NEWS

Dispatches from IMFAR 2015

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*These short reports from our journalists give you the inside scoop on developments at the **2015 International Meeting for Autism Research**.*

How dolphin whistles helped researchers hear early sounds of autism

Communication difficulties are one of the hallmarks of autism. Studies of infants who are later diagnosed with the disorder suggest that these problems may begin at a very young age. For example, 9-month-old siblings of children with autism who eventually receive an autism diagnosis themselves produce **fewer syllables** than other babies their age.

In a new analysis presented Thursday, researchers went back to listen to recordings of sounds that '**baby sibs**' made when they were younger, at 6 months of age. The researchers found subtle communication abnormalities in those who were later diagnosed with autism.

In an interesting twist, whistles from bottlenose dolphins helped indirectly with the analysis. **Lauren DiNicola**, a research fellow at the Yale Child Study Center who presented the work, had analyzed the sounds dolphins make to communicate with each other. She applied her knack for evaluating

these calls to the sounds that babies make.

Together with **Elizabeth Schoen Simmons**, a speech and language pathologist at Yale, DiNicola analyzed five-minute-long recordings of 6-month-old babies interacting with their mothers. In all, she analyzed the sounds of 21 baby sibs, 11 of whom were later diagnosed with autism, and 9 controls with no family history of the disorder. She classified the babies' sounds as either neutral or expressing emotion, and software analyzed each sound's pitch, frequency and duration.

All of the babies produced similar proportions of expressive and neutral sounds. But some of the sounds made by the babies later diagnosed with autism have distinct acoustic properties. In particular, some sounds that express happiness, such as squeals and sighs following laughs, vary in pitch more in the baby sibs with autism than those made by the controls and baby sibs without the disorder.

The researchers cannot actually hear pronounced differences when listening to the various babies' gurgles, coos and other noises, DiNicola says. "But when we look at their unique individual acoustic properties, that's where we see the differences emerge."

— Nicholette Zeliadt / 18 May

A smarter trial for fragile X drugs

The past few years have been a rollercoaster for people working on drugs for **fragile X syndrome**. A number of candidates that seemed to work spectacularly well in mouse models just did not translate into benefits in people with the syndrome.

"We've been stuck in translation," **Elizabeth Berry-Kravis**, a researcher who has led some of these trials, said at a keynote panel this morning.

Berry-Kravis recapped the ups and downs of the past few years — including the usual-suspect reasons for why these drugs failed: Treating adults and adolescents may be too late for improvement; brain connections may not reset on their own **without behavioral training**. And trials need **more objective measures of success**.

Anyone who follows this field has heard all of this before. But toward the end of Berry-Kravis' talk, I heard something I hadn't heard before: a possible solution.

She and her colleagues are designing a trial to revive drugs that inhibit mGluR5 activity, the same candidates that were **so promising in animal models**. The trial will focus on children, with the participants getting both a drug and behavioral training at the same time, and for longer than other trials — hopefully long enough to see benefits.

The researchers plan to start the trial in children ranging in age from 3 to 6 years, then slowly increase the amount of the drug to find the highest safe dose.

While taking this optimal dose, the children will then get language training for six months. The researchers plan to use brain imaging and **eye tracking** to look for objective biological indicators that the language training works.

The second arm of the trial will be another six months of treatment for the same participants, which will give the researchers a longer time to be able to track its effects.

This method seems to carefully address many of past trials' fatal flaws. It's still in development, but Berry-Kravis says she hopes to start sometime in the next eight months.

— Jessica Wright / 16 May

Brain size in autism gets a closer look

Some children with autism have abnormally large brains and some teens and adults with the disorder do not. Based on these findings, researchers have suggested that the brain of a person with autism **overgrows during early childhood and then shrinks** during adolescence. But an ongoing study is showing early hints that this might not be the case.

The previous studies came to their conclusion about shrinkage after comparing snapshots of the brains of individuals with autism across a range of ages. But to really understand the dynamics of brain growth in autism, they would need to follow the same individuals over time.

That's what **David Amaral** and his colleagues at the University of California, Davis MIND Institute **set out to do** nine years ago. **Lauren Libero**, a postdoctoral fellow in Amaral's lab, reported the group's preliminary findings yesterday.

The researchers used magnetic resonance imaging to measure brain size in 150 children with autism and 61 typically developing controls over time, starting at age 3. They repeated the scans when the children were 4 and 5.

After controlling for height, which can influence brain size, the researchers found that 21 of the children with autism had abnormally large brains at age 3. This enlargement persisted for the next two years.

Now that the participants are about 11 years old, the researchers are measuring their brains a fourth time.

"My hypothesis is that they're still going to be enlarged," Amaral told me after the presentation.

“Our take on it is that only by following a cohort of kids longitudinally, from very young ages, will we ever really come to a true answer.”

— Nicholette Zeliadt / 16 May

The case intensifies for an autism gene

The quest for the ‘white unicorn’ of autism research — a bona fide autism gene — may be coming to a close. In a talk at a genetics session this morning, **Raphael Bernier** showed data from 10 new individuals with **CHD8** mutations — all of whom have autism.

Researchers first identified autism-linked **mutations in CHD8**, a regulatory gene, just three years ago. Now it is one of the ‘hottest’ new autism genes — so much so that even being a target of CHD8 **bolsters other genes’ links** to the disorder.

Last year, Bernier’s team at the University of Washington reported **an in-depth characterization of the features** of 15 adults and children with a CHD8 mutation. The resulting constellation of symptoms looks a lot like an autism ‘syndrome,’ with constipation, large head size and sleep problems as its hallmarks.

All but two of the participants met strict criteria for an autism diagnosis based on an in-person assessment. The two participants who were not diagnosed with autism have not been thoroughly evaluated, as they live in Europe. Bernier won’t say it directly, but I suspect that such an evaluation would reveal autism in these adults as well.

Although the autism proportions published in the study are striking, experts cautioned that they are somewhat skewed. They point out that most of the participants were identified from groups of people already known to have autism.

Now, researchers have added 10 more participants. Three came from clinical referral and not an autism database. They all have autism.

The other features of the CHD8 syndrome hold up in these new numbers: Of the 25 people, 65 percent have enlarged heads, 83 percent have constipation and 72 percent have sleep problems.

As before, only about half (12) of the participants have intellectual disability, further supporting the idea that this gene is excitingly close to being autism-specific. It can be hard to distinguish a low intelligence quotient from the social deficits or **repetitive behaviors** that characterize autism. But if a person has good cognitive ability, his autism symptoms are probably emerging independently.

An intriguing new symptom reported today is that 54 percent of people with the CHD8 mutations are extremely tall. One young man, described as a “gentle giant” by his mother, is 7 feet tall.

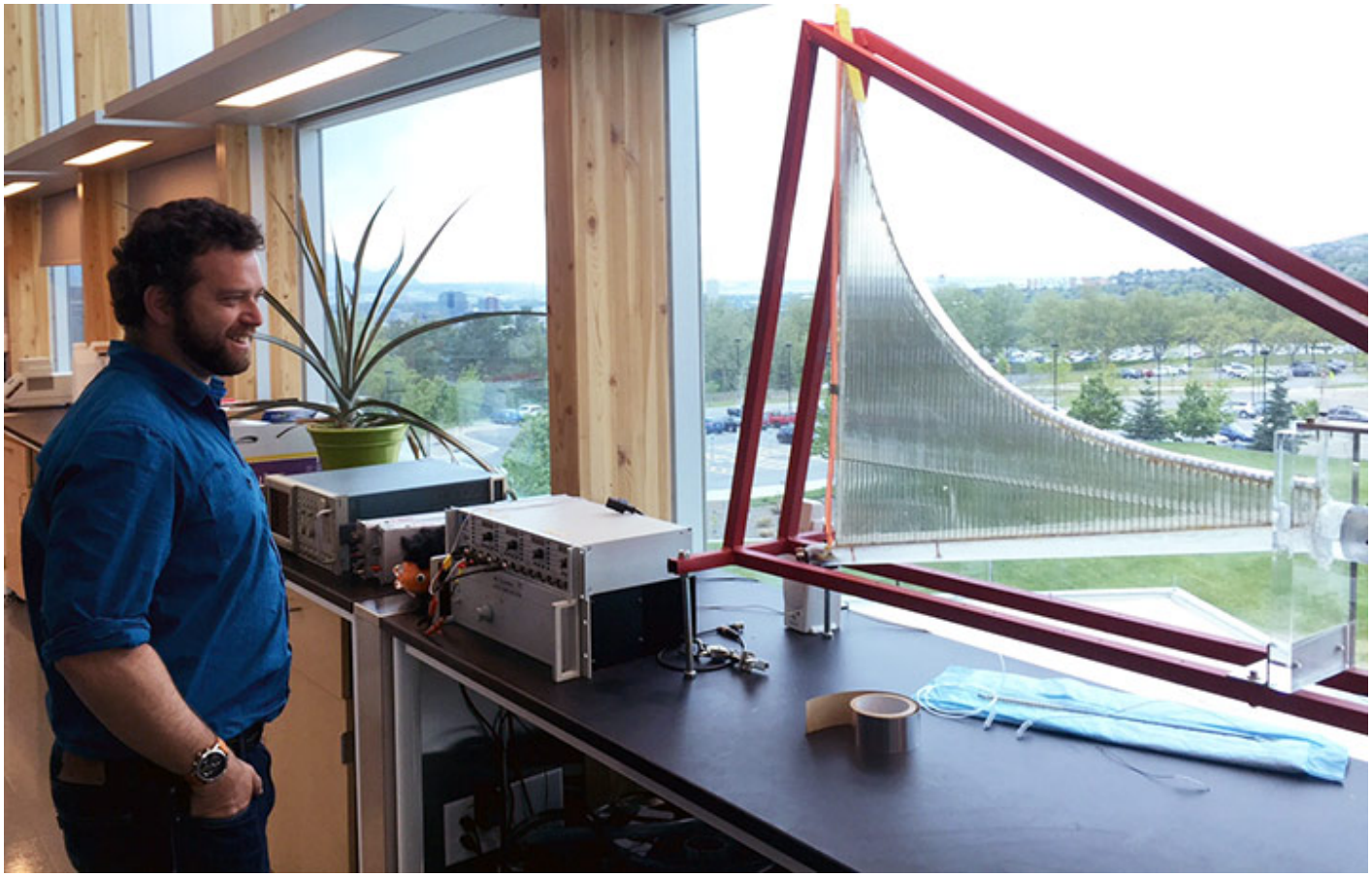
A wonderful byproduct of identifying as many people as possible with such a rare mutation is the opportunity it provides for families to come together and compare notes. Many children with autism have sleep problems, but perhaps not to the same extent as a girl with a CHD8 mutation who can only sleep in a special tent in her bedroom, says Bernier.

He and his team have set up a **website for CHD8** so that individuals diagnosed with CHD8 mutations can learn that they are not alone. There is also a Facebook discussion page.

Despite the mutations being extremely rare, more individuals with them are likely to emerge. It will be interesting to see if the strong autism association continues to hold up.

— Jessica Wright / 15 May

In search of coffee, I arrive at a spectacular lab



Jason Shepherd runs a systems neuroscience lab in the foothills of Salt Lake City.

During the afternoon break — in search of a drinkable cup of coffee and an excuse to get some air — I accepted an impromptu offer from a neuroscientist I met through our **Facebook discussion group**. I took the city's streetcar into the foothills to visit **Jason Shepherd's** new lab at the University of Utah. Shepherd, a former trainee in **Mark Bear's** group at the Massachusetts Institute of Technology, has a sprawling 'systems neuroscience' lab with sweeping views of the Oquirrh Range. He showed me around a glass-and-concrete neo-Brutalist building filled with the fruits of his lab start-up money: wet-lab benches overlooking the Salt Lake Valley, next-generation brain imaging machines, in-vivo two-photon microscopy equipment, and a device that pulls in real-time, field-of-vision recordings from animals as they attempt to solve mazes.

A newly minted professor who welcomes collaborations from unexpected places, Shepherd has launched a number of intriguing interdisciplinary pilot studies. Some involve building on **his work** in Bear's lab looking at synaptic function related to a protein called **ARC** that is associated with **Angelman syndrome**. In another project that he dubs "the crazy one that might just work," he's looking at the connection between autism and the gut microbiome. Collaborating with an immunologist, he plans to transplant fecal matter from people with and without autism into germ-free mice. He suspects that the microbiota will have an effect on brain development in the mice.

Shepherd also hopes to collaborate with geneticists. He claims that the University of Utah is home to some of the best-characterized genetic and phenotypic data in the world. Well utilized in the cancer and pulmonary medicine fields, these data haven't yet been tapped to study neurological conditions, he says.

An active member of our online discussion group for researchers, Shepherd embraces social media as much as he welcomes new technology. A friend recently convinced him to host an 'Ask Me Anything' session on the social platform Reddit. When he saw that his **rapid-fire Q&A session** received "hundreds of thousands of views," he instantly thought about how he could use such scalability for research. "Scientists are often afraid of social media, but there's real power there," he says.

And as a community manager tasked with bringing together autism researchers online, I tend to agree.

— Greg Boustead / 15 May

Going global with autism awareness

The International Meeting for Autism Research has often been a misnomer, given that it's traditionally dominated by North American scientists and societies.

Two years ago, that changed when British researcher **Francesca Happé** took over from **Helen Tager-Flusberg** (also originally from the U.K., but based in Boston) as president of the

International Society for Autism Research (INSAR), which hosts the meeting. That year, 2013, the **meeting was held in San Sebastián**, Spain, another nod to the importance of broadening the conference's appeal.

Raising awareness of autism and bringing people into autism research worldwide are big goals for the organization, Happé told me. At her welcome address this morning, she announced that for the first time, INSAR will host a conference in China, **where awareness of autism is sorely lacking**. Beating out bids from South Africa, Japan and South America, Shanghai is the designated host for the first **Asia Pacific Regional IMFAR**, scheduled for 6-8 November.

If the meeting goes well, it could be the first of many, Happé says. "We want to be genuinely international."

— Apoorva Mandavilli / 14 May

For more reports from the 2015 International Meeting for Autism Research, please click here.

REFERENCES:

1. Libero L.E. *et al. Autism Res.* Epub ahead of print (2016) **Abstract**