRCPC; Laura Mato, HSc; Cynthia Xu, MD; Margaret Anne Ricie, MD; FRCPC;
Alan Kahr, FRCP; Stephen J. Kish, PhD; Sylvain Lhote, MD, PhD; FRCPC;
Laura Ravidran, MD, FrCPs; Jeffrey H. Meyer, MD, PhD, FRCPC
JAMA Psychiatry | Original Investigation 2017

Transcriptome Analysis of the Human Striatum in Tourette Syndrome
Jessica B. Lennington, Gianfilippo Coppola, Yuko Kataoka-Sasaki, Thomas V. Fernandez,
Dean Palejev, Yifan Li, Anita Huttner, Mihovil Pletikos, Nenad Sestan, James F. Leckman,
and Flora M. Vaccarino
Biological Psychiatry 2016

Autism = 213; Schizophrenia = 334; Bipolar = 80; Major Depression = 244; Anxiety = 213; OCD + TS = 25
What is happening in the brain?

We obtained the basal ganglia transcriptome by RNA sequencing in the caudate and putamen of 9 TS and 9 matched control subjects.

We found 309 down-regulated and 822 up-regulated genes. Using data-driven gene network analysis, we identified 17 gene co-expression modules. The top-scoring down-regulated module was enriched for interneuron transcripts. However, the top-scoring up-regulated module was enriched in immune-related genes.
Transcriptome Analysis of the Basal Ganglia

Lennington et al. (2016)
Transcriptome Analysis of the Basal Ganglia

*Multiple Components of the Immune System were found to be up-regulated including:*

- Innate immune system (TLR2 – TLR9)
- Adaptive immune system (MHC class II molecules & complement system)
- Multiple pro-inflammatory cytokines (TNF-alpha, IL-1, IL-10, IL-12, IL-17)
- *Pathway analyses point to the likely role of the microglia!!!*

Lennington et al. (2016)
Adaptive Immunity

Adaptive immune system: Like the innate system, the adaptive system includes both cell-mediated immunity components (T-cells, B-cells) and humoral components (e.g., cytokines, antibodies). It works in concert with the innate immune system to eliminate or prevent pathogen growth. It also establishes immunological memory. This leads to an enhanced response to subsequent encounters with that pathogen (e.g., vaccination).
A Need for Homeostasis

While immune protection is key to host survival, there are also active homeostatic processes that regulate and limit inflammatory responses.

[Diagram of pro-inflammatory and anti-inflammatory cytokines]
What about the cytokines?

Cytokine Profile in Autism Spectrum Disorders in Children
   Bryn et al. *Journal of Molecular Neurosciece* 2018
   Autism = 482

Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder
   Misiak et al. *Schizophrenia Research* 2018
   Schizophrenia = 1,216
   Bipolar = 474

Inflammatory cytokine-associated depression.
   Lotrich *Brain Research* 2015
   Depression = 2,230

Immune Aberrations in Obsessive-Compulsive Disorder: a Systematic Review and Meta-analysis
   Cosco et al. *Molecular Neurobiology* 2018
   OCD + TS = 72 + 31
Cytokines and neurocircuitry

Felger, *Current Neuropharmacology*, 2018
Does what happens early in brain development matter?

Maternal Immune Activation (MIA)

- The developing brain is sensitive to environmental signals that influence the expression of genes that are involved in neural development
- *MIA during pregnancy can have a profound impact on developing neural circuits*
- Strong epidemiological data link exposure to various infections during pregnancy and a greater risk of ASD and schizophrenia
- *Microglia appear to play a key role in MIA*
- MIA also contributes to the brain's responsiveness to cumulative lifetime exposure to environmental insults
- *Targeting of immune-related pathways may represent a promising therapeutic strategy in ASD and other neuropsychiatric disorders*
Maternal Immune Activation (MIA)

Maternal Immune Activation (MIA)

Genetic predisposition
Perinatal hypoxia, infections, autoimmune disorders
Diet and parental age

Developmental ‘priming’ pathways
- Cytokines/inflammatory mediators
- Adaptive immune system
- Complement pathway
- Maternal and autoantibodies
- Reactive gliosis
- Blood-brain barrier integrity and permeability
- Epigenetic changes

Targeted developmental mechanisms

Aggravating postnatal hits

Knuesel et al., *Nature Reviews*, 2016
What is the Evidence?


A total of 15 studies involving more than 40,000 ASD cases were included. Maternal infection during pregnancy was associated with an increased risk of ASD in the offspring. This was especially true for those requiring hospitalization (OR=1.30, 95% CI: 1.14-1.50). This risk may be modulated by the type of infectious agent, time of exposure, and site of infection. Possible mechanisms may include direct effects of pathogens and, more indirectly, the effects of inflammatory responses on the developing brain.

Autism = 199; Schizophrenia = 248; Bipolar = 13; Major Depression = 15; Anxiety = 49; OCD + TS = 4
Children who experience early adversity at increased risk to develop to emotional and physical health problems across the lifespan. What are the biological mechanisms that confer this vulnerability to a number of mental and physical illnesses?
Neuro-immune Network

Nusslock & Miller *Biological Psychiatry*, 2016
We have also co-evolved with certain microbiota (our *microbiome*). Indeed, we live with at least 10 times more non-human cells than human cells. The more we learn, the more we realize that our health and well-being depends in part on these organisms.
The microbiome is part of who we are

Within the first moments following birth, we are colonized by commensal microbiota.

Our microbiome is important for not only healthy bodies, but also for healthy brain function.

Indeed, alterations in microbiota can activate neural pathways and influence stress-related behaviors.
Our microbiome is ever changing
Microbiome: Gut-Brain Axis

Collins et al., 2012

Autism = 348; Schizophrenia = 115; Bipolar = 53; Major Depression = 167; OCD + TS = 11
Microglia - Microbiome

Microbiome Influences Prenatal and Adult Microglia in a Sex-Specific Manner

Thion et al., Cell, 2017

• This study reports that microglia undergo differentiation phases, discernable by transcriptomic signatures which can diverge in adult males and females. *Remarkably, the absence of microbiome in germ-free mice had a time and sexually dimorphic impact both prenatally and postnatally: microglia were more profoundly perturbed in male embryos and female adults.*

• This study also demonstrates that microglia respond to environmental challenges in a sex- and time-dependent manner from prenatal stages.

• These findings have major implications for our understanding of microglial contributions to health and disease.
Another truly amazing finding is that bacteria appear to be present in both healthy human (n=34) and mouse brains (Roberts et al., 2018)!

The density of the bacteria varied by brain region, with abundant bacteria in the substantia nigra, hippocampus and prefrontal cortex. The bacteria were present in intracellular locations near the blood brain barrier.

RNA sequencing revealed that most of the bacteria were from phyla common to the gut: Firmicutes, Proteobacteria, and Bacteroidetes.

If replicated, it will be important to examine postmortem tissue from individuals with neurodevelopmental and neuropsychiatric disorders to determine if microbiota are present and if so how they vary from disorder to disorder.
An emerging area of science

Special Issue: What Does Immunology have to do with Brain Development and Neuropsychiatric Disorders?
August 2015

Special Issue: Immune Cells & the Brain
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January 2019
Unanswered Questions

• Are there specific immune mediated subtypes of neurodevelopmental and neuropsychiatry disorders?
• Will a deeper understanding of the role the immune system plays advance our ability to treat and perhaps PREVENT these conditions?
What is the promise of immunomodulatory interventions?

Microglia and Autism Spectrum Disorder: Overview of current evidence and novel immunomodulatory treatment options

Kim *et al.*. *Clin Psychopharmacol Neurosci*. 2018

Immunological aspects of the treatment of depression and schizophrenia

Müller *et al.*. *Dialogues Clin Neurosci*. 2017

Altered peripheral immune profiles in treatment-resistant depression: Response to ketamine and prediction of treatment outcome

Kiraly *et al.*. *Transl Psychiatry*

Autism = 381; Schizophrenia = 719; Bipolar = 190; Major Depression = 1,003; Anxiety = 510; OCD + TS = 93
To date, no immunomodulatory intervention has been consistently shown to improve the social and communication impairments of ASD with the possible exception of fecal transplants.
Emerging immune treatments?

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Kang et al. *Microbiome*, 2017
What is the promise of immunomodulatory interventions?

Severe chronic psychosis after allogeneic stem cell transplantation from a schizophrenic sibling
Sommer et al., Bone Marrow Transplant 2015

Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation
Miyaoka et al., Front Psychiatry 2017

Serendipitous improvement of schizophrenia after triple bone marrow stem cell transplant for cancer
Llano et al. Poster 30th annual Psych Congress 2017
Treatment and Clinical Course

- PANSS-Total
- QTP 800 mg/day
- RIS 12 mg/day
- OLZ 20 mg/day
- BMT

GAF

Month

Miyaoka et al., Front Psychiatry 2017
Inflammatory Mediators in Mood Disorders: Therapeutic Opportunities.

Pfau et al. *Annual Rev Pharmacol Toxicol.* 2018
What is the promise of immunomodulatory interventions?

Controlled trial of intravenous immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

Williams et al., *J Am Acad Child Adolesc Psychiatry* 2016
IVIG Trial

Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Kyle A. Williams, MD, PhD, Susan E. Swedo, MD, Cristan A. Farmer, PhD, Heidi Grantz, LCSW, Paul J. Grant, MD, Precilla D'Souza, CRNP, Rebecca Hommer, MD, Liliya Katsovich, MA, Robert A. King, MD, James F. Leckman, MD, PhD


Funding. Grifols Laboratories the IVIG for the trial, as well as financial support to the Yale investigators. Additional support was provided by the NIH Bench-to-Bedside Program, and by the Intramural Research Program of the National Institute of Mental Health (NCT01281969)
During the double-blind phase, the mean decrease in OCD severity was not statistically significant. However, following open-label IVIG at week 6, the mean improvement from baseline was 62% at week 24.
Key Points

• Neural development is an enormously complex and dynamic process.

• *From very early in brain development ‘immune cells’ play a key role in a number of processes including the formation and refinement of neural circuits.*

• There is a growing body of evidence that the immune system plays an important role in the pathobiology of neurodevelopmental and neuropsychiatric disorders.
Key Points

• In this complex, interconnected world, the more we learn, the more we realize how little we truly understand.

• As we gain a deeper understanding of the role of immune system plays in neuropsychiatric disorders, novel forms of treatment and preventative interventions will likely emerge.
In sum

• There are multidirectional interconnections across multiple biological systems in our brains and bodies that are mediated in part by the immune system.

• At present, however, the ‘promise’ of this field remains greater than the ‘deliverables’.

• Time will tell whether novel interventions will be developed that will make a positive difference in the care of our patients.

• It is also possible that valid biomarkers will emerge that will guide a more personalized approach to treatment.
Perspective

*We are all interconnected in our ever changing world*
Thank you!!!