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Reviewing biomedical and educational research in the field of autism and related disorders

Virtual reality room can help some individuals with autism quickly overcome severe phobias

Immersive virtual reality therapy can help some children and adults with autism spectrum disorder (ASD) overcome their phobias, according to researchers in Britain.

Morag Maskey and colleagues note that anxiety is one of the most common problems for individuals with ASD, and that many individuals with ASD have specific phobias—such as a fear of dogs, elevators, airports, or balloons—that interfere significantly with daily life. The researchers also note that cognitive behavioral therapy (CBT), the most commonly used therapy for phobias, can be difficult for individuals with ASD to benefit from because it requires abstract thinking.

Maskey comments, "It is incredibly rewarding to see the effect it can have for some, overcoming a situation which just a week previously would have been so distressing."

In the virtual reality approach, participants enter a "Blue Room" where they navigate through a 360-degree video projection of a scene (accompanied by audio) that replicates the feared object or experience. They do not need to wear goggles because a therapist manipulates the scene using iPad controls. The therapist also uses CBT techniques to help participants become less anxious during exposure to their phobias.

Participants move through a hierarchy of exposure (for instance, seeing a small dog first and later a larger one), proceeding to the next level only when they feel secure. This allows them to gain confidence through repeated practice at one level of challenge.

Recently Maskey and colleagues reported the results of two studies of the Blue Room's effects on phobias in ASD. One involved children, while the other involved adults.

In the first study, Maskey and colleagues randomized 32 children with ASD to a treatment group or a wait list. Children in the active treatment group underwent one 45-minute introductory session and four 20-minute virtual reality sessions conducted over two weeks. Children initially on the wait list later participated in the active treatment.

The researchers report, "One-third of children from the treatment group showed improvements in their real-life targeted phobia, with children able to manage everyday activities and situations that were not possible previously. By contrast, no children in the control group showed improvement in their specific phobia during their wait phase of the trial period. Furthermore, five control group children showed a clear deterioration in target behavior rating from baseline, compared with one treatment group child. When the control group later received treatment, a similar proportion were classified as responders as to the immediate treatment group."

In the second study, the researchers found that Blue Room treatment was also effective for many adults with ASD. In this study, eight adults ranging in age from 18 to 57 participated in virtual reality sessions. The researchers report, "For all participants, phobia was having a major impact on their lives (e.g., preventing attendance at university, preventing travel, and/or involving extensive safety rituals that limited their participation in everyday activities). Five of the eight adults improved in their ability to tackle their real-life phobia, and four adults were able to function in everyday life without any impact from their phobia."

Maskey comments that the Blue Room is effective because "we are providing the feared situation in a controlled way through virtual reality and we are sitting alongside them to help them learn how to manage their fears." She adds, "It is incredibly rewarding to see the effect it can have for some, overcoming a situation which just a week previously would have been so distressing."

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"A randomised controlled feasibility trial of immersive virtual reality treatment with cognitive

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Inhibition-excitation alterations in ASD: a surprising finding

The findings of a new study cast doubt on the hypothesis that autism symptoms such as sensory oversensitivity stem from too little inhibition or too much excitation of neurons, causing hyperexcitability or increased "spiking" that interferes with brain function.

Michelle Antoine and colleagues tested four mouse models of autism, each involving a single genetic defect similar to one found in humans with autism spectrum disorders (ASD). They did find that inhibition was lower than normal in the neurons of the mice, and that excitation was reduced to a lesser degree, resulting in an increase in the excitation-inhibition ratio. However, they discovered that the neurons maintained a normal spiking rate because the changes in inhibition and excitation were precisely coordinated to offset each other. The researchers say that this may be how the neurons compensate for the genetic mutations so they can stabilize brain activity.

Lead author Daniel Feldman says, "Many groups are searching for ways to increase inhibition in the brain, either through drugs or through gene therapy, on the assumption that increasing inhibition will restore the brain back to normal. But actually, our results suggest that loss of inhibition might represent a useful compensation that the brain is doing, or might be unrelated to disease symptoms. And if you go in there and increase inhibition, you might make things worse or you might not affect things at all."

Feldman says that while decreased inhibition appears to help neurons maintain stable brain activity, it may cause unwanted secondary effects. "Changes in the excitation-inhibition ratio might be successfully compensating to maintain a relatively normal firing rate, but a side effect of that compensation may be that they degrade the precision of the coding information," he says. "So even though there are not more spikes, the spiking could encode information less precisely."

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"Increased excitation-inhibition ratio stabilizes synapse and circuit excitability in four autism mouse models," Michelle W. Antoine, Tomer Langberg, Philipp Schnepel, and Daniel E. Feldman, *Neuron*, January 21, 2019 (online). Address: Michelle Antoine, mwantoine@berkeley.edu.

—and—

"Mouse studies question 'inhibition' theory of autism," Robert Sanders, Berkeley News, January 21, 2019.

New study finds medical marijuana may help reduce behavior problems, anxiety, hyperactivity

New research from Israel adds to earlier evidence that medical marijuana can reduce symptoms of autism spectrum disorders (ASD) in many children.

In the new study, Dana Barchel and colleagues evaluated the effects of oral cannabidiol and tetrahydrocannabinol (constituents of marijuana) administered to 53 children and young adults with ASD for a median duration of 66 days. The researchers report that based on information collected from parents in biweekly telephone interviews, self-injury and rage attacks improved in 67.6% of the children with these symptoms, worsening in 8.8%. Hyperactivity improved in 68.4% of the children with this symptom and worsened in 2.6%. Sleep problems improved in 71.4% of the children with this issue and worsened in 4.7%. Anxiety improved in 47.1% of the children with this symptom and worsened in 23.5%.

The most commonly reported side effects were sleepiness and changes in appetite, which were mild and temporary.

The researchers conclude, "Based on parents' reports, our findings suggest that cannabidiol may be effective in improving ASD comorbid symptoms. However, CBD efficacy and safety should be further evaluated in children with ASD in large-scale clinical trials."

In a previous study (see ARRI 32/3, 2018), a separate team of Israeli researchers found that oral treatment with cannabidiol and tetrahydrocannabinol reduced behavior problems and anxiety and improved communication.

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"Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities," Dana Barchel, Orit Stolar, Tal De-Haan, Tomer Ziv-Baran, Naama Saban, Danny Or Fuchs, Gideon Koren, and Matitiahu Berkovitch, *Frontiers in Pharmacology*, Vol. 9, January 2019 (online). Address: Matitiahu Berkovitch, mberkovitch@asaf.health.gov.il.

Simple microbe therapy may improve social behavior in autism

A study conducted by a team of researchers at Baylor University suggests that administering a specific strain of gut microbes to individuals with autism may help ameliorate their social deficits.

Study coauthor Mauro Costa-Mattioli says, "In 2016, we discovered in mice that the offspring of mothers fed a high-fat diet had social deficits and changes in their gut microbiome were characterized by a reduction in the abundance of the bacterial species *L. reuteri*. More importantly, restoring *L. reuteri* levels in the offspring reversed their social deficits. This model of ASD represents only one of the numerous heterogeneous underpinnings of the condition. Therefore, we decided to investigate whether our findings would apply to other models with different origins."

When the researchers tested the effects of *L. reuteri* on a range of mouse models, they found that the microbe reversed social deficits in all models tested—whether the autism was environmentally caused, genetically caused, or idiopathic (meaning that the cause was unknown). The researchers also found that the effects of *L. reuteri* did not result from changes to the composition of the gut microbiome, which was altered in all of the models tested. Instead, study coauthor Martina Sgritta says, "We discovered that *L. reuteri* promotes social behavior via the vagus nerve, a nerve that bidirectionally connects the gut and the brain and the oxytocin-dopamine reward system." Activation of this nerve stimulates neurons that produce oxytocin, a hormone that promotes social bonding.

"Interestingly," Sgritta says, "we found that when the vagus nerve was severed and the brain-gut connection was disrupted, *L. reuteri* could no longer restore social behavior in ASD mice. In addition, when we genetically engineered mice to lack oxytocin receptors in reward neurons or blocked the receptors with specific drugs, the treatment with *L. reuteri* also failed to reverse the social deficits in the ASD mice."

The researchers emphasize that their findings are preliminary, and that the effects of *L. reuteri* need to be tested in clinical trials on humans. However, they conclude, "Treatment with *L. reuteri* emerges as a promising non-invasive microbial-based avenue to combat ASD-related social dysfunction."

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"Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder," Martina Sgritta, Sean W. Dooling, Shelly A. Buffington, Eric N. Momin, Michael B. Francis, Robert A. Britton, and Mauro Costa-Mattioli, *Cell*, December 3, 2018 (online). Address: Mauro Costa-Mattioli, costamat@bcm.edu.

—and—

"The power of the microbiome: A microbe-based treatment reverses social deficits in mouse models of autism," *From the Labs*, Baylor College of Medicine, December 13, 2018.

—and—

"Can autism be treated with a simple microbial-based therapy?", ScienceBlog.com, December 21, 2018.

The Kids First Initiative: Giving Back to Families

The Hartwell Foundation Kids First initiative seeks to help every family who has a child with an autism spectrum disorder. The goal is to create detailed categories that accurately reflect individual behavior and personality, with the expectation of advancing personalized, targeted approaches for care and intervention that will be more successful than what is available today.

The Kids First approach is conducted using IRB-approved confidential survey methodology by prominent universities. Survey questions are simple, focused on basic behavioral and medical information, and can be completed in about 10 minutes. Results will be shared confidentially with all survey participants. The collected data will provide a unique opportunity for researchers to begin classification of ASD, and as new categories are identified, the effort will expand to more sophisticated requests for information.

We invite you to participate in the Kids First confidential survey, joining a growing network of families, clinicians, and scientists involved in this innovative research project to improve the lives of children and families affected by ASD. To learn more and begin your survey, visit kidsfirst.stanford.edu and when asked, type ARI as your referral code.

Virtual reality therapy helps some individuals with ASD overcome phobias

(continued from page 1)

behaviour therapy for specific phobias in young people with autism spectrum disorder," Morag Maskey, Jacqui Rodgers, Victoria Grahame, Magdalena Glod, Emma Honey, Julia Kinnear, Marie Labus, Jenny Milne, Dimitrios Minos, Helen McConachie, and Jeremy R. Parr, *Journal of Autism and Developmental Disorders*, February 15, 2019 (free online). Address: Jeremy R. Parr, Institute of Neuroscience, Sir James Spence Institute Level 3, Royal Victoria Infirmary, Newcastle University, Newcastle upon Tyne NE1 4LP, UK, jeremy.parr@ncl.ac.uk.

—and—

"Using virtual reality environments to augment cognitive behavioral therapy for fears and phobias in autistic adults," Morag Maskey, Jacqui Rodgers, Barry Ingham, Mark Freeston, Gemma Evans, Marie Labus, and Jeremy R. Parr, *Autism in Adulthood*, Vol. 1, No. 2, 2019 (free online). See address above.

—and—

"Virtual reality therapy treats autism phobias," news release, Newcastle University, February 15, 2019.

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EDITORIAL: Stephen M. Edelson, Ph.D.

Standardizing Proper Medical Care for Individuals with Autism

For more than 50 years, doctors and researchers viewed autism solely as a neurodevelopmental disorder. In recent decades, however, we have begun to focus increasing attention on medical co-morbidities in autism spectrum disorders (ASD), including seizures, immune and metabolic dysfunction, gastrointestinal (GI) impairment, anxiety, and sleep disorders.

Countless studies and scientific surveys have documented medical comorbidities in people with ASD. In addition, more than half of individuals diagnosed with autism suffer from one or more medical issues.

Given the high prevalence rate of autism, it might be assumed that health-related government agencies, professional medical organizations, and insurance companies closely monitor the progress of research in autism, and that physicians are continually updated on best practice. Yet a standard of medical care for individuals with ASD has not been established. As a result, many of the medical problems of people with ASD go unnoticed and thus untreated.

What should medical care for individuals with ASD look like?

For patients with ASD to receive proper medical care, doctors and their clinical staffs must possess four types of knowledge:

- They need to be aware of the medical conditions commonly associated with autism.
- They need to know how to determine whether their patients with ASD have any of these comorbidities.
- They need to know which laboratory tests are required to evaluate specific problems.
- They need to be knowledgeable about appropriate treatments and should also know when to refer a patient to a specialist for further testing.

Here are steps we can take to foster each type of knowledge.

Awareness of common medical conditions. Currently, physicians have opportunities to learn about medical problems associated with autism, but this is optional. Given the high rate of autism, knowledge about common comorbidities in ASD should be mandatory for physicians to be in good standing in professional organizations such as the American Medical Association, the American Academy of Pediatrics, and the American Academy of Neurology.

The information physicians need is readily available to them. Several organizations host webinars on medical issues associated with autism, and some of them offer continuing medical education (CME) credit. ARI offers, in joint providership with the Cleveland Clinic, complimentary AMA PRA Category 1 Credit™ to physicians and the general public.

Parents can also play a role in educating physicians and medical staff by sharing links to informative, science-based websites as well as specific articles of interest.

Identification of medical problems. Experts in the field of autism should work together to develop a standardized intake form to help doctors screen for possible medical conditions. This form could be completed by a care provider or a patient with ASD prior to a visit (using an online form) or at the doctor's office. The intake form should include questions regarding allergies, anxiety, GI problems, possible signs of seizures, sensory sensitivities, and sleep problems. Work is already in progress on this front; for example, a checklist designed to identify GI disorders was recently published by Kara Gross Margolis and her colleagues.

After reviewing the intake form, medical professionals should ask additional questions in order to avoid any misinterpretation as well as to learn more specifics about possible medical problems.

Physicians should also be aware that patients with ASD may not express any signs of discomfort or pain, or may react by engaging in a challenging behavior. Regarding the former, we have heard reports of individuals with ruptured eardrums or appendixes who gave no indication of any distress prior to, during, or after the rupture. Regarding the latter, medical conditions associated with behavior problems may include ear infections and ear-hitting, headaches and head banging, sinus infections and face-slapping, excessive scratching and rash, and sleep problems and stomachaches.

Laboratory testing and referral. If a physician suspects an underlying medical condition, he or she should know which laboratory tests to order. If the patient is referred to a specialist, the referring physician should be able to describe, at least to some degree, the procedures likely to be involved in the specialist's evaluation.

Furthermore, it would be ideal for the referring physician or medical staff to provide information about specialists, including the types of health insurance they accept and the amount of experience they have in examining individuals with ASD. Specialists with little or no experience may need guidance from patients or care providers.

Care providers, for their part, should consider the use of social stories to reduce anxiety during medical tests and procedures.

Treatment. The medical protocol for patients with ASD should include only evidence-based treatments. This will prevent patients and caregivers from wasting precious time and financial resources on interventions that may sound reasonable in theory, but have no effect or could possibly lead to adverse effects.

Some physicians hesitate to prescribe certain treatments for which there is little or no research involving individuals with ASD, even when these treatments have been shown to be effective in treating the neurotypical population. Examples include treatments for constipation, allergies, GERD, rashes, and infections. In such cases, physicians should carefully weigh the costs and benefits of treatment.

Physicians should be mindful when prescribing treatments that may impact multiple biological systems, either directly or indirectly. For example, many psychiatric medications, such as antidepressants and anticonvulsants, can slow stool motility, and this could worsen an already constipated bowel. In addition, laxatives can lead to dehydration, which is already a problem among many individuals with ASD.

Furthermore, physicians have a responsibility to provide unbiased and accurate information to care providers and individuals with ASD who inquire about treatments that may not be included in a standard medical protocol. It would be advantageous, and could be part of the informed consent process, to make "white papers" available on all popular interventions, whether evidence-based or not.

What can be done now?

Given what we already know, it is disconcerting that many individuals with ASD do not receive treatment for mild, moderate, or even severe medical issues.

There is no reason for the medical community to wait any longer to develop a comprehensive standard of care for autism. We do not need to know all the answers before such a protocol is written. It is safe to state that all medical care progresses over time.

If a standard medical protocol is agreed upon, then an important but delicate question would be, "Who will oversee the protocol?" All stakeholders in the autism community should have a say in answering this question.

Where there is a will, there's a way!

Research Updates

Severe morning sickness associated with increase in autism spectrum disorder

A new study suggests that the odds of developing autism may be significantly elevated for children of mothers who experience hyperemesis gravidarum (HG), or severe morning sickness.

Marlena Fejzo and colleagues compared 267 children delivered by 177 mothers with HG to 93 children delivered by 60 mothers who did not experience this problem. At 12 years of age, the children of the mothers with HG had a more than three-fold increase in the odds of having a diagnosis of neurodevelopmental disorder. Eight percent of the children of mothers with HG received a diagnosis of autism spectrum disorder (ASD) by the age of 12, compared to none of the children in the control group.

The researchers say, "As early intervention for ASD can be critical to prognosis, larger studies are urgently needed to determine whether ASD is associated with exposure to hyperemesis gravidarum."

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"Analysis of neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum reveals increased reporting of autism spectrum disorder," Marlena Fejzo, Alyssa Kam, Amanda Laguna, Kimber MacGibbon, and Patrick Mullin, *Reproductive Toxicology*, Volume 84, March 2019, 59-64. Address: Marlena Fejzo, Department of Maternal-Fetal Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, mfezjo@mednet.ucla.edu.

Lasting benefits seen from horseback riding therapy

A follow-up study on the effects of therapeutic horseback riding suggests that it has significant long-term benefits for children with autism spectrum disorders.

In previous research in 2015, involving 127 participants with ASD, a team led by Robin Gabriels found that children participating in a 10-week therapeutic riding program exhibited improvements in irritability and hyperactivity as well as increased word fluency compared to children participating in activities in a barn setting but not interacting with horses.

In the new study, the researchers re-evaluated 64 of the children six months after their therapy sessions ended. They found that the children continued to exhibit reductions in irritability (although not hyperactivity) compared to the controls. In addition, the riding group sustained their initial improvements in social communication and word fluency.

Gabriels comments, "There is growing evidence that human-animal interventions can improve emotional health and social wellness in youth, particularly those with autism spectrum disorder. Our study was rigorous and the findings remarkable."

—

"Long-term effect of therapeutic horseback riding in youth with autism spectrum disorder: a randomized trial," Robin L. Gabriels, Zhaoxing Pan, Noémie A. Guérin, Briar Dechant, and Gary Mesibov, *Frontiers in Veterinary Science*, July 16, 2018 (free online). Address: Robin Gabriels, robin.gabriels@childrenscolorado.org.

—and—

"Children with autism spectrum see benefits from equine therapy," David Kelly, news release, University of Colorado Anschutz Medical Campus, October 30, 2018.

In animal model of ASD, the brain does not pause its growth during delivery

Brain growth may not pause in a normal way around the time of delivery in children with autism spectrum disorders (ASD), a new study suggests.

Robin Cloarec and colleagues used an imaging technique called iDISCO to study a rat model of ASD (in which the researchers created "ASD" by exposing the unborn rats to valproate). This imaging technique can create 3-D images of an unborn rat's brain.

The researchers found that the brains of control rats stopped growing in size during the period just prior to, during, and immediately after birth. They believe that this helps the brain cope with the trauma of birth. In the ASD rats, however, the brain was larger after birth (particularly in the hippocampal region), indicating that its growth had not stopped during this period.

In addition, the researchers examined the effects of giving the drug bumetanide to pregnant rats before delivery. This drug, which can ameliorate some symptoms of autism, reduces the concentration of chloride in neurons. Administering bumetanide prevented abnormal brain growth in the ASD rats, which the researchers say suggests that "high levels of chloride during labor and birth are pathogenic."

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"Pyramidal neuron growth and increased hippocampal volume during labor and birth in autism," R. Cloarec, B. Riffault, A. Dufour, H. Rabiei, L.-A. Gouty-Colomer, C. Dumon, D. Guimond, P. Bonifazi, S. Eftekhari, N. Lozovaya, D. C. Ferrari, and Y. Ben-Ari, *Science Advances*, Vol. 5, January 23, 2019 (online). Address: Yehezkel Ben-Ari, Neurochlore, Ben-Ari Institute of Neuroarcheology (IBEN), Zone Luminy Biotech Entreprises, 13288 Cedex 09, Marseille, France, ben-ari@neurochlore.fr.

Early motor problems seen in children with ASD

Children with autism spectrum disorders (ASD) show very early evidence of impaired motor skills, according to a new study.

Lori-Ann Sacrey and colleagues analyzed data from three groups of children, all recruited into a longitudinal study when they were between 6 and 12 months of age and followed through the age of 36 months. Ten of the children were "high-risk" children (because they had an older sibling with ASD) who later received an autism diagnosis themselves. Ten were high-risk children who did not later receive an ASD diagnosis, and 10 were neurotypical controls.

The researchers used videos of the children to evaluate their reach-to-grasp movement at 6, 9, 12, 15, 18, 24, and 36 months of age. This movement, they say, is a good indicator of how skilled hand movement and its sensory control are developing. The reach-to-grasp movement involves five components:

- Orienting (moving the head and eyes to fixate visually on an object, and disengaging visually once the object is grasped).
- Lifting (raising a hand, repositioning it, and semi-flexing the fingers).
- Advancing (moving the hand toward the object and stopping above it).
- Pronating (rotating the hand and shaping the fingers in order to grasp the object).
- Grasping the object.

The researchers report that children later diagnosed with ASD had poorer total scores on the reach-to-grasp movement, as well as poorer scores on the orienting, lifting, and pronating components of the movement, compared to children in the other two groups.

They conclude, "Our results support the growing literature indicating that children who are later diagnosed with ASD show impaired early motor performance." Monitoring of children at elevated risk for ASD, they say, should include screening them for motor and sensory issues.

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"The reach-to-grasp movement in infants later diagnosed with autism spectrum disorder: a high-risk sibling cohort study," Lori-Ann R. Sacrey, Lonnie Zwaigenbaum, Susan Bryson, Jessica Brian, and Isabel M. Smith, *Journal of Neurodevelopmental Disorders*, December 2018 (free online). Address: Lori-Ann Sacrey, sacrey@ualberta.ca.

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Research Updates

DAT mutation alters behavior in fruit flies

A mutation in one gene associated with autism causes abnormal behavior in fruit flies, according to a new study.

The mutation studied by Nicholas Campbell et al. encodes for the dopamine transporter, or DAT, a brain protein that pumps the neurotransmitter dopamine back into nerve cells after it has been released. The mutant gene produces a variant of the protein that is missing a single amino acid.

The researchers found that fruit flies with this gene mutation are hyperactive and exhibit repetitive behavior, grooming themselves 23% of the time compared to 6% of the time for other fruit flies. In addition, they are more fearful, freezing for longer periods in response to the sound of a predatory wasp. The flies with the mutant gene also exhibit impaired social interactions, "herding together" in response to a threat in a different manner than other fruit flies do.

The researchers have identified several other mutations in the DAT gene that affect its function in individuals with ASD. For these people, they say, disruption of dopamine transport appears to be a risk factor that promotes complications associated with ASD.

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"Structural, functional, and behavioral insights of dopamine dysfunction revealed by a deletion in SLC6A3," Nicholas G. Campbell, Aparna Shekar, Jenny I. Aguilar, Dungeng Peng, Vikas Navratna, Dongxue Yang, Alexander N. Morley, Amanda M. Duran, Greta Galli, Brian O'Grady, Ramnarayan Ramachandran, James S. Sutcliffe, Harald H. Sitte, Kevin Erreger, Jens Meiler, Thomas Stockner, Leon M. Bellan, Heinrich J. G. Matthies, Eric Gouaux, Hassane S. Mchaourab, and Aurelio Galli, *Proceedings of the National Academy of Sciences*, February 12, 2019 (epub prior to print publication). Address: Eric Gouaux, gouauxe@ohsu.edu.

—and—

"Human brain protein associated with autism confers abnormal behavior in fruit flies," Jeff Hansen, University of Alabama at Birmingham, February 11, 2019.

Children with ASD respond differently to mom's voice

Children with autism have a diminished response to the sound of their mother's voice, a new study reports.

Daniel Arthur Abrams and colleagues conducted functional magnetic resonance imaging on 42 children between 7 and 12 years of age. Half of the children had ASD, while the other half were neurotypical controls. The children listened to three different recorded sounds: their mother's voice, voices of unfamiliar women, and non-vocal environmental sounds. The women spoke nonsense words to avoid activating brain regions involved in language comprehension.

The researchers say that the brain response to unfamiliar voices, when compared with the response to environmental sounds, was fairly similar between the two groups. However, in the children without autism, many more brain areas "lit up" in response to their mothers' voices. These areas included part of the hippocampus, which is involved in learning and memory, and face-processing regions. Brain-connectivity patterns in a network including auditory processing regions, reward processing regions, and regions that determine the salience of incoming information also differed between the two groups. The degree of social communication impairment in individual children with ASD correlated with the degree of abnormality in their brain responses to their mother's voice.

In addition, children with autism were less adept at differentiating their mother's voice from the voices of unfamiliar women. They were able to identify their mother's voice only 87.8% of the time, compared to 97.5% for the control group.

Senior study author Vinod Menon comments, "Mom's voice is the primal cue for social and language communication and learning. There is an underlying biological difference in the brain circuitry in autism, and this is a precision-learning signal we can target."

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"Impaired voice processing in reward and salience circuits predicts social communication in children with autism," Daniel Arthur Abrams, Aarthi Padmanabhan, Tianwen Chen, Paola Odriozola, Amanda E. Baker, John Kochalka, Jennifer M. Phillips, and Vinod Menon, *eLIFE*, February 26, 2019 (free online). Address: Daniel Arthur Abrams, daa@stanford.edu or Vinod Menon, menon@stanford.edu.

—and—

"Brain response to mom's voice differs in kids with autism," Erin Digitale, Stanford News Center, February 26, 2019.

ARRI Survey: Seniors with Autism Spectrum Disorder

https://www.autism.com/adult_survey

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population's quality of life issues.

Stem cells offer clues about early neural development in ASD

Researchers at the Salk Institute report that stem cells derived from the skin cells of individuals with autism spectrum disorders (ASD) develop in a different pattern and at different speeds compared to stem cells created from the skin cells of individuals without ASD.

Simon Schafer and colleagues took skin cells from eight people with ASD and five controls and transformed them into pluripotent stem cells, which have the ability to develop into any type of cell. The researchers then chemically induced the cells to develop into neurons.

Using molecular "snapshots" from various stages during this process, the researchers tracked genetic programs that switched on as the stem cells developed into neurons. They found that the cells from individuals with ASD developed differently than the cells from controls. For instance, the genetic program associated with the neural stem-cell stage turned on earlier in the cells from individuals with ASD than it did in cells from controls. This program includes many genes associated with an increased risk for ASD. In addition, the neurons that developed from the stem cells of individuals with ASD grew faster and had more complex branches than those from controls.

Schafer comments, "It's currently hypothesized that abnormalities in early brain development lead to autism, but the transition from a normally developing brain to an ASD diagnosis is blurred. A major challenge in the field has been to determine the critical developmental periods and their associated cellular states. This research could provide a basis for discovering the common pathological traits that emerge during ASD development."

The researchers plan to extend their investigation by developing three-dimensional brain organoids to study the interactions between different brain cell types.

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"Pathological priming causes developmental gene network heterochronicity in autistic subject-derived neurons," S. T. Schafer, A. C. M. Paquola, S. Stern, D. Gosselin, M. Ku, M. Pena, T. J. M. Kuret, M. Liyanage, A. A. Mansour, B. N. Jaeger, M. C. Marchetto, C. K. Glass, J. Mertens, and F. H. Gage, *Nature Neuroscience*, January 7, 2019 (epub prior to print publication). Address: Fred H. Gage, Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, CA, gage@salk.edu.

—and—

"Salk team reveals clues into early development of autism spectrum disorder," news release, Salk Institute, January 7, 2019.

Suicide rate rising in ASD; increase stems from greater number of female suicides

A new study suggests that suicide rates are climbing among people with ASD, and that this is due to an increased rate of suicide among females.

In the study, Anne Kirby and colleagues collected information from two Utah databases: the Utah Registry of Autism and Developmental Disabilities, and suicide surveillance data collected by the Utah Office of the Medical Examiner. The information from these databases was linked to the Utah Population database, a state-wide database containing demographic information, vital records, and medical and genealogical data.

The researchers analyzed data collected between 1998 and 2017. During this time, 7 females and 42 males with autism died by suicide in Utah. When Kirby and her team broke their data down into five-year periods, they found that:

- Only two people with ASD, both male, committed suicide between 1998 and 2002.
- Five males and no females with ASD committed suicide between 2003 and 2007.
- Fourteen males and no females with ASD committed suicide between 2008 and 2012.
- Twenty-one males and 7 females committed suicide between 2013 and 2017.

For the first three of these periods, the relative risk of suicide was similar for individuals with and without ASD. However, during the most recent period, the cumulative incidence of suicide was significantly higher for individuals with ASD than for their peers (.17% versus .11%). The researchers note that women with autism accounted for this change.

"There has been an unfortunate assumption that people with autism are in their own world and are not affected by social influences commonly associated with suicidality," Kirby says. "There is now growing realization among clinicians and families that suicidal thoughts and behaviors can be a real concern for autistic individuals." The researchers emphasize, however, that the risk of suicide is small for individuals with ASD.

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"A 20-year study of suicide death in a statewide autism population," Anne V. Kirby, Amanda V. Bakian, Yue Zhang, Deborah A. Bilder, Brooks R. Keeshin, and Hilary Coon, *Autism Research*, January 21, 2019 (epub prior to print publication). Address: Anne V. Kirby, Department of Occupational and Recreational Therapies, University of Utah, Salt Lake City, UT, avkirby@gmail.com

—and—

"Suicide risk in people with autism," Science Daily, January 23, 2019.

Studies show association between infections, ASD diagnosis

Two new studies, one involving children in Denmark and the other involving children in the United States, suggest an association between early childhood infections and an increased risk for autism spectrum disorders (ASD).

In the Danish study, Ole Köhler-Forsberg and colleagues analyzed data on more than one million people born between January 1, 1995 and June 30, 2012. The researchers identified all treated infections the individuals experienced between birth and June 30, 2013, including both severe infections requiring hospitalizations and less severe infections treated with antibiotics by primary care doctors. In addition, they identified all mental disorders diagnosed in a hospital setting and any filled prescription for psychotropic medication.

The researchers found that infections requiring hospitalizations were associated with a significantly increased risk of developing a mental disorder. "In particular," they say, "schizophrenia spectrum disorders, obsessive-compulsive disorder, personality and behavior disorders, mental retardation, autistic spectrum disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder, and tic disorders were associated with the highest risks after infections." The risk of receiving a psychiatric diagnosis following an infection requiring a hospital stay was highest in the first three months, lessening after that. Minor infections slightly increased the risk for some diagnoses, but not for ASD.

In the U.S. study, Katherine Sabourin and colleagues reviewed data collected on children through the Study to Explore Early Development (SEED) project. The researchers report, "We found that children with ASD were more likely to have an infection in the first 28 days of life and before age three compared to children with typical development. Children with ASD were also more likely than children with other developmental delays or disorders to have an infection in the first 28 days of life." In addition, they found that children with regressive ASD had 1.6 times the odds of infection during the first year of life compared to cases without regression.

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"A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents," O. Köhler-Forsberg, L. Petersen, C. Gasse, P. B. Mortensen, S. Dalsgaard, R. H. Yolken, O. Mors, and M. E. Benros, *JAMA Psychiatry*, December 5, 2018 (epub prior to print publication). Address: Ole Köhler-Forsberg, Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark.

—and—

"Infections in children with autism spectrum disorder: Study to Explore Early Development (SEED)," K. R. Sabourin, A. Reynolds, D. Schendel, S. Rosenberg, L. A. Croen, J. A. Pinto-Martin, L. A. Schieve, C. Newschaffer, L. C. Lee, and C. DiGuiseppi, *Autism Research*, Vol. 12, No. 1, January 2019, 136-146. Address: Katherine Sabourin, Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, katherine.sabourin@ucdenver.edu.

Hearing test may help identify children at higher risk for ASD

A particular type of hearing test may allow doctors to identify infants at elevated risk for autism spectrum disorders (ASD), according to a new study.

Amanda Smith and colleagues say that while infants undergo routine hearing tests, these tests merely determine whether the children can hear on a pass/fail basis. In contrast, they say, stapedial reflex testing—a noninvasive procedure that measures pressure changes in the middle ear in response to sounds—assesses an infant's sensitivity and response times to a wide range of frequencies.

The researchers note that there is "an abundance of data" showing that the structure and function of the auditory brainstem are abnormal in many individuals with ASD. "Furthermore," they say, "there is evidence from a number of functional studies for asymmetries in brainstem processing of sound in ASD." They add, "Both functional and anatomical investigations indicate that auditory issues are present at birth."

The researchers stress that an abnormal stapedial reflex test would not be diagnostic for autism, since it could be an indication of other problems. However, they say, "At the very least, auditory function could be used to raise suspicion of ASD or identify children at high risk of ASD manifesting later in life."

The researchers say that early identification of at-risk children could lead to intervention while the brain is still very plastic. For instance, they note, "There is… evidence that auditory integration training normalizes brainstem responses in children with ASD and even improves behaviors."

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"Structural and functional aberrations of the auditory brainstem in autism spectrum disorder," Amanda Smith, Samantha Storti, Richard Lukose, and Randy J. Kulesza, Jr., *Journal of the American Osteopathic Association*, Vol. 119, No. 1, January 2019, 41-50 (free online). Address: Randy J. Kulesza, Jr., Department of Anatomy, Lake Erie College of Osteopathic Medicine, 1858 W. Grandview Blvd., Erie, PA 16509-1025, rkulesza@lecom.edu.

—and—

"Researchers say auditory testing can identify children for autism screening," news release, American Osteopathic Association, January 7, 2019.

Gene region linked to rapid evolution may play role in ASD

A little-studied part of the human genome may influence the severity of autism symptoms, according to a new study.

James Sikela and colleagues are investigating a region of the genome that encodes most copies of the Olduvai protein domain, a gene coding family that helped to spur the rapid evolution of humans. Their theory is that there was a trade-off for this evolutionary progress in the form of conditions such as autism and schizophrenia.

In their latest study, the researchers analyzed the genomes of individuals with autism and found that as the number of copies of Olduvai increased, the severity of autism symptoms increased as well. The research replicates two earlier studies by the team. Sikela says, "We hope that by showing that the link with autism severity holds up in three independent studies, we will prompt other autism researchers to examine this complex family."

While many scientists are investigating the role of genes in autism, Sikela and colleagues note, "Even whole-genome sequencing approaches are limited in their ability to accurately assemble and measure changes in complex, highly duplicated genomic regions, and there are sequences in the genome, among them dynamic, high copy number gene coding regions [such as Olduvai], that are missed by each of these methods."

The researchers propose that "Olduvai sequences can play both a beneficial role (in brain evolution and cognition) and a detrimental role (in autism and schizophrenia), and which outcome occurs depends on which, where, how, and when copies are changing." They say this may explain why autism and schizophrenia, which tend to adversely affect survival and reproduction, persist at a high frequency across human populations.

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"A third linear association between Olduvai (DUF1220) copy number and severity of the classic symptoms of inherited autism," Jonathan M. Davis, Ilea Heft, Stephen W. Scherer, and James M. Sikela, *American Journal of Psychiatry*, February 15, 2019 (online). Address: James Sikela, James.Sikela@ucdenver.edu.

—and—

"Genomic trade-offs: are autism and schizophrenia the steep price of the human brain?", James M. Sikela and V. B. Searles Quick, *Human Genetics*, January 15, 2018 (online). See address above.

—and—

"New study shows hidden genes may underlie autism severity," news release, University of Colorado Anschutz Medical Campus, February 15, 2019.

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Diane Adreon, Ed.D.

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Saliva RNA test helps spot young children with ASD

It may be possible to identify children with autism spectrum disorders (ASD) with fairly high accuracy using a saliva-based RNA panel, according to a new report.

Steven Hicks and colleagues compared saliva samples from 238 young children with ASD to samples from 218 children without ASD. All of the children were between 9 and 83 months of age. The control group included both neurotypical children and children with developmental delays.

The researchers measured levels of human and bacterial RNA in saliva samples from the children, using machine-learning algorithms to identify the top ASD-related RNAs in the first 372 children and then validating their findings in the remaining samples (which were taken from children from two different geographical areas). They found that a panel of 32 small RNAs could differentiate children with ASD from neurotypical or developmentally delayed children with 85% accuracy.

Study coauthor Frank Middleton comments, "The ability to accurately discriminate between children with autism and their peers with non-ASD developmental delay is of paramount importance in the field. While the algorithm is not designed as a screening tool, it can provide valuable information in children with a positive MCHAT-R screen [a screening test for ASD], over 80% of whom will not have ASD. In this way, it can be used to prioritize specialist referral or to provide an objective aid to an autism diagnosis."

Also, Hicks and colleagues note, their test may allow researchers to investigate multiple environmental and genetic factors implicated in ASD in a single, non-invasive analysis.

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"Validation of a salivary RNA test for childhood autism spectrum disorder," Steven D. Hicks, Alexander T. Rajan, Kayla E. Wagner, Sarah Barns, Randall L. Carpenter, and Frank A. Middleton, *Frontiers in Genetics*, November 9, 2018 (free online). Address: Steven D. Hicks, shicks1@pennstatehealth.psu.edu.

—and—

"Saliva-based RNA panel distinguishes children on autism spectrum from non-autistic peers," news release, Eurekalert, November 9, 2018.

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