



NEWS IN NEUROVIROLOGY

Official newsletter of the
International Society for NeuroVirology

Editor: Dianne Langford, PhD | Associate Editor: Fred Krebs, PhD

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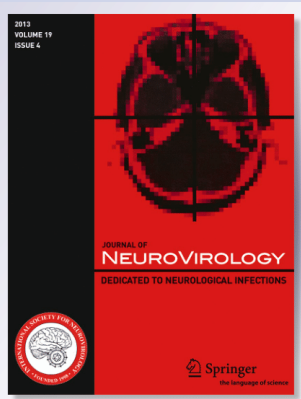
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2018 joint ISNV/SNIP meeting summary

By Lynn Pulliam and Brian Wigdahl

The 15th International Society for Neurovirology and 2018 Conference on HIV in the Central Nervous System was held from April 11th through the 14th at the Swissotel Chicago. Held jointly for the first time with the Society on NeuroImmune Pharmacology, this meeting was a tremendous success. Taking advantage of the heart of the midwest, the symposia had a strong presence of attendees from Rush University Medical Center, University of Illinois at Chicago, University of Chicago, Northwestern and Loyola University. Over 400 scientists from 10 countries attended the joint meeting. The gathering consisted of 330 poster presentations, 22 scientific sessions and 4 lectureships over a span of 4 ½ days. A total of 104 speakers took the platform and presented their work.

The National Institutes of Health provided support for the meeting through several mechanisms. The NIMH conducted a satellite meeting on 'The Impact of Astrocyte Infection on HIV Strategy', and additional scientific officers from the different institutes presented an overview, 'The NIH HIV Agenda: From Priorities to Grant Review'.

Pioneers in NeuroVirology at the 2018 joint ISNV/SNIP Meeting. From left to right: Avindra Nath (2012), Peter Kennedy (2018), and Brian Wigdahl (2013). Also in attendance but not pictured: Kamel Khalili (2010) and Howard Gendelman (2016).



The Pioneer Award was presented to Professor Peter Kennedy, former ISNV President. A number of the past pioneer awardees were also in attendance.

An important aspect of the meeting was the emphasis on the Early Career Investigators. The symposium included 2 platform sessions devoted to oral presentations where 24 early career stage scientists presented brief overviews of their current research. A total of 38 young investigators were recognized for their scientific achievements.

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The Relationship between Herpes Simplex Virus Infection and Alzheimer's Disease

By Raj Dave and Josue Perez Santiago

As early as the 1950s, scientists believed that viruses or other infectious microbes may contribute to Alzheimer's disease (AD) (1,2). However, little information regarding potential mechanisms has emerged. Several scientists have focused on analyzing the relationship between herpes virus infection and susceptibility to AD.

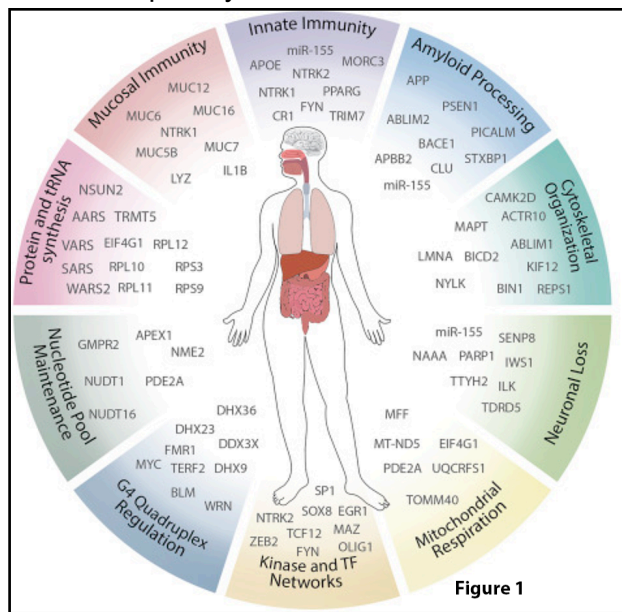


Figure 1. Findings from this study indicate complex relationships between viral and host factors that are likely to be relevant across a range of timescales and organ systems. Key biological processes that have been highlighted are shown, along with top candidate molecular mediators. Reprinted from *Neuron* 99, 64–82, July 11, 2018 with permission.

A recent study by Readhead *et al* in *Neuron* mapped and compared biological networks associated with two distinct AD-phenotypes from among multiple independent datasets (3). In this study, researchers began by building probabilistic causal networks constructed from laser captured neuronal gene expression collected from the hippocampus and entorhinal cortex of individuals with preclinical AD. By focusing on these especially vulnerable brain regions, and samples from individuals with significant neuropathology, but without a history of cognitive impairment, the authors hoped that these results might help uncover protective mechanisms.

Exploration of separate networks constructed from preclinical AD, and healthy control samples revealed multiple lines of evidence consistent with a potential viral perturbation occurring in the preclinical AD samples. Their data showed enrichment for C₂H₂ zinc finger transcription factor binding motifs, as well as links to several genes with well described proviral or antiviral functions. Particularly, the count of G-quadruplex motifs was significantly higher in introns, exons, 3'UTR regions and the coding and non-coding strands in network drivers of the control group, and was negatively associated with AD related genes.

Given that these networks were constructed from gene expression microarrays, the authors weren't able to directly search for viral sequences within the samples, however, they wondered whether some of the large next-generation sequence cohorts being collected by the NIH Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD), might represent an opportunity to systematically explore whether viruses are...

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Share your news with us!

By Fred Krebs

One goal of the ISNV newsletter is to connect our members as part of a community with a common interest in neurovirology. To meet that goal, future issues of the ISNV newsletter will include a regular feature that we call **"Member Milestones."** This column will be a place where members can share news about important events and milestones in their research and careers.

If you just published a paper, received a new grant or prestigious award, or were recently promoted, we want to hear from you! If you have reached an important milestone or have significant news that you want to share with members of the ISNV, send a short summary of your news to Dianne Langford (tdl@temple.edu) and we'll consider it for publication in the next issue of the ISNV newsletter. We're looking forward to hearing from you!

EMERGING TOPICS:

Maternal inflammation effects on fetal brain development and cognition

By Leah Rubin

Maternal inflammation during pregnancy —whether in response to a viral or bacterial infection, stress, genetic makeup, or an autoimmune process—may contribute to worse neurodevelopmental outcomes. For example, epidemiological and animal studies support a link between maternal inflammation during pregnancy and an increased risk of neuropsychiatric conditions including schizophrenia and autism.

A recent study by Dr. Marc Rudolph and colleagues provides insights into the link between systemic maternal inflammation during pregnancy on offspring functional brain organization and cognitive abilities at 2 years of age (<https://doi.org/10.1038/s41593-018-0128-y>). Specifically, Dr. Rudolph and team conducted a longitudinal study examining maternal interleukin-6 (IL-6) levels that were obtained across each trimester. At 4 weeks of age, infants underwent functional magnetic resonance imaging (fMRI) to measure functional brain networks at rest (e.g., default mode, salience, frontoparietal networks). At 2 years of age, the toddlers returned and completed a measure of executive function—working memory. Working memory is important for temporarily maintaining information in mind so that it can be manipulated. This ability which can be measured reliably at 2 years of age is predictive of later academic and social skills.

The study demonstrated that maternal IL-6 levels are robustly associated with a number of large-scale resting-state functional brain networks. IL-6 levels were strongly associated within the salience network, a network which is anchored in the insula and anterior cingulate cortex and important for affective and cognitive processing. Maternal IL-6 levels were also associated with between-network associations including connectivity between the subcortical-dorsal attention (frontal eye fields, intraparietal sulcus) networks; subcortical-cerebellar networks; visual-dorsal attention networks, and salience-cingulo-opercular (anterior insula/operculum, dorsal anterior cingulate cortex, thalamus) networks (**Fig. 1**). Notably, maternal IL-6 levels predicted working memory performance when the child was 2 years of age.

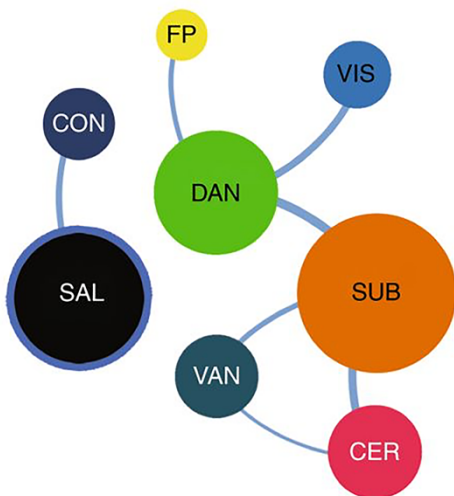


Figure 1. A network schematic demonstrating significant associations within and between large-scale functional resting state networks and mean maternal IL-6 across three trimesters. Nodes (circles) represent individual networks and are scaled according to their overall degree of association with mean maternal IL-6 (number of associations passing criteria for statistical significance and effect size). Nodes with thick borders represent significant within-network associations (salience network) with mean maternal IL-6. Line width between nodes represents the relative effect size of between-networks models (e.g., salience-cingulo-opercular network). Functional brain networks: visual (VIS), cingulo- opercular (CON), salience (SAL), fronto- parietal (FP), subcortical (SUB), dorsal attention (DAN), ventral attention (VAN) and cerebellar (CER) systems. Reprinted from Rudolph et al., *Nature Neuroscience* 21: 756-772, Figure 2b with permission.

Taken together, these findings highlight the association of maternal inflammation during pregnancy on newborns' functional brain organization and working memory abilities at 2 years of age. Future studies are needed to understand the source of maternal inflammation, the specificity of cognitive effects, and the longer-term implications.

...detectable in the ageing brain, and whether they might play a role in Alzheimer's disease. Beginning with the Mount Sinai Brain Bank, they used functional and regulatory network analyses based on genomic, transcriptomic, proteomic, histopathological and clinical data from post-mortem brain from individuals with AD vs. healthy controls. The complexity of relationships between viral and host factors is illustrated in Figure 8B in the manuscript and shown here with permission (Figure 1). When authors measured viral abundance by RNA-seq across four brain regions, they identified an increased abundance of HHV-6A, and HHV-7 in the superior temporal gyrus and the anterior prefrontal cortex of samples from individuals with AD compared with controls. They validated these results using three additional independent cohorts in which they consistently saw an increase in HHV-6A and HHV-7 in AD and that this increase in viral abundance was not a general feature of neurodegenerative diseases. For HHV-6A in particular, they showed the viral DNA that may have undergone reactivation from subtelomeric regions in AD. To evaluate viral risk factors for AD development, they investigated host DNA variants' loci that were most associated with viral abundance. They found associations in loci for mucosal and innate immunity and anti-viral sensing. HHV-6A was the virus with the greatest amount of associations, particularly with multiple AD traits including dementia and neuropathology. Through network analysis, they found that HHV-6A may interact directly with host AD-associated genes, amyloid processing genes and cellular death pathways in neurons. They proposed that this was due in part to downregulation of miR-155 that induced the accumulation of amyloid plaques and A β 42 in brain or dysregulation of host kinase activities, and by altering host protein synthesis machinery resulting in neuronal loss. In summary of the findings, Dr. Readhead states, *"It's not yet clear how exactly these pathogens relate to Alzheimer's pathophysiology, and whether their role is as causal driver, an accelerant of established disease, or perhaps an opportunistic hitch-hiker. What we have seen in this study though, is that some of these viruses (such as HHV-6A) are operating right in the middle of known Alzheimer's molecular networks, and this gives us some very specific, and very testable hypotheses that could help investigators build a more sophisticated understanding of the role of microbes in Alzheimer's disease."* To read the entire article, please visit <https://www.ncbi.nlm.nih.gov/pubmed/29937276>

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2. Sjogren, T., Sjogren, H., and Lindgren, A.G. (1952). Morbus Alzheimer and morbus Pick; a genetic, clinical and patho-anatomical study. *Acta Psychiatr. Neurol. Scand.*, Suppl. 82, 1–152.
3. Readhead et al., Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, *Neuron* (2018), <https://doi.org/10.1016/j.neuron.2018.05.023>
4. Sigurðsson, B. (1954). Rida, a chronic encephalitis of sheep: with general remarks on infections which develop slowly and some of their special characteristics. *Brit. Vet. J.* 110, 341–344.
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6. Readhead et al., Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus, *Neuron* (2018), <https://doi.org/10.1016/j.neuron.2018.05.023>

2018 Meeting summary

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A Mentoring/Networking event (focused on inclusion and diversity), Mentorship luncheon, and SNIP/JNV Editorial Board reviews were some of the activities offered where the emphasis was on our future scientific leaders in the field. All events were well attended.

Lastly, we wish to extend our gratitude to the SNIP meeting organizers for their hard work and contributions. The two societies came together for a week of cutting edge science where both groups engaged in discussions and established future collaborations for advancing the fields of neurovirology and neuroimmune pharmacology while at the same time remaining focused on diagnosing, treating and curing these disorders.

We look forward to seeing everyone at the next ISNV gathering in Atlanta, Georgia in the fall of 2019.

NIH Agenda Outcomes: From priorities to grant review

By Tory Johnson

Submitting a proposal to the National Institutes of Health on HIV or AIDS? Great! But, which study section will you submit to? Recent changes have been made to the HIV study sections. Here is some new information to help you plan your application.

The Center for Scientific Review (CSR) has announced changes to the AIDS and Related Research (AARR) Integrated Review Groups study sections. The current study sections, including NeuroAIDS and other End-organ Diseases, have been in place since 2003. In the past 15 years, the scientific community has generated important new discoveries that have substantially altered the HIV epidemic. To reflect these advancements and to emphasize the current and emerging areas of HIV research, such as the cure initiative, prevention interventions and the consequences of living with HIV, the decision was made to update the study sections. The new study sections were formulated based on guidance from both internal and external working groups.

There are several new study sections encompassing basic, translational and clinical research where applications pertaining to NeuroAIDS are likely to be of interest. The new study sections are (see figure below): HIV Molecular Virology, Cell Biology, and Drug Development (HVCD), HIV Immunopathogenesis and Vaccine Development (HIVD), HIV Comorbidities and Clinical Studies (HCCS), HIV Coinfections and Associated Cancers (HCAC), HIV/AIDS Individual Level Determinants and Behavioral Interventions (HIBI) and Population and Public Health Approaches (PPAH) to HIV/AIDS. For more details and description of each study section, see the [CSR Web site](#). These changes will go into effect for applications that will be reviewed starting this fall (submission dates September 2018).

If you are unsure which new study section your application will best align, you are encouraged to reach out to Dr. Robert Freund, Chief, AARR Integrated Review Group, Center for Scientific Review, National Institutes of Health at freundr@csr.nih.gov. ISNV thanks him for his presentation at our meeting in Chicago and ongoing support for NeuroAIDS research.

CSR Website:

<https://public.csr.nih.gov/StudySections/IntegratedReviewGroups/AARRIRG/Pages/default.aspx>

Join us in Atlanta in 2019

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Fall 2019
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