NEWS

Reactions from Neuroscience 2022

BY **MICHAEL FERGENSON**

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The following comments were lightly edited for clarity and style.

16 November 2022: Day 5

David Beversdorf

Professor, University of Missouri

***Lovastatin in fragile X*: Nuria Garcia Font**, a postdoctoral associate in **Richard Morris**' lab at the University of Edinburgh in Scotland, presented a **study** in which she treated a rat model of fragile X syndrome with the cholesterol-lowering drug lovastatin, which has effects on the mTOR pathway. The treatment rescues the atypical social interaction the researchers observed with their model. Of course, rats are not humans, so we don't know how this might translate clinically, but if this line of work continues to succeed, examination of repurposed agents would have a markedly more rapid translation to the clinic than would novel compounds. It will be interesting to see how this goes.

15 November 2022: Day 4

Tiffany Woynaroski

Assistant professor, Vanderbilt University School of Medicine

***Path to precision medicine*: Jeremy Veenstra-VanderWeele**, professor of developmental neuropsychiatry at Columbia University, held a **Meet-the-Clinician-Expert** session, which was fabulous, almost like a fireside chat. First, attendees got to hear him reflect on his own path, from his foundations in conducting patient-oriented research and elucidating the genetic basis of autism

as an undergraduate research assistant at the University of Chicago to his current status as a rock star leading the charge in cutting-edge clinical-translational research. Then, Veenstra-VanderWeele summarized our present position in the pathway to biology-based treatments in autism. We were hit with his assessment that, at present, we have essentially no well-established neurobiologically based treatments for people on the autism spectrum. His conclusion is sobering, but he's not wrong. It begs the question, what exactly are we doing here?

As a clinician scientist myself, I really hope that our work will ultimately translate to practice, to the development and validation of supports and services that improve the lived experiences and long-term outcomes of autistic individuals. I think many autism researchers here at Neuroscience 2022 share these goals. Are we on a path to nowhere? How do we respond to this conclusion regarding the state of our science? I think we can all take a second to be disappointed in ourselves.

Ok, we did that. Now let's get inspired. Let's use what we know about brain and behavior to design novel intervention approaches that have the potential to work, at least for a subset of those with autism (on this note, by the way, I think that identifying an approach that works for even 1 percent can and should be counted as a success). Let's conduct rigorous studies that allow us to evaluate the effects of these candidate interventions on meaningful outcomes. Let's ascertain which neural measures are most likely to be psychometrically sound and to precede and predict effects on those outcomes and statistically evaluate them (mediation analyses, anyone?). Let's identify the biobehavioral factors that are most likely to predict a differential response to these interventions and use advanced analytic approaches (think moderation, peeps!) to test them. Let's be systematic. Let's get on the path to precision medicine.

Jacqueline Crawley

Professor emerita, MIND Institute, University of California, Davis

***Mouse behavior bonanza*:** The "**Animal models of autism: Behavior**" poster session had an outstanding collection of new discoveries emerging from mouse behavioral analyses. Included were findings from the BTBR mouse model of autism: Deep-brain stimulation of the nucleus accumbens reduced their repetitive self-grooming, according to **work** by graduate student Kaiwen Zhang, postdoctoral researcher Flavia Venetucci Gouveia and pediatric neurosurgeon **George Ibrahim**, all at the Hospital For Sick Children in Toronto, Canada. And ribosome biogenesis is reduced in the animals, **showed** the lab of Kathy Chadman at the New York State Institute for Basic Research in Staten Island. Also noteworthy were **behavioral and molecular investigations** of SYNGAP1 mice, from the labs of **Jill Silverman**, professor of psychiatry and behavioral sciences, and **Alex Nord**, associate professor of neurobiology, physiology and behavior, both at the University of California, Davis MIND Institute; and the consequences of sleep deprivation on social behavior and sensory processing in a SHANK3 c-terminal truncated mutant **mouse model of autism**, from the lab of **Sheryl Moy**, professor of psychiatry at the University of North Carolina

at Chapel Hill.

***History lesson*: Huda Akil**, professor of neuroscience at the University of Michigan in Ann Arbor, delivered an inspiring lecture on the history of neuroscience called "**Neuroscience redefines the stress concept: From 'fight or flight' to neuroplasticity and affective disorders.**" Her talk began with a dedication to the late, great behavioral neuroendocrinologist Bruce McEwen. Professor Akil proceeded to introduce us to scientific giants who made fundamental discoveries about the neuropharmacology and neural circuitry of fight-or-flight behaviors. She then walked us through her own early-career discovery of stress-induced analgesia, mentioning that her remarkable findings provided clues to John Hughes and Hans Kosterlitz about the connection between stress and opiates, culminating in their identification of endogenous enkephalins. Huda's original work on the role of pituitary ACTH in stress responses led to her lifelong commitment to understanding the biological mechanisms through which stress can lead to depression and addiction. Her astonishing wealth of research and professional contributions, spanning a 50-year career, define Huda Akil as a contemporary giant. This talk is a must-watch for graduate students.

Ciara Bagnall-Moreau

Postdoctoral research fellow, Feinstein Institute

***Nets and social memory*:** This year's SfN meeting featured several posters on perineuronal nets, specialized extracellular matrix components that assemble around a specific subgroup of neurons and regulate synaptic plasticity. **Emma Diethorn**, a graduate student in **Elizabeth Gould**'s lab at Princeton University, presented a **poster** on the contribution of perineuronal nets to the social memory dysfunction observed in SHANK3B and FMR1 mutant mice. Mutations in SHANK3 and FMR1 have been linked to the autism-related conditions Phelan-McDermid syndrome and fragile X syndrome.

Diethorn found that perineuronal net intensity was altered in the CA2 region of the hippocampus, known to be involved in social memory. Specifically, SHANK3B knockout mice showed an increase in the intensity of hippocampal CA2 perineuronal nets, whereas FMR1 knockouts had a decrease, compared with controls. Furthermore, reducing hippocampal CA2 perineuronal nets by targeted treatment with the enzyme chondroitinase ABC rescued social deficits in the SHANK3B knockout pups. One approach proposed to normalize the nets in the FMR1 knockout mice includes inhibition of proteins called matrix metalloproteinases, enzymes that are implicated in extracellular matrix remodeling.

Ultimately, the authors suggested that normalizing perineuronal nets, at least in the CA2, could serve as a therapeutic approach to improving synaptic function and social memory in these mouse models. Although an extracellular matrix pathology has been observed in other neuropsychiatric conditions associated with a social memory dysfunction, the role of perineuronal nets in autism

remains unclear. It would be interesting to see whether the modulation of perineuronal nets affects social behaviors associated with the condition.

David Beversdorf

Professor, University of Missouri

***SHANK3 and sleep*: Graham Diering**, assistant professor of cell biology and physiology at University of North Carolina at Chapel Hill, reported a very interesting finding. He found that early sleep disruption in SHANK3 heterozygous mice resulted in decreased sociability specific to males and decreased risk avoidance specific to females. The homozygous SHANK3 mice typically have autism-associated behaviors, but mice with only one copy of the mutation did not demonstrate such a strong phenotype. However, early sleep disruption does induce these behaviors in males in heterozygous mice. The effect does not occur with sleep disruption later in development. This highlights the need for a greater understanding of the role of sleep in autism across a variety of contexts.

Courtney McDermott

Graduate student, Rutgers University

***SHANK3 and sleep, cont.*: Graham Diering** gave an incredible presentation of his **lab's work** at the "**Animal Models of Autism: Behavior**" poster session. This work characterized the effects of early-life sleep disruption on sociability, risk aversion, sensory gating and locomotion in SHANK3 heterozygous male and female mice. These mice have typical baseline sleep patterns, which in turn were altered following the early-life sleep deprivation. The deprivation affected behavioral outcomes in both male and female SHANK3 mice, with specific reductions in sociability for males and reductions in risk aversion for females. Insights into how sleep deprivation may alter behavior is highly informative, given the increased prevalence of sleep problems in people with autism.

I appreciated how rigorously Diering conducted this study and how clear he was in presenting his interpretations of the data. This study included a post-adolescence sleep disruption group and remarkably observed no alterations in sociability or risk aversion in both male and female SHANK3 mice, underscoring the critical timing of sleep disruptions during early life, when REM sleep is most prominent, as well as synapse numbers, perhaps contributing to this phenotype. I learned so much from this poster and look forward to reading future studies from his lab!

14 November 2022: Day 3

Tiffany Woynaroski

Assistant professor, Vanderbilt University School of Medicine

***Sensory subtypes*:** One of the best things about the return to in-vivo meetings is that we can network with all the fabulous folks we haven't seen over the course of the pandemic. Today, catching up with a colleague (poolside — because we are in San Diego, after all!), I got the inside scoop about some new findings.

As most people connected to autism know, autistic children sense their world differently than their non-autistic peers do, though these differences vary from one person to another. For instance, their sensory differences can appear across all five senses (e.g., touch, hearing, etc.) or may involve difficulties with some senses and strengths in others. There has been a lot of work recently evaluating how these sensory differences may cluster together in discrete sensory phenotypes. For example, a 2021 **study** from the Sensory Perception Lab at the University of Western Ontario in London, Canada, has identified five sensory phenotypes in autism.

Kathleen Lyons, a postdoctoral fellow working with **Ryan Stevenson** at the university, has exciting new data measuring the neural mechanisms underlying these sensory differences in autistic children from the **POND Network**.

This team found five distinct groups based on sensory differences reported by parents: sensory adaptive; generalized sensory differences; taste and smell sensitivity; under-responsive and sensory seeking; and movement difficulties with low energy. Children in these groups differed in their functional brain connectivity, a measure of correlated brain activity that is thought to reflect how different brain regions interact with each other. Their functional brain architecture differed not only in regions of the brain involved in sensory processing, but also in regions that are involved in complex cognitive processes.

Compared with those in the sensory adaptive group, who reported minimal to no differences in sensory processing, children in the generalized sensory differences and taste and smell sensitivity groups tended to show patterns of hyperconnectivity (i.e., more correlated activity). By contrast, the under-responsive and sensory-seeking group, as well as the movement difficulties with low energy group, tended to show patterns of underconnectivity. These results support findings over the past decade that have shown that sensory differences influence higher-level cognitive development.

Maria Chahrour

Associate professor, University of Texas Southwestern Medical Center

***Of fish and frogs*:** Two talks at the "**Zebrafish and *Xenopus* models of neurodevelopmental**

disorders" minisymposium focused on identifying convergent mechanisms in autism. **Helen Willsey**, assistant professor of psychiatry at the University of California, San Francisco, presented **work** on how her lab identified tubulin biology as a convergent mechanism for top autism-linked genes. They found that many autism-linked genes, especially chromatin regulators, interact with centrosome proteins and regulate microtubule stability. They also demonstrated that disrupting the autism-linked chromatin regulator CHD2 results in spindle defects.

Ellen Hoffman and her lab at Yale University **targeted** 10 autism-linked genes in zebrafish and looked for divergent and convergent pathways at the behavioral, structural and brain-activity levels. They found that although there were subgroups of genes that have highly correlated phenotypes, each gene had a unique set of phenotypes. They pinpointed the forebrain and cerebellum as points of vulnerability across genes, and the thalamus was a point of convergence in terms of brain-activity phenotypes. So the answer was somewhere in the middle, between convergent and divergent phenotypes!

13 November 2022: Day Two

Maria Chahrour

Associate professor, University of Texas Southwestern Medical Center

***Synapse symposium*:** I enjoyed the many interesting talks at the "Autism and synapse development" **nanosymposium** in the morning, especially the **talk** by **Yudong Gao**, a postdoctoral fellow from **Scott Soderling**'s lab at Duke University in Durham, North Carolina. They used high-throughput gene editing coupled with proximity-based proteomics to explore mechanisms of 14 genes linked to autism. They tagged the genes' encoded proteins via HiUGE-iBioID technology and constructed protein proximity networks.

They utilized this approach to inform a rescue strategy in a mouse model carrying an autism-linked missense mutation in the sodium channel gene SCN2A. They demonstrated that the mutation results in loss of function of the sodium channel, and by comparing the interactomes from the wildtype and SCN2A mice, they identified two proteins that are downregulated in the mutant. The function of the channel could only be fully rescued when the expression of these two proteins was also upregulated, as opposed to upregulating the SCN2A level on its own, which only resulted in partial rescue of channel function.

Another highlight was the session from a graduate student in my lab, **Shayal Vashisth**, who presented her **work on UBE3B**, an E3 ubiquitin ligase mutated in neurodevelopmental conditions, and its role in brain development and function. Of course, I might be a little biased!

Tiffany Woynaroski

Assistant professor, Vanderbilt University School of Medicine

***Sleep loss cascades*:** It turns out that disruptions in a young child's sleep may lead to more than just sleepless nights (and lost productivity… and sanity) for parents! Today at SfN, **Adriana Rios**, a graduate student in **Inna Fishman**'s lab at San Diego State University, shared intriguing new findings from an NIH-funded **study** suggesting that autistic children are more likely than their non-autistic peers to present with irregular sleep patterns in the first year of life, which not only predicts persistent sleep problems, but is also linked with later alterations in resting-state functional connectivity, sensory sensitivity and social differences.

This study has some notable limitations, including a reliance on retrospective caregiver reports of early sleep patterns, which the team readily acknowledges. But it accords with developmental theory and provides some preliminary empirical support for the hypothesis that poor sleep, particularly early in life, may yield cascading effects on downstream skills in children with an elevated likelihood of a diagnosis of autism. (I highly recommend reading the recent paper by Bradshaw and colleagues on the broader application of the "developmental cascades" framework for better understanding complexity in autism, if you have not already done so.)

There is nothing better than a compelling and polished presentation by an up-and-coming autism researcher. Kudos to you for conducting this innovative research, Adriana, and best of luck in your training and future endeavors!

Courtney McDermott

Graduate student, Rutgers University

***Prenatal and postnatal brain development*:** The highlight of Day Two for me included listening to all of the incredible presentations in the "Autism: Genetics to phenotypes" **nanosymposium**. **Lee Kissel**, a graduate student in **Donna Werling**'s lab at the University of Wisconsin-Madison, presented exciting work that characterized sex differences during human prenatal cortical development using BrainVar, an RNA-sequencing dataset of human dorsolateral prefrontal cortex tissue. They found male-specific differentially expressed genes to be enriched for genes related to glial cells and immune processes, suggesting that the biology of sex differences and autism may interact in an indirect or downstream fashion. This is incredibly important given the 4-to-1 ratio of autism prevalence in males versus females.

I was also fascinated by the **research** presented by **Cesar Canales**, a postdoctoral researcher in **Alex Nord**'s lab at University of California, Davis. Part of this work leveraged bulk RNA sequencing to determine if CHD8 haploinsufficiency differentially impacts gene expression in the

postnatal mouse cortex, cerebellum and hippocampus. The greatest differences were in the cerebellum, with an increase in genes involved in translation and mitochondrial function, and a decrease in those involved in cellular proliferation. Out of the roughly 500 differentially expressed genes, 15 were dysregulated across all three brain regions. This convergence is impactful for the field, given that these brain regions are robustly implicated in autism pathogenesis, according to human postmortem, neuroimaging and gene enrichment studies.

12 November 2022: Day One

Jacqueline Crawley

Professor emerita, MIND Institute, University of California, Davis

***Touch sensitivity*:** **Ardem Patapoutian**, professor of neuroscience at Scripps Research in La Jolla, California, gave a brilliant Presidential Special Lecture entitled **"How do you feel? The molecules that sense touch."** Investigating mechanosensory neurons, the **Patapoutian lab** discovered the ion channels PIEZO1 and PIEZO2. The unusual structure of PIEZO proteins confers exquisite sensitivity to our sense of touch. They mediate a remarkable range of tactile somatosensory processes — from light touch (assayed by placing tape on the back of a mouse) to neuropathic pain, from the proprioceptive ability to locate our limbs in space to blood-pressure baroreceptors, and even plant root growth.

Many people with autism have hypersensitivities to sensory stimuli, including touch. Mutations in PIEZO2 have been reported in several human sensory conditions. However, autism was not mentioned in this lecture. Quick searches for PIEZO1 and PIEZO2 in the SFARI gene database, and for PIEZO and autism in PubMed, came up empty. Future investigation of PIEZO ion channel functions that might mediate sensory abnormalities in people with autism could prove interesting.

Patapoutian shared the 2021 Nobel Prize in Physiology or Medicine with **David Julius**, professor of physiology at University of California, San Francisco, for their complementary explications of sensory ion channels. His continuing modesty was evident in how he opened the talk. Ardem looked out and asked, "How many of you are out there?" Then he aimed his phone and photographed the audience, as a tribute to the return of in-person SfN in San Diego.

Professor, University of Missouri

***Astrocyte knockout*:** I saw an interesting **study** out of University of California, Riverside today. They did a selective knockout of the fragile X gene only in astrocytes in a rodent model and found that impacting the astrocytes selectively in this manner was sufficient to dysregulate GABA expression and also affected responses to sound in a manner seen in fragile X syndrome. This increases the evidence that we need to be thinking about the role of astrocytes in autism.

[*Spectrum* **covered this presentation**.]

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