Volume 31, No. 4 2017

Autism Research Review

INTERNATIONAL

A quarterly publication of the Autism Research Institute—www.Autism.com

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

New research points to role of RCrusI in autism symptoms, hints at possible treatment

New research reveals that a specific part of the cerebellum plays a key role in autism spectrum disorders (ASD) and suggests that neuromodulation of this area may help treat the social deficits of individuals with the condition.

Catherine Stoodley, Peter Tsai, and their colleagues focused on an area of the cerebellum called the Right Crus I (RCrusI). While abnormalities in this area are consistently reported in ASD, the researchers say that the contribution of RCrusI dysfunction to ASD has been unclear.

In their study, the researchers established that in both humans and mice, the Right Crus I is functionally connected to multiple brain networks. "Given the extensive functional connectivity of RCrusI," they say, "the structural and functional abnormalities in RCrusI often reported in ASD could have wide-ranging impacts on the function of multiple, distributed cortical regions implicated in ASD." The researchers also found that in neurotypical adults, neuromodulation via transcranial direct current stimulation (tDCS) altered functional connectivity in cerebellar-cerebral networks associated with ASD.

Using a mouse model of autism, the researchers found that structural connectivity between the RCrusI and the cortex's inferior parietal lobule (IPL) was atypical in these mice. They also analyzed data from a large sample of children with ASD and found that the children exhibited abnormalities in functional RCrusI-IPL connectivity.

"The left IPL is believed to integrate visuospatial, motor, and cognitive information," the researchers say, "and it has been shown to be critical for imitating and interpreting the gestures of others. These functions are consistent with evidence that children with ASD struggle to efficiently integrate visual information to guide skilled behaviors, which is necessary for both imitation and normal social interaction and may be critical to the development of core ASD symptoms."

Additionally, the researchers determined that disrupting RCrusI function in normal mice resulted in impaired social interaction and abnormal repetitive behaviors. Finally, they found that stimulation of the RCrusI in the "autistic" mice improved social behavior but not repetitive behaviors.

Tsai comments that the limited effects of neuromodulation may indicate that additional parts of the cerebellum are involved, or that there is a restricted time in which to correct repetitive behaviors. However, he notes that neuromodulation restored social behaviors even in adult mice.

> Tsai and colleagues say neuromodulation of the cerebellum may be a promising therapy for social problems in ASD..

Tsai says, "Our findings have prompted new thoughts on how the cerebellum may be involved in autism and most importantly suggest that the cerebellum could be a therapeutic target for treatment." The researchers note that the RCrusI is a more accessible target for brain stimulation than other autism-related networks that are deep within the brain. However, they caution that the safety of cerebellar neuromodulation for individuals with ASD needs to be tested, although the intervention is already used in treating schizophrenia.

—

"Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice," Catherine J. Stoodley, Anila M. D'Mello, Jacob Ellegood, Vikram Jakkamsetti, Pei Liu, Mary Beth Nebel, Jennifer M. Gibson, Elyza Kelly, Fantao Meng, Christopher A. Cano, Juan M. Pascual, Stewart H. Mostofsky, Jason P. Lerch, and Peter T. Tsai, *Nature Neuroscience*, Vol. 20, No. 12, December 2017, 1744-51. Address: Catherine Stoodley, Department of Psychology and Center for Behavioral Neuroscience, American University, Washington, DC, stoodley@american.edu.

—and—

"Autism therapy: Social behavior restored via brain stimulation," news release, UT Southwestern Medical Center, December 13, 2017.

Study supports link between ASD, inflammatory bowel disease

A new study adds to evidence that children with autism spectrum disorders (ASD) have a higher prevalence of inflammatory bowel disease (IBD) than children without ASD.

Maunoo Lee and colleagues conducted a retrospective study using records from the TRICARE MHS database. They identified all children between the ages of 2 and 18 years enrolled in the database between October 2000 and September 2013 who received a diagnosis of ASD. Each child was matched to five controls who were the same age and sex and were enrolled in the same time frame.

The researchers then identified children in the ASD and control groups who had received a diagnosis of IBD (either Crohn's disease or ulcerative colitis). They used strict criteria that included both a diagnosis and the outpatient prescription of at least one medication commonly used to treat IBD, excluding treatments such as systemic and enteric steroids that are used less specifically.

The researchers found that children with ASD had 67% higher odds of having IBD compared to controls. While these odds are lower than those reported in a previous study, they emphasize that their new study used stricter criteria.

In addition, the researchers found that children with ASD and IBD had higher prescription rates for second-tier biologics than children with IBD but not ASD, possibly indicating greater disease severity. However, they note that this could instead be due to noncompliance with first-tier oral medications, leading to a need for injected drugs.

They comment, "Children with ASD are often non-verbal and may have difficulties communicating abdominal discomfort. With increased prevalence of IBD in children with ASD with potentially increased severity, it is important for providers to recognize early or possible signs and symptoms of IBD." These signs, they note, include failure to thrive, down-trending growth charts, and diarrhea.

—

"Association of autism spectrum disorders and the inflammatory bowel disease," Maunoo Lee, Jayasree Krishnamurthy, Apryl Susi, Carolyn Sullivan, Gregory H. Gorman, Elizabeth Hisle-Gorman, Christine R. Erdie-Lalena, and Cade M. Nylund, *Journal of Autism and Developmental Disorders*, November 23, 2017 (online). Address: Maunoo Lee, Dept. of Pediatrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, maunoolee@gmail.com.

Inflamed astrocytes may contribute to autism, could point to treatment

Inflammation of astrocytes—star-shaped cells that provide support for neurons in the brain and central nervous system—may play a role in autism, according to new research.

In the study, Fabiele Baldino Russo and colleagues took dental pulp cells from the baby teeth of three children with non-syndromic autism spectrum disorders (ASD)—that is, ASD not due to any known cause. The researchers reprogrammed the cells to become either neurons or astrocytes, and grew them into organoids, or "mini-brains."

Examining these organoids microscopically, the researchers found that the neurons had too few synapses and exhibited other networking defects. In addition, some astrocytes had high levels of a pro-inflammatory protein called interleukin 6 (IL-6). An excess of IL-6 is toxic to neurons.

The researchers then combined astrocytes from the dental pulp of children with ASD with neurons from neurotypical controls and cultured them. They found that the neurons from the controls behaved like the neurons from the children with ASD. Conversely, they say, "When we co-cultured ASD neurons with normal astrocytes, we could rescue the cellular defects. The neurons reverted to normal functioning and behavior."

The researchers say their findings suggest that it may be possible to help some children with ASD by treating them with anti-inflammatory medications.

—

"Modeling the interplay between neurons and astrocytes in autism using human induced pluripotent stem cells," Fabiele Baldino Russo, Beatriz Camille Freitas, Graciela Conceição Pignatari, Isabella Rodrigues Fernandes, Jonathan Sebat, Alysson Renato Muotri, and Patricia Cristina Baleeiro Beltrão-Braga, *Biological Psychiatry*, October 3, 2017 (online). Address: Patricia Cristina Baleeiro Beltrão-Braga, Av. Prof. Dr. Orlando Marques de Paiva 87, Cidade Universitária, 05508-270, São Paulo, SP, Brazil. patriciacbbraga@usp.br.

—and—

"Inflamed support cells appear to contribute to some kinds of autism," Scott LaFee, UC San Diego Health, October 18, 2017.

Ubiquitin gene defect leads to excess of cerebellar synapses

An excess of brain synapses—the connections between cells that allow them to signal one other—may be a key factor in autism, according to new research.

Pamela Valnegri and colleagues investigated six genes that attach a molecular tag called *ubiquitin* to proteins. These genes tell a cell what to do with the proteins—for instance, whether to discard them or reroute them to another area of the cell. Previous research has linked defects in ubiquitin genes to autism.

To study how ubiquitin genes affect brain development, the researchers removed the ubiquitin gene RNF8 in neurons in the cerebellum—a brain region affected by autism—of young mice. They found that neurons lacking the RNF8 protein formed about 50 percent more synapses. This doubled the strength of signals received by cells. (Research conducted after the publication of the study revealed that inhibition of any of the ubiquitin genes can cause an increase in synapses in the cerebellum.)

"This study raises the possibility that there may be too many synapses in the brains of patients with autism," senior author Azad Bonni says. "You might think that having more synapses would make the brain work better, but that doesn't seem to be the case. An increased number of synapses creates miscommunication among neurons in the developing brain that correlates with impairments in learning, although we don't know how."

The researchers note that as the cerebellum plays a crucial role in movement and the learning of motor skills, an excess of synapses in this region may explain some symptoms of autism such as toe-walking and poor coordination. Consistent with this idea, the mice that lacked the RNF8 gene had difficulty learning motor skills. In addition, the cerebellum is involved in higher cognitive functions that are impaired in autism, such as language and attention.

Bonni says that if the researchers' findings are replicated, "then you can start looking at ways of controlling the number of synapses. It could potentially benefit not just people who have these rare mutations in ubiquitin genes but other patients with autism."

—

"RNF8/UBC13 ubiquitin signaling suppresses synapse formation in the mammalian brain," P. Valnegri, J. Huang, T. Yamada, Y. Yang, L. A. Mejia, H. Y. Cho, A. Oldenborg, and A. Bonni, *Nature Communications*, Vol. 8, No. 1, November 2, 2017. Address: Azad Bonni, Department of Neuroscience, Washington University School of Medicine, St. Louis, MO, 63110, bonni@wustl.edu.

—and—

"In autism, too many brain connections may be at root of condition," news release, Washington University School of Medicine, November 2, 2017.

New research supports "magic world" hypothesis of autism

A new study presented at the 2017 Society for Neuroscience annual meeting supports the theory that some of autism's core features stem from an inability to detect patterns and predict the future. Individuals with such a deficit may find social situations challenging and be hypersensitive to sensory stimuli.

"We sometimes affectionately call this the magical world theory of autism," MIT researcher Pawan Sinha commented to the *Los Angeles Times* in discussing an earlier, related study. "The hallmark of a magical performance is the surprise, the unpredictability of the outcome. … Although for a brief period of time, a magic show might be pleasurable, if one is constantly immersed in that kind of a magical world, one can begin to get overwhelmed."

In the new study, Wasifa Jamal, Sinha, and colleagues repeated the same beep 300 times at a regular pace (once per second), recording the brain responses of 10 children with ASD and 21 neurotypical children as they listened to the beeps. The researchers found that while the neurotypical children habituated normally to the noise, as shown by a reduction in brain activity spikes, many of the children with autism did not. In fact, some children's brain responses actually intensified.

Jamal comments, "They can't disengage with the stimulus. They can't tune it out."

The researchers next conducted a different experiment, showing the children a checkerboard pattern that flashed on a screen once every second for 300 seconds. Again, the neurotypical children habituated normally to the stimulus, while the children with ASD did not. This indicates, the researchers say, that impairments in habituation in ASD affect more than one sense.

The researchers also found that children with more severe autism showed greater impairments in habituating to the beeps than children with milder features. However, there was no relationship between autism severity and habituation to the checkerboard pattern.

—

"Study of recurring beeps supports 'magical world' theory of autism," Sarah DeWeerdt, *Spectrum*, November 12, 2017. Wasifa Jamal and colleagues presented their unpublished findings at the 2017 annual meeting of the Society for Neuroscience. Address: Wasifa Jamal, MIT Department of Brain and Cognitive Sciences, 77 Massachusetts Avenue, Cambridge, MA 02139.

—see also—

"Is autism like a magic show that won't end?," Geoffrey Mohan, *Los Angeles Times*, October 6, 2014.

ARI's 50-Year Legacy: The Perspective of Researchers

On ARI's 50th anniversary, we asked leading researchers in the autism field to share their stories about what ARI has meant to them. Here are their responses.

—

James Adams, Ph.D.
Arizona State University

ARI has been the most important influence on both my role as a father of a daughter with autism and as an autism researcher. For over two decades, I have benefitted tremendously from the workshops, think tanks, newsletters, and webinars that ARI has organized. For my daughter, I have learned about many different treatment options and tried many of them, and over time she has made substantial progress and is now a happy adult working part-time with a great loving relationship with her family.

For my research, I have benefited tremendously from interactions with top clinicians and researchers, and working together with them on new research studies that are moving us closer to finding the causes of autism, how to prevent it, and how to treat it. ARI's seed grant funding has been of tremendous help—for example, one seed grant of $30,000 from ARI led to a $300,000 grant from our university, followed by a $1.3 million federal grant. Overall, Bernie Rimland and Steve Edelson are two leading heroes of the autism community.

David G. Amaral, Ph.D.
University of California, Davis

Bernie Rimland's *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior* figured prominently in my early education as an autism researcher. His attempt through the Autism Research Institute to establish subtypes of autism and move rapidly to targeted treatments has also influenced the research program of the UC Davis MIND Institute, another parent-initiated research effort. I congratulate Dr. Edelson on maintaining and expanding the programs of the Autism Research Institute and hope, like the parents of the MIND Institute, that it will not need to go another 50 years before effective treatments for the disabilities of autism are found.

Sidney M. Baker, M.D.

Bernard Rimland debunked the refrigerator mom consensus. His reward was the gratitude of children, parents, practitioners, and scientists who followed him into ARI's collaborative view of nutritional, toxicological, and immunological paths to healing when common sense is focused on the individual. It simply would not have happened without his voice, hand, and heart. Thank you, Bernie.

Margaret L. Bauman, M.D.
Boston University Medical Center

From the beginning, the focus of ARI was to provide a forum through which clinical and basic science research could be encouraged and sponsored, and directed toward the identification of potential causes and effective treatments. This institution continues to stand as a testament to Dr. Rimland's early work, as well as his foresight and dedication to finding answers relative to the autism spectrum disorders, a legacy that lives on through the many families he has encouraged and supported, as well as through the many avenues of research that he fostered throughout his lifetime. Based on the past work of its founder, a man who was ahead of his time, ARI continues to play a significant role in supporting clinical and basic science research and continues to work toward expanding our understanding of this complex disorder now known as the autism spectrum disorders. Dr. Rimland's life-long impact on ASD lives on as reflected by the clinical and research efforts that ARI continues to pursue and support.

Manuel Casanova, M.D.
University of South Carolina School of Medicine Greenville

Autism is now recognized as a neurodevelopmental condition. This was not always the case. Several decades ago, one man stood against the prevailing views of psychoanalytically inclined health professionals and, in the end, changed public and medical opinion. This man, Bernard Rimland, became a one-stop center for those parents and patients who needed help and information in regard to autism. Rimland's legacy lives in the Autism Research Institute (ARI), an organization he started in order to improve the health and well-being of people on the autism spectrum through research and education. Fifty years after its foundation, the ARI has given a voice to autistic individuals through legislation, education, research, health care, accommodations, and employment at a global level. I look forward to the next fifty years of ARI's pace-setting accomplishments.

Mary Coleman, M.D.
Foundation for Autism Research, Sarasota, Florida

Bernie Rimland's book (*Infantile Autism*, 1964) was handed to me by my chief of pediatric neurology and that is how I got involved in autism. As soon as I examined my first autism patients, I realized that my chief was correct to give me that book—autism clearly was a pediatric neurological disorder, not a disorder caused by inadequate mothering. Bernie later helped find patients to participate in my famous study of 100 patients and 100 carefully matched controls (*The Autistic Syndromes*, 1976) that established that autism was more than one disease and identified several biochemical subgroups.

Sidney M. Finegold, M.D.
Veteran's Administration / University of California at Los Angeles

I know ARI from the viewpoint of a researcher who sees the kids' stools but not the kids, and I have been rescued from "drowning" by ARI on more than one occasion. It's always a pleasure to get together with the ARI group, a most impressive warm group of investigators.

Temple Grandin, Ph.D.
Emergence: Labeled Autistic
Thinking in Pictures

The Autism Research Institute has been a pioneer in both the understanding and treatment of autism. When I was looking for information on autism during the 1970s, ARI was one of the few places where I could find it. Bernard Rimland was definitely ahead of his time.

Jon B. Pangborn, Ph.D., Ch.E., FAIC (emeritus)

Thanks to the Autism Research Institute, autism came to be understood as primarily a medical rather than a psychological problem. Through the efforts of ARI and its parent-doctor organization, "Defeat Autism Now!" (DAN!), autistic individuals were more likely to be treated effectively and parents were less often blamed for the condition. DAN! clinicians noted high correlations of autistic behavior with toxic exposures of various types—pesticides, herbicides, fungicides, heavy metals, and other environmental insults. Digestive problems, including intestinal yeast overgrowth, food allergies/intolerances, and digestive enzyme insufficiency, together with poor diet and nutritional deficiency, are now treated as necessary by knowledgeable clinicians. In doing so, the "gut-brain connection" is being addressed as best we are able for individuals on the autism spectrum.

Judy Van de Water, Ph.D.
University of California, Davis

ARI can be credited with many things over the course of its 50 years as an organization, but to those working in autism research, it has been a cornerstone for the concept of a biologic approach to understanding ASD. As a researcher investigating the immunobiology of ASD, ARI has provided me with the ability to interact with clinicians and explore an integrated approach to autism research, as well as

continued on page 6

Research Updates

Researchers explore effects of Kctd13 deletion and possible drug treatments

Researchers are exploring two potential treatments for autism linked to deletion of a gene called Kctd13.

While previous research linked deletion of this gene to abnormal brain size in autism, new research on mice by Christine Ochoa Escamilla and colleagues found the deletion did not affect brain size. Instead, the deletion reduced the number of synaptic connections between neurons in the animals' brains. This decrease correlated with higher levels of a protein called RhoA, which impairs synaptic transmission.

The researchers then tested the effects of two RhoA-inhibiting drugs, Rhosin and Exoenzyme C3. Both treatments restored normal synaptic transmission in less than 4 hours. However, the effects were short-term. "In the future," lead author Craig Powell says, "we hope to perform experiments to determine if long-term in vivo administration of these or similar drugs might also lead to long-lasting restoration of synaptic function in the brain."

—

"Kctd13 deletion reduces synaptic transmission via increased RhoA," Christine Ochoa Escamilla, Irina Filonova, Angela K. Walker, Zhong X. Xuan, Roopashri Holehonnur, Felipe Espinosa, Shunan Liu, Summer B. Thyme, Isabel A. López-García, Dorian B. Mendoza, Noriyoshi Usui, Jacob Ellegood, Amelia J. Eisch, Genevieve Konopka, Jason P. Lerch, Alexander F. Schier, Haley E. Speed, and Craig M. Powell, *Nature*, Vol. 551, November 9, 2017, 227-31. Address: Craig M. Powell, Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8813.

—and—

"Study: Autism treatments may restore brain connections," James Beltran, UT Southwestern Medical Center, November 1, 2017.

Pig study: maternal infection can alter offspring's sociability

More evidence that maternal infections during pregnancy can alter the behavior of offspring comes from a recent study of pigs.

In the study, Adrienne Antonson and colleagues gave pregnant pigs a virus that causes flu-like symptoms and compared their offspring to the offspring of non-infected mothers. The researchers did not detect learning problems, memory problems, or altered immune responses in the offspring of infected mothers. However, these piglets behaved very differently in social tests, avoiding unfamiliar piglets while the piglets born to non-infected mothers preferred to visit them.

The researchers suspected that maternal viral infection altered the piglets' behavior by affecting immune cells in the brain called microglia during prenatal development. While these cells play an important role in brain development, altered microglia could attack healthy synapses or prevent new neurons from forming.

Surprisingly, Johnson says, the piglets born to infected mothers did not display a change in microglial activity after birth. She adds, "If microglial cells are contributing to antisocial behavior, those changes are likely happening in utero. It's possible microglia become activated during maternal immune activation, alter fetal brain development, and then return to normal before birth."

While previous studies investigating the effects of maternal infection on the behavior of offspring have primarily involved rodents, the researchers note that the brain anatomy, neurochemistry, and growth and development trajectories of pigs correspond more closely to those of humans in prenatal and early postnatal life.

—

"Maternal viral infection during pregnancy elicits anti-social behavior in neonatal piglet offspring independent of postnatal microglial cell activation," Adrienne M. Antonson, Emily C. Radlowski, Marcus A. Lawson, Jennifer L. Rytych, and Rodney W. Johnson, *Brain, Behavior, and Immunity*, Vol. 59, 2017, 300-12. Address: Rodney W. Johnson, 227 Edward R. Madigan Laboratory, 1201 W. Gregory Drive, Urbana, IL 61801, rwjohn@illinois.edu.

—and—

"Infection in pregnant pigs leads to antisocial piglets," news release, University of Illinois College of Agricultural, Consumer and Environmental Sciences, September 20, 2017.

Prenatal vitamins may reduce autism risk

Mothers who take prenatal nutritional supplements may reduce the risk that their children will have an autism spectrum disorder (ASD) with intellectual disability, a new international study reports.

Researchers in Britain, Sweden, and the United States used three separate analytical methods to investigate data from more than 273,000 mother-child pairs in Stockholm, Sweden. Children included in the analysis were four to 15 years of age by the end of 2011 and were born between 1996 and 2007.

The data included information as to whether the women were taking folic acid, iron, and/or multivitamin supplements at their first prenatal visit. After adjusting for factors including child sex, birth year, number of maternal pregnancies, and maternal hospital stays, the researchers found that children of women who took multivitamins, with or without additional iron or folic acid, had a lower likelihood of being diagnosed with ASD with intellectual disability. They did not detect an association between folic acid or iron use and a diagnosis of ASD.

The researchers say their findings cannot establish cause and effect. However, they note that all three of their analyses resulted in similar conclusions.

They add, "Whether the association is specific to autism or reflects the risk of intellectual disability needs to be explored in future research."

—

"Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort: population based cohort study," Elizabeth A. DeVilbiss, Cecilia Magnusson, Renee M. Gardner, Dheeraj Rai, Craig J. Newschaffer, Kristen Lyall, Christina Dalman, and Brian K. Lee, *British Medical Journal*, October 4, 2017 (free online). Address: Elizabeth A. DeVilbiss, Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, 3215 Market St., Philadelphia, PA 19104, ead77@drexel.edu.

—

"Multivitamins in pregnancy may be linked to lower autism risk in children," news release, *British Medical Journal*, October 4, 2017.

Research Updates

Cortical responses to social stimuli differ in infants with later ASD

Children who later develop autism spectrum disorders (ASD) exhibit unusual cortical reactions to social stimuli early in infancy, a new study reports.

Sarah Lloyd-Fox and colleagues used a technique called functional near infrared spectroscopy (fNIRS) to study the brain responses of high-risk infants—younger siblings of children with ASD—to social videos showing people playing peek-a-boo and non-social images of vehicles. In addition, they studied the infants' responses to human voices and non-vocal sounds.

The researchers say that at four to six months of age, the five infants who went on to develop ASD showed reduced activation across the inferior frontal and posterior temporal regions of the cortex in response to visual social stimuli when compared to 16 low-risk infants (those without older siblings with autism). In addition, they showed reduced activation to vocal sounds and greater activation to non-vocal sounds in the left lateralised temporal regions compared to low-risk and high-risk infants who did not develop ASD. Moreover, the researchers say, "The degree of activation to both the visual and auditory stimuli correlated with parent-reported ASD symptomology in toddlerhood."

—

"Cortical responses before six months of life associate with later autism," S. Lloyd-Fox, A. Blasi, G. Pasco, T. Gliga, E. J. Jones, D. G. Murphy, C. E. Elwell, T. Charman, M. H. Johnson, and the BASIS Team, *European Journal of Neuroscience*, October 23, 2017 (epub prior to print publication). Address: Sarah Lloyd-Fox, Centre for Brain and Cognitive Development, The Henry Wellcome Building, Birkbeck, University of London, London, WC1E 7HX, s.fox@bbk.ac.uk.

Video games help to improve attention, gaze

A home-based video game program may be effective in improving gaze and attention in individuals with autism spectrum disorders (ASD), according to a new study.

Leanne Chukoskie and colleagues note that individuals with ASD have difficulty re-orienting their attention quickly and efficiently. "Similarly," they say, "fast re-orienting saccadic eye movements [movements of the eyes between fixation points] are also inaccurate and more variable in both endpoint and timing." Atypical gaze and attention are among the earliest symptoms observed in ASD, and the researchers say that "disruption of these foundation skills critically affects development of higher level cognitive and social behavior." Thus, they suggest, correcting gaze and attention deficits may have a broad effect on ASD symptoms.

To test the efficacy of specially designed video games in improving gaze and attention skills in ASD, the researchers conducted an eight-week pilot study. In the study, eight adolescents with ASD (six of whom completed the study) spent 30 minutes per day, five days per week, playing video games designed to train fixation, speed, and accuracy of eye movements, as well as control of visuo-spatial attention. After initial training, the intervention was carried out in the participants' homes.

The researchers report that following training, all six participants showed improvement in attention, eye movement control, or both. In addition, all participants could use the video games independently, making the intervention convenient and cost-effective.

—

"A novel approach to training attention and gaze in ASD: A feasibility and efficacy pilot study," Leanne Chukoskie, Marissa Westerfield, and Jeanne Townsend, *Developmental Neurobiology*, December 2017 (in press). Address: Leanne Chukoskie, Institute for Neural Computation, University of California, San Diego, CA 92093, lchukoskie@ucsd.edu.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

February 7, 2018:
Strategies for Teaching Emotional Control to Persons with ASD
Carla Mazefsky, Ph.D.

February 14, 2018:
Chronic Inflammatory Response Syndrome and ASD
Nancy O'Hara, M.D.

These webinars are offered at 1 p.m. Eastern time (U.S.). Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars in our archives at https://www.autism.com/webinars.

**We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.*

Perceptual issues may explain "contagious yawning" differences in individuals with ASD

Research shows that individuals with autism spectrum disorders (ASD) are less likely than other people to exhibit "contagious yawning"—that is, to yawn in response to another person yawning. While some experts have suggested that this may stem from a deficit in empathy, new research points to perceptual differences instead.

In the new study, which involved 41 neurotypical subjects, Meingold H. M. Chan and Chia-Huei Tseng induced yawning by showing participants a video and photos of people yawning. The researchers also measured participants' levels of autistic traits with the Autism Spectrum Quotient, evaluated their eye gaze patterns, and analyzed their ability to detect either yawning or emotion in photos of human faces.

The researchers found that participants who were more likely to detect yawning were also more likely to yawn in response. They also found a positive association between participants' duration of fixation on the eye region and the detection of yawning.

However, sensitivity to happy or angry faces did not correlate significantly with contagious yawning. Little association was seen between contagious yawning and scores on the Autism Spectrum Quotient. The researchers did find that females exhibited contagious yawning more often than males.

Tseng comments, "We find that for [the] non-clinical population, perceptual ability is more closely related to contagious yawning than empathy is. Since it's been documented that people with autism tend to suffer from impaired perception such as an atypical eye gazing on faces and a difficulty in judging facial emotions, it's possible that their perceptual limitation causes them to be unable to detect someone else's yawning expression."

—

"Yawning detection sensitivity and yawning contagion," Meingold H. M. Chan and Chia-Huei Tseng, *i-Perception*, August 25, 2017 (free online). Address: Chia-Huei Tseng, Research Institute of Electrical Communication, Tohoku University, Sendai, Japan, CH_Tseng@alumni.uci.edu.

—and—

"Contagious yawning more closely associated with perceptual sensitivity than empathy," news release, Tohoku University, September 5, 2017.

Moving?
Please let us know well in advance, so your next issue will reach you on time!

Drug affecting gene linked to autism shows possible usefulness in animal tests

Animal research suggests that a new drug called NitroSynapsin, which affects the function of a gene called MEF2C, may potentially be useful in treating autism.

In 1993, Stuart Lipton and colleagues found that MEF2C plays a key role in brain development. In addition, the researchers discovered that disrupting this gene in the brains of mice early in fetal development leads to severe, autism-like abnormalities. Since that time, other researchers have identified a similar disorder—now known as MEF2C haploinsufficiency syndrome, or MHS—in a number of children with autism.

While only a small percentage of cases of autism involve MHS, genomic research has shown that mutations underlying autism often involve genes whose activity is switched on by MEF2C. Thus, Lipton says, "we're hopeful that a treatment that works for this MEF2C-haploinsufficiency syndrome will also be effective against other forms of autism, and in fact, we already have preliminary evidence for this."

The researchers created a mouse model of MHS by deleting one copy of the mouse variant of MEF2C. The altered mice displayed impaired spatial memory, abnormal anxiety, abnormal repetitive movements, and other signs resembling human MHS. The brains of the mice exhibited an increase in excitatory as compared to inhibitory signaling—a common finding in humans with autism as well.

The researchers treated the mice with NitroSynapsin, a drug related to the Alzheimer's drug memantine, for three months. They report that the drug helped to reduce the excitatory/inhibitory imbalance in the brains of the mice, as well as reducing abnormal behaviors and boosting the animals' performance on cognitive and behavioral tests.

The researchers are currently testing the drug on a cell-based model of MHS using skin cells from children with the syndrome, and report that it appears to be effective in this model as well.

—

"NitroSynapsin therapy for a mouse MEF2C haploinsufficiency model of human autism," Shichun Tu, Mohd Waseem Akhtar, Rosa Maria Escorihuela, Alejandro Amador-Arjona, Vivek Swarup, James Parker, Jeffrey D. Zaremba, Timothy Holland, Neha Bansal, Daniel R. Holohan, Kevin Lopez, Scott D. Ryan, Shing Fai Chan, Li Yan, Xiaofei Zhang, Xiayu Huang, Abdullah Sultan, Scott R. McKercher, Rajesh Ambasudhan, Huaxi Xu, Yuqiang Wang, Daniel H. Geschwind, Amanda J. Roberts, Alexey V. Terskikh, Robert A. Rissman, Eliezer Masliah, Stuart A. Lipton, and Nobuki Nakanishi, *Nature Communications*, November 14, 2017 (free online). Address: Shichun Tu, Neuroscience and Aging Research Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, 92037, shichuntu@scintillon.org.

—and—

"New autism drug shows promise in preclinical study," GEN News Highlights, November 14, 2017.

Attention training shows promise for students with ASD

Computerized activities designed to improve attention skills may benefit young children with autism, according to a new study.

Mayra Muller Spaniol and colleagues enrolled 15 young children with autism spectrum disorders (ASD) from two different schools (one mainstream and one special needs school) in a two-month intervention. Eight children participated in activities that are included in the Computerised Progressive Attentional Training program and are designed to foster three types of attention:

- Sustained attention, or the ability to attend for a prolonged time.
- Selective-spatial attention, or the ability to focus on relevant stimuli while ignoring distractions.
- Executive attention, or the ability to solve conflicts and inhibit irrelevant information.

A control group of seven students played video games and received one-on-one attention from an experimenter.

The researchers say, "Overall, the data indicated promising comprehensive improvements for the children in the CPAT intervention group, which were over and above any improvements obtained in the control group in attention and academic performance." In particular, they say, children in the CPAT group showed improvement in math, reading comprehension, and copying speed, and their scores on a non-verbal cognitive assessment improved. Teachers and aides also detected more improvements in academic skills and attention in the CPAT group, even though the educators believed that all children were taking part in an attention-training program.

The researchers say that the results of CPAT training are promising and the program appears to be feasible for use in both mainstream and special schools, but they note that their findings need to be replicated in a larger group of children.

—

"Attention training in autism as a potential approach to improving academic performance: A school-based pilot study," Mayra Muller Spaniol, Lilach Shalev, Lila Kossyvaki, and Carmel Mevorach, *Journal of Autism and Developmental Disorders*, November 8, 2017 (epub prior to print publication). Address: Mayra Muller Spaniol, mayramspaniol@hotmail.com.

ARI's 50-Year Legacy: the Perspective of Researchers

(continued from page 3)

offering a conduit for information sharing at a high level amongst the autism community. ARI has supported novel research ideas that have driven the field toward an expanded view of both the causes and treatments for ASD, to great success. It is the ability of an organization to think outside the box that has benefited so many families.

Harland Winter, M.D.
Massachusetts General Hospital for Children

The Autism Research Institute is celebrating 50 years of supporting families and individuals with autism. Beginning at a time when there was little knowledge about what causes autism and how to improve the lives of individuals with autism, ARI advocated and provided the voice for these families. As the scientific community began to understand more about central nervous system function and the impact of medical conditions on behavior, ARI has supported research that enables clinicians to better care for their patients.

Through its leadership, ARI continues its advocacy by providing bridges between patients, families, healthcare providers, and investigators. We are all grateful for your ongoing support and for enabling the autism community to be heard.

IN MEMORIAM

Nancy Herndon Cale, the warm, compassionate voice behind ARI's helpline for more than a decade, passed away unexpectedly August 11, 2017. She was 73.

Often the first friend parents looking for support could reach, Nancy persisted as an advocate in the autism community for more than 20 years. After her grandson was diagnosed with autism, she co-founded Unlocking Autism in his honor. Nancy worked in partnership with state and local governments and was recognized with a Certificate of Special Congressional Recognition for her efforts.

In 2006, after the passing of Dr. Rimland, Nancy began taking calls to ARI from parents and caregivers. In 2008, she became a key administrative staff member for ARI conferences, coordinating fulfillment for event mailings and eventually serving as the vendor manager through the conference's conclusion in 2012. Through it all, she answered the ARI/Unlocking Autism resource line daily, continuing to field calls until the day she was admitted to the hospital in mid-August.

We gratefully pay tribute to our vibrant, kind friend, whose hard work will continue to inspire all of us at ARI and those whose lives she touched for so many years.

Researchers explore links between autism, synesthesia

Individuals with synesthesia exhibit two characteristics—increased sensory sensitivity and enhanced attention to detail—that are also common in autism, according to a new study.

In synesthesia, people experience "crossed" reactions to stimuli. For instance, people with grapheme-color synesthesia (GCS) perceive letters or numbers to have colors, while people with spatial-sequence synesthesia (SSS) perceive sequential concepts such as numbers and calendar dates as existing in physical space—for instance, to their right or floating over their heads. While synesthesia and autism co-occur more often than expected by chance, the vast majority of people with synesthesia do not have autism.

In the first part of the new study, Jamie Ward and colleagues used the Glasgow Sensory Questionnaire (GSQ) and the Autism Spectrum Quotient (ASQ) to evaluate sensory sensitivity and autistic traits in 182 synesthetes. All of the participants either had GCS or SSS, but not both. A number of them also had other forms of synesthesia.

The researchers found that compared to controls, synesthetes had elevated scores for sensory sensitivity on the GSQ as well as elevated scores on the "attention to detail" subscale on the AQ. (While they exhibited elevations on other AQ subscales, the researchers say the effect size was small.) Moreover, the researchers detected a "dose-like" effect: The more forms of synesthesia participants had, the higher their scores for sensory sensitivity and attention to detail were.

In the second study, which involved 56 participants, the researchers looked for evidence that the enhanced sensory sensitivity and attention to detail seen in individuals with synesthesia translate into superior cognitive abilities. In two tests, one involving spotting embedded figures and the other involving detecting changes in a scene, the researchers found that individuals with synesthesia out-performed controls.

They comment, "Synesthetes appear to occupy an important cognitive niche: They gain many of the benefits linked to autism without necessarily incurring the impairments (but with an elevated risk of doing so)." They speculate that "synesthesia has the potential to become an important model for understanding the symptoms and neurodevelopment of autism."

—

"An autistic-like profile of attention and perception in synaesthesia," Jamie Ward, Paris Brown, Jasmine Sherwood, and Julia Simner, *Cortex*, October 25, 2017 (epub prior to print publication). Address: Jamie Ward, School of Psychology, University of Sussex, Falmer, Brighton, BN1 9QH, UK, jamiew@sussex.ac.uk.

Mainstream schooling may lead to low self-esteem, isolation

While mainstream classrooms can help students with autism spectrum disorders (ASD) learn important social, academic, and communication skills, a new report indicates that these benefits may come at a price in the form of reduced self-esteem and increased isolation.

Emma Williams and colleagues analyzed information from 17 studies investigating the effects of mainstream schooling on individuals with ASD. The researchers found that many students with ASD internalized the negative attitudes and responses of other students toward them. This, combined with unfavorable social comparisons to their classmates, led to a sense of being "different" and more limited than other students.

The researchers say that this negative self-perception could lead to increased isolation and low self-esteem, making students with ASD more susceptible to mental health problems.

Williams and her team also found that students with ASD experienced challenges in dealing with noisy classrooms and playgrounds. This too, they say, could increase social isolation and a feeling of being "different."

The researchers say that students with ASD who developed supportive friendships and felt accepted by their classmates had fewer social difficulties and felt better about themselves. They say this indicates that it is crucial for schools to create a culture of acceptance for all students.

Williams says, "We are not saying that mainstream schools are 'bad' for pupils with autism, as other evidence suggests they have a number of positive effects, including increasing academic performance and social skills. Rather, we are suggesting that by cultivating a culture of acceptance of all and making small changes, such as creating non-distracting places to socialize, and listening to their pupils' needs, schools can help these pupils think and feel more positively about themselves."

—

"How pupils on the autism spectrum make sense of themselves in the context of their experiences in a mainstream school setting: A qualitative metasynthesis," Emma I. Williams, Kate Gleeson, and Bridget E. Jones, *Autism*, November 15, 2017 (epub prior to print publication). Address: Emma I. Williams, e.i.williams@surrey.ac.uk.

—and—

"School exacerbates feelings of being 'different' in pupils with autism spectrum conditions," news release, University of Surrey, November 16, 2017.

Letter to the Editor:

Dear Dr. Edelson:

I read the lead article of Volume 31, no.3, "Ancient mitochondrial DNA variants may affect autism risk, lead to metabolic therapies," with considerable interest and enthusiasm. The speculation that "estrogen may increase beneficial antioxidant activity ..." is a welcome one to me. I wish to call attention to a nutritional supplement that I brought forth nearly 35 years ago and have since recommended often with good results in children and adults who have experienced certain toxic insults or oxidant stress—alpha-ketoglutaric acid (buffered), also referred to as alpha-ketoglutarate. It's described in my book, *Nutritional Supplement Use for Autism Spectrum Disorder* (available from ARI).

We usually think of alpha-ketoglutaric acid (α-kg) as the amino group receptor in transaminations that are enzyme-activated by pyridoxal 5-phosphate (active vitamin B6). For mitochondria, α-kg operates in the "malate shuttle" which brings reducing equivalents from the cytosol of a cell across the mitochondrial membrane and into the mitochondrion. This transport process involves glutamate, malate, aspartate and α-kg, and it results in formation of NADH from NAD inside the mitochondrion. Nutritional use of α-kg is described in my book.

Sincerely,
Jon B. Pangborn, Ph.D.

Quotable:

"Scientists analyzing mineral deposits in the baby teeth of twins, one of whom had autism [in each pair], found a discrepancy in heavy metals and nutrients. This discovery adds support to the argument that the environment, as much as genes, can lead to the disorder…

"'I think there is consensus in the scientific community that the prevalence of autism is increasing and our genes don't change so quickly,' said Manish Arora, an environmental scientist and dentist at the Icahn School of Medicine at Mount Sinai in New York and lead author of the study. 'Essentially there are environmental drivers for autism that are interacting with our genetic makeup.'"

"Scientists link autism with high amounts of heavy metals found in baby teeth: study," Laura Kelly, *Washington Times*, June 1, 2017

Autism Research Institute
4182 Adams Avenue
San Diego, CA 92116
USA

Address Service Requested

NONPROFIT ORG
U.S. POSTAGE
PAID
SAN DIEGO, CA
PERMIT #1

Autism Research Review International
Vol. 31, No. 4

**********AUTO
Sample Name
Any Street
Any Street 2
Any City, State Zip_Code

Subscriptions

____ Please send me the *Autism Research Review International* (Four quarterly issues—U.S. $20; outside the U.S. $24) $ _____ (U.S. funds)

____ Advance subscription for __1 yr. __2 yrs. (see rates above) $ _____

____ I am enclosing a donation to assist the work of ARI $ _____
*Federal Exempt Designation 501(c)(3)

NOTE: If you donate $50 or more to ARI, you will receive a free one-year subscription to the Autism Research Review International!

TOTAL..... $ _____

☐ **NEW SUBSCRIPTION** ☐ **RENEWAL** ☐ **GIFT**

☐ **I AM DONATING $50 OR MORE—Start my free one-year subscription!**

Name _____ ☐ **new address**

Address _____

_____ Email _____

Phone _____ Fax _____

Credit card: __MasterCard __Visa __Discover __Am. Express

_____ CVV# _____ Exp. _____

Signature _____

IF THIS IS A GIFT, please list the name and address of the recipient here:

_____

_____

Make checks payable to ARI and mail to the Autism Research Institute, 4182 Adams Avenue, San Diego, CA 92116 • (866) 366-3361 (toll-free)

31/4

—About ARI—

The Autism Research Institute (ARI) is the oldest autism research organization in the world, founded by Dr. Bernard Rimland in 1967.

ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (more than $400,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

•

Networking researchers, physicians, and parents to speed the development and dissemination of safe and effective treatment methods.

•

Hosting webinars and one of the largest informational websites on autism in the world.

•

Sponsoring one or two major think tanks a year, involving researchers and experienced clinicians.

ARI's work relies on charitable contributions from individuals and organizations. All donations are tax deductible. We are proud to have earned Charity Navigator's highly respected "Four Star Award" for fiscal management, accountability, and transparency.

The Autism Research Review International is a quarterly publication of the Autism Research Institute,
Stephen M. Edelson, Ph.D., Director:
The Autism Research Institute is a non-profit organization.
Editor: Stephen M. Edelson, Ph.D. • www.Autism.com

 ISSN No. 0893-8474