

# Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—[www.Autism.org](http://www.Autism.org)

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

## Shank3 gene mutation may impair brain's ability to distinguish self from other

Researchers studying a mutation in a gene linked to autism spectrum disorders (ASD) say the mutation appears to disrupt the brain's ability to distinguish "self" from "other."

Daniel Lee and colleagues disrupted and then restored the expression of the Shank3 gene—which is mutated in about one percent of people with ASD—in adult male mice. They recorded the activity of neurons in the medial prefrontal cortex (a brain region linked to social behavior and cognition) when the mice were exposed to several scenarios with other mice.

The researchers say they found that "Shank3 disruption led to a reduction of neurons encoding the experience of other mice and an increase in neurons encoding the animal's own experience." The shift was associated with a loss of neurons' ability to distinguish others from self.

The researchers were able to restore the function of the Shank3 gene in the experimental mice using the drug tamoxifen. They report, "Restoration of Shank3 expression in medial prefrontal cortex reversed this encoding imbalance and increased sociability over 5 to 8 weeks." Selectively activating Shank3 in the medial prefrontal cortex rather than the entire brain resulted in the same changes.

The researchers conclude, "These findings reveal a neuronal-encoding process that is necessary for social behavior and that may be disrupted in ASD."

"Reduced sociability and social agency encoding in adult Shank3-mutant mice are restored through gene re-expression in real time," Daniel K. Lee, S. William Li, Firas Bounni, Gabriel Friedman, Mohsen Jamali, Leah Strahs, Omer Zeliger, Pauline Gabrieli, Michael A. Stankovich, Jack Demaree, and Ziv M. Williams, *Nature Neuroscience*, July 12, 2021 (online). Address: Ziv Williams, Massachusetts General Hospital, Thier Research Building, 70 Blossom St, Boston, MA 02114, [zwilliams@mgh.harvard.edu](mailto:zwilliams@mgh.harvard.edu).

—and—

"Autism-linked mutation may blur brain's boundary between self, others," Angie Voyles Askham, *Spectrum News*, July 15, 2021.

## Study points to possible role of microbial metabolite in ASD

A new study adds to evidence that alterations of the gut microbiome may play a key role in autism spectrum disorders (ASD).

Noting that urinary and fecal levels of the microbial metabolite *p*-Cresol are more abundant in individuals with ASD than in neurotypical individuals, and that urinary *p*-Cresol levels correlate with the severity of ASD, Patricia Bermudez-Martin and colleagues exposed mice to *p*-Cresol to see if the metabolite induced ASD-like behavior. The researchers exposed the mice to *p*-Cresol for four weeks, placing it in their drinking water.

Bermudez-Martin and her team found that the exposed mice exhibited social deficits, stereotypies, and perseverative behaviors, but no changes in anxiety, locomotion, or cognition. "This suggests," they say, "a possible causal relationship between elevated *p*-Cresol levels and ASD core symptoms." They also determined that the abnormal social behaviors detected in the experimental mice were associated with decreased activity of dopamine neurons in the ventral tegmental area (VTA), which is part of the brain's social reward circuit.

The researchers next transferred microbiota from the *p*-Cresol-exposed mice to control mice. They found that the mice receiving the transplants developed social deficits and stereotypy and exhibited increased fecal excretion of *p*-Cresol com-

pared to mice receiving transplants from control mice.

Finally, the researchers transplanted microbiota from control mice into the experimental mice. They report, "The microbiota of control mice rescued social interactions, dopamine neurons excitability, and fecal *p*-Cresol levels when transplanted to *p*-Cresol-treated mice."

They conclude, "[T]he ability of a control microbiota to normalize *p*-Cresol levels, VTA dopamine neurons excitability, and social behavior when transplanted to *p*-Cresol-treated mice provides a rationale for clinical trials aimed at studying the beneficial impact of microbiota interventions targeting *p*-Cresol production to alleviate core social deficits in ASD."

"The microbial metabolite *p*-Cresol induces autistic-like behaviors in mice by remodeling the gut microbiota," Patricia Bermudez-Martin, Jérôme A. J. Becker, Nicolas Caramello, Sebastian P. Fernandez, Renan Costa-Campos, Juliette Canaguet, Susana Barbosa, Laura Martínez-Gim, Antonis Myridakis, Marc-Emmanuel Dumas, Aurélie Bruneau, Claire Cherbuy, Philippe Langellet, Jacques Callebert, Jean-Marie Launay, Joëlle Chabry, Jacques Barik, Julie Le Merrer, Nicolas Glaichenhaus, and Laetitia Davidovic, *Microbiome*, 2021 (free online). Address: Laetitia Davidovic, Institut de Pharmacologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, Université Côte d'Azur, 660 route des Lucioles, 06560 Valbonne, France, [davidovic@pmc.cnrs.fr](mailto:davidovic@pmc.cnrs.fr).

## Feedback, "feed-forward" loop impairments detected in ASD

The sensorimotor problems seen in many individuals with autism spectrum disorders (ASD) may involve impairments in feedback and "feed forward" loops in the brain, according to a new study.

Kathryn Unruh and colleagues compared the fine motor control and eye movements of 109 individuals with ASD and 101 age-matched controls, all between five and 29 years of age. The participants performed a precision grip force test that required them to squeeze their thumb and forefinger together while reacting to objects on a monitor, as well as tests that measured their eye movements in response to dots appearing on the screen.

"Precision grip and eye movement are supported by separate brain systems that utilize sensory and motor information in different ways," Unruh says. "By measuring features of motor behavior across both of these systems, we're able to develop a more complete picture of what sensorimotor deficits look like in ASD and how those may vary across individuals."

The study explored both feedback and feed-forward systems. Feedback systems are involved in perceiving and using sensory information—for instance, visual, auditory, or tactile sensations—to produce motor movements that can be "tweaked"

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## Researchers explore effects of sulforaphane on behavior, biomarkers of children with ASD

While research indicates that sulforaphane—a molecule found in cruciferous vegetables such as broccoli—can improve the symptoms of individuals with autism spectrum disorders (ASD), a new study suggests that the benefits for children may be modest. However, it also indicates that sulforaphane can improve biomarkers of oxidative stress, inflammation, and mitochondrial function.

In previous research, Andrew Zimmerman and colleagues found that administering sulforaphane to young men with ASD led to significant clinical benefits that persisted at a three-year followup. A separate open-label trial detected clinical improvements and changes in urinary metabolites in children and young adults after sulforaphane treatment.

In the new study, Zimmerman and his team administered sulforaphane to 57 children with ASD between three and 12 years of age. In the first phase of the study, which was randomized and double-blind, participants took either sulforaphane or a placebo for 15 weeks. In the second open-label phase of the study, all participants took sulforaphane for another 15 weeks. (Forty children completed both phases.) The study concluded with a six-week “washout” period.

The researchers report, “We found that sulforaphane was safe, but based upon the OACIS-1 [Ohio Autism Clinical Impressions Scale], our primary clinical outcome measure, its effects were not significant. Effect size estimates showed small improvements with sulforaphane, though not significant, for the general level of autism on the OACIS-I scale. There was significant improvement on one of the secondary measures (the Aberrant Behavior Checklist) but not on the Social Responsiveness Scale-2.” Larger beneficial effects were seen in a subsample of participants with non-severe ASD.

Both groups of children improved during the open label trial, during which all of them were taking sulforaphane. “Notably,” the researchers say, “the social interaction severity subscale improved greatly among the (former) placebo group at week 22 when taking sulforaphane. While it may have been an ‘open-label’ effect, this finding coincides with the results from our previous trial of sulforaphane in young men.”

While the improvements seen in children taking sulforaphane were small, the researchers say, “The clinical efficacy of sulforaphane in ASD in children in this trial and our previous trial in young men com-

pares favorably to intranasal oxytocin and bumetanide in recent placebo-controlled clinical trials. Although outcome measures and statistical power differed between this study and the other two, sulforaphane appears to enhance socialization like oxytocin and improves other core features of ASD similar to bumetanide.” They add, “As a ‘natural’ dietary component, sulforaphane may have less potential for toxicity than either drug with long term use, although further studies of sulforaphane are needed in children with ASD, for both long-term safety and efficacy.”

The researchers also report, “Biomarkers provided strong evidence for the biologic effects of sulforaphane, especially with respect to markers of glutathione redox status [a biomarker for oxidative stress], inflammatory cytokines, and mitochondrial function... These were promising findings that require further investigation of both the clinical effects and mechanisms of action of sulforaphane.”

Side effects of sulforaphane treatment were mild, the researchers say, and included rare insomnia, irritability, and intolerance to sulforaphane’s taste and smell.

“Randomized controlled trial of sulforaphane and metabolite discovery in children with autism spectrum disorder,” Andrew W. Zimmerman, Kanwaljit Singh, Susan L. Connors, Hua Liu, Anita A. Panjwani, LiChing Lee, Eileen Diggins, Ann Foley, Stepan Melnyk, Indrapal N. Singh, S. Jill James, Richard E. Frye, and Jed W. Fahey, *Molecular Autism*, May 25, 2021 (free online). Address: Andrew Zimmerman, Department of Pediatrics, University of Massachusetts Medical School, 55 N. Lake Avenue, Worcester, MA 01655, Andrew.Zimmerman@umassmemorial.org.

## Study finds SSRI use during pregnancy not linked to ASD

Women with psychiatric conditions who take serotonin reuptake inhibitors (SSRIs) during pregnancy have an increased risk of having a child with an autism spectrum disorder (ASD) or developmental disability (DD). However, a new study suggests that the maternal psychiatric conditions themselves—not the SSRIs—are associated with this elevation in risk.

Jennifer Ames and colleagues analyzed data from the Study to Explore Early Development (SEED), which contains information on thousands of U.S. children born between 2003 and 2011. They looked at data for three groups: 1,367 children with ASD, 1,750 children with DD, and 1,671 children from the general population. About one third of mothers in the study had a psychiatric condition before or during pregnancy, and about a quarter of these women took SSRIs or other antidepressants.

The researchers found that the risk for ASD or DD was approximately doubled for children of mothers with a psychiatric condition compared to those without a psychiatric diagnosis. However, they say, “Odds of ASD were similarly elevated among mothers with psychiatric conditions who did not use SSRIs during pregnancy as in mothers who did use SSRIs.” Maternal psychiatric conditions were most strongly associated with subtypes of ASD and DD without co-occurring intellectual disability.

The researchers note that secondary analyses did show some association between prenatal SSRI exposure and DDs without co-occurring intellectual disability. However, they suggest that this may be due to chance because of the large number of secondary analyses they performed.

“Maternal psychiatric conditions, treatment with selective serotonin reuptake inhibitors, and neurodevelopmental disorders,” Jennifer L. Ames, Christine Ladd-Acosta, M. Daniele Fallin, Ying Qian, Laura A. Schieve, Carolyn DiGiuseppi, Li-Ching Lee, Eric P. Kasten, Guoli Zhou, Jennifer Pinto-Martin, Ellen M. Howerton, Christopher L. Eaton, and Lisa A. Croen, *Biological Psychiatry*, June 24, 2021 (free online). Address: Jennifer Ames, jennifer.l.ames@kp.org.

—and—  
“Risk of autism increases with maternal depression, but not SSRI use: study,” news release, Elsevier, June 24, 2021.

## Puppets may be a useful tool for teaching social skills to children with ASD

While the use of robots to teach social skills to children with autism spectrum disorders (ASD) is increasing, a new study suggests that a lower-tech intervention—the use of puppets—may also be effective.

Suzanne Macari and colleagues examined the responses of 37 children with ASD and 27 typically developing (TD) controls to a video showing a puppet and a human engaged in conversation. The researchers report, “Unlike TD controls, the ASD group exhibited limited visual attention to and chance-like visual preference for the human speaker. However, attention to and preference for the puppet speaker’s face was greater than chance and comparable across the two groups.” While children with more severe symptoms of autism showed less attention to the human speaker than those with

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### New to autism?

If so, the Autism Research Institute has valuable information on seeking appropriate medical care.

For a list of important questions to ask a potential medical provider, see:

<https://www.autism.org/finding-a-clinician>

**EDITORIAL: Stephen M. Edelson, Ph.D.**

## Dr. Ruth Sullivan, Dr. Bernard Rimland, and the rise of parent advocacy

On September 16, pioneering autism advocate Dr. Ruth Christ Sullivan passed away. Dr. Sullivan was a powerful advocate for individuals with autism and their families, and together, she and Dr. Bernard Rimland changed the lives of generations of autistic individuals for the better.

I knew Dr. Sullivan quite well over the years. She introduced herself to me at the 1979 Autism Society of America conference after hearing that I was working with both Dr. Ivar Lovaas and Dr. Rimland, and we soon developed a collegial friendship that lasted for decades.

There are several published descriptions of Dr. Sullivan's and Dr. Rimland's early advocacy efforts in the U.S. Here is my own account, based largely on my conversations with them.

In 1959, Dr. Rimland's son, Mark, was diagnosed with autism. Conducting a relentless search to figure out how to help his son, Dr. Rimland read every article ever written on autism and even hired interpreters to translate papers written in foreign languages. Quickly, he realized that the entire professional autism community was blaming parents for causing autism in their children.

Having just received a Ph.D. in experimental psychology, Dr. Rimland decided to write an editorial about autism, focusing on the outrageous claim that it was caused by emotionally neglectful parents. He discussed the inconsistencies in the descriptive literature, highlighted the lack of scientific evidence for a psychogenic theory, and argued convincingly that autism is a biological condition. He theorized, for the first time in the literature, that autism was a result of genetics and/or a genetic susceptibility to one or more environmental insults, leading in turn to some form of neurological impairment.

Over the next five years, Dr. Rimland's paper grew quite long, and his wife suggested he consider writing a book instead. The book, titled *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*, was published in 1964. Immediately, it caused the entire autism field to begin focusing on biomedical causes and treatments.

In 1963, Dr. Sullivan's son, Joseph, was diagnosed with autism at three years of age. Joe was the fifth of seven children. At this time, before the publication of Dr. Rimland's book, Dr. Sullivan and thousands of other women were referred to as "refrigerator mothers," because psychiatrists claimed that autism stemmed from maternal coldness and a lack of affection.

In 1964, soon after *Infantile Autism* was published, parents throughout the world began writing to Dr. Rimland. These letters often contained lengthy descriptions of their children and requested guidance. The next year, while spending a one-year residency at a think tank sponsored by Stanford University, Dr. Rimland realized that future research in autism needed to be distributed to parents so they could help their children. At that time, most pediatricians knew very little about autism given its relatively low prevalence rate (about 1 in 2,000, much lower than the prevalence today).

Dr. Rimland decided to write to parents with whom he was corresponding on a regular basis and tell them about his idea of forming a parent network. Around the same time, Dr. Sullivan wrote to him with a similar idea. Dr. Rimland called her immediately, and they soon began planning the details of a national support group.

Drs. Rimland and Sullivan convened a meeting in Teaneck, New Jersey in late 1965. Dr. Rimland wrote to parents living in nearby states, encouraging them to attend. The meeting was a great success, and many of those in attendance agreed to work together to establish a network of regional chapters throughout the country. The support group was initially titled the National Society for Autistic Children (or NSAC) but was later changed to the Autism Society of America (ASA) and then to the Autism Society (AS).

As Dr. Rimland recommended, one of NSAC's primary goals was to share the latest research findings with families through its chapters. Dr. Rimland also made a commitment to establish the very first chapter in San Diego. (The Autism Research Institute is currently located across the street from the first NSAC chapter. A photo of the first NSAC chapter is located at [www.FirstNSACchapteroffice.com](http://www.FirstNSACchapteroffice.com).) He then wrote to parents throughout the country and encouraged them to establish chapters in their own communities.

Around the same time, Dr. Ivar Lovaas was conducting groundbreaking research on treating children with autism at UCLA. Dr. Rimland scheduled a visit to see first-hand how behavior therapy was administered. He also made a point to interview families whose children attended Dr. Lovaas' clinic. Dr. Rimland was so impressed with their reports that he instructed NSAC to disseminate information on the efficacy of behavioral therapy to its chapter members.

In 1967, Dr. Rimland established the Institute for Child Behavior Research, the

name of which was later changed to the Autism Research Institute (ARI). The primary mission of the institute was to support research on autism. The plan was for ARI to encourage and monitor research throughout the world and summarize the most relevant findings for NSAC/ASA members.

In 1968, Dr. Rimland produced the first documentary on autism, *The Invisible Wall*, which was shown to college classes throughout the country. (This was my first introduction to autism.) In the film, Dr. Sullivan gave a detailed description of her son. You can view this segment at [www.InvisibleWall-RuthSullivan.com](http://www.InvisibleWall-RuthSullivan.com), and watch the entire documentary at [www.TheInvisibleWall-Autism.com](http://www.TheInvisibleWall-Autism.com). During this same year, Dr. Sullivan established an Information and Referral Service for parents throughout the world.

Over the years, NSAC/ASA/AS and ARI gradually went their separate ways. AS continues its efforts to provide information and support to chapters throughout the country, while ARI continues to support research by awarding grants and sponsoring regional and national think tanks in addition to disseminating research findings through its quarterly science newsletter, the *Autism Research Review International*, books, and near-weekly webinars.

Throughout her life, Dr. Sullivan continued to be active in the autism community, both nationally and regionally. She was one of the first to advocate for services for adults with ASD in her seminal paper titled "The National Crisis in Adult Services for Individuals with Autism," and her "Call to Action" paper was adopted as a position paper by ASA in 2001. She founded the Autism Services Center in Huntington, West Virginia, was instrumental in establishing numerous group homes, and was one of the strongest advocates for Public Law 94-142 (IDEA), which gives disabled children the right to fair and equal access to education. She and Dr. Rimland both served as technical advisors for the Academy Award-winning movie *Rain Man*, and Dustin Hoffman based his character in part on Dr. Sullivan's son.

Throughout the years, Drs. Rimland and Sullivan were close friends and colleagues, and they enjoyed discussing autism-related issues before his passing in 2006. Both of them were true trailblazers, and their heroic leadership prepared the groundwork for scientific research on autism and the provision of much-needed services to those on the autism spectrum and their family members. Their dedication and tireless efforts will never be forgotten.

## Research Updates

### Does being bilingual benefit children with ASD?

While many educators believe it may be harder for children with autism spectrum disorders (ASD) to cope in bilingual households, a new study suggests that bilingualism actually offers these children significant advantages.

Research involving neurotypical children indicates that bilingual children have better “theory of mind”—that is, the ability to understand the thoughts and feelings of others. In addition, they appear to have better executive function skills such as planning, impulse control, and flexible thinking. Noting that these skills are difficult for children with ASD to master, Eleni Peristeri and colleagues wondered if growing up in a bilingual household might be beneficial for them.

Peristeri and her team followed 103 children with ASD between 7 and 15 years of age. Of the group, 43 were bilingual. The researchers grouped the children based on their age, gender, and severity of ASD symptoms.

Asking the participants to perform tasks that measured their theory of mind and executive function skills, the researchers found that the bilingual children scored significantly higher than the children who spoke only one language. “On tasks relating to theory of mind, i.e. their ability to understand another person’s behavior by putting themselves in their place, the bilingual children gave 76% correct answers, compared with 57% for the monolingual children,” Peristeri says. The bilingual children’s scores on the executive function tests were twice as high as the scores for monolingual children.

Peristeri suggests several reasons for these findings. “Bilingualism requires the child to work first on skills directly related to theory of mind,” she says, “i.e., he or she must constantly be concerned with the knowledge of others: Does the person I am speaking to speak Greek or Albanian? In what language should I talk to him or her? Then, in a second phase, the child uses his executive functions by focusing his attention on one language, while inhibiting the second.”

Study coauthor Stephanie Durrleman notes that bilingual families often give up using one language in order to help their children with ASD. “However,” she says, “it is now clear that far from putting autistic children in difficulty bilingualism can, on the contrary, help these children to overcome several aspects of their disorder,

serving as a kind of natural therapy,”

“The cognitive benefits of bilingualism in autism spectrum disorder: Is theory of mind boosted and by which underlying factors?,” Eleni Peristeri, Eleni Baldimtsi, Margreet Vogelzang, Maria Tsimpli, and Stephanie Durrleman, *Autism Research*, May 19, 2021 (online). Address: Eleni Peristeri, Department of Neurology, University Hospital of Larissa, Faculty of Medicine, University of Thessaly, Biopolis, Mezourlo Hill, Larissa 41100, Greece, eperiste@uth.gr.

—and—

“Bilingualism as a natural therapy for autistic children,” news release, University of Geneva, June 3, 2021.

### Acetaminophen again linked to autism, ADHD

Prenatal exposure to acetaminophen (the active ingredient in Tylenol) may raise children’s risk for autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), according to a large-scale study.

Silvia Alemany and colleagues analyzed data on 73,881 children in six different European birth cohorts. The researchers controlled for a range of maternal variables including age and education, body mass index, use of alcohol or tobacco, mental health problems, number of pregnancies, and fever

or infections during pregnancy. In addition, they controlled for variables involving the children, including sex, age, and occurrence of colds and respiratory infections during the first two years of life.

The researchers found that children exposed to acetaminophen before birth were 19% more likely to develop symptoms of ASD and 21% more likely to develop symptoms of ADHD than children who were not exposed. The findings were similar for boys and girls. The researchers found no increased risk related to children’s exposure to acetaminophen after birth.

Two previous meta-analyses also pointed to an association between acetaminophen and autism or ADHD, but they were criticized because of the heterogeneity of the studies the meta-analyses reviewed. The new study, Alemany says, addresses these concerns. “The sample is large,” she says, “and it includes cohorts from multiple European countries: the United Kingdom, Denmark, the Netherlands, Italy, Greece and Spain. We also used the same criteria for all of the cohorts, thereby reducing the heterogeneity of criteria that has hampered previous studies.”

The researchers conclude, “[W]e agree with previous recommendations indicating that while acetaminophen should not be suppressed in pregnant women or children, it should be used only when necessary.”

“Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population based cohorts,” Silvia Alemany, Claudia Avella-García, Zeyan Liew, Raquel García-Esteban, Kosuke Inoue, Tim Cadman, Mónica López-Vicente, Lúcia González, Isolina Riño Galán, Ainara Andiarena, Maribel Casas, Katerina Margetaki, Katrine Strandberg-Larsen, Deborah A. Lawlor, Hanan El Marroun, Henning Tiemeier, Carmen Iñiguez, Adonina Tardón, Loreto Santa-Marina, Jordi Júlvez, Daniela Porta, Leda Chatzi, and Jordi Sunyer, *European Journal of Epidemiology*, May 28, 2021 (free online). Address: Silvia Alemany, silvia.alemany1983@gmail.com.

—and—

“Prenatal exposure to acetaminophen associated with ADHD and autism,” news release, Barcelona Institute for Global Health, May 28, 2021.

#### ARI Resources for Coping with COVID-19

To aid individuals with autism and their families during the COVID-19 pandemic, ARI is offering these resources:

- Free presentations offering evidence-based strategies to manage at home during extended school closures.
- Social stories and short videos on hygiene and medical procedures.
- Physician resources for supporting patients diagnosed with autism.

To view these, visit this link:

<https://www.autism.org/>

In addition, we are inviting families to tell their stories about how they are coping during the COVID-19 pandemic. We invite you to share your snapshots and stories about life at home. We will share your stories on social media with #AutismCOVID19Stories.

#### — Employment Resources —

Free Resources for Job Seekers, Families and Caregivers, Job Coaches, and Employers

Visit <https://www.autism.org/employment-resources-for-individuals-with-autism>

## Research Updates

### Virtual reality interventions appear effective for ASD

A new meta-analysis from Iran offers evidence that virtual reality (VR) programs are an effective intervention for individuals with autism spectrum disorders (ASD).

Behnam Karami and colleagues reviewed 33 studies on the effects of VR and found that individuals undergoing VR training exhibited relatively large improvements. The strongest effect was for daily living skills, they say, while the effects for cognitive skills, emotion regulation and recognition, and social and communication skills were moderate. Overall, they say, VR appeared more beneficial to older children than younger ones, and less beneficial for individuals with comorbid disorders.

They add, “Comparing the results of the current meta-analysis with those of more conventional training programs, it is evident that VR-based training is at least as effective in most study endpoints as traditional programs.”

The researchers also say that five studies on interventions using augmented reality—which involves virtual reality superimposed by virtual data—showed promising results.

They caution, however, that while their study found strong effectiveness in uncontrolled trials, it found only moderate effectiveness in controlled trials. In addition, they say, most studies involved small and heterogeneous groups of participants. Finally, they say, long-term assessments need to be conducted to see if the gains experienced by individuals with ASD who undergo VR training are lasting.

“Effectiveness of virtual/augmented reality-based therapeutic interventions on individuals with autism spectrum disorder: a comprehensive meta-analysis,” Behnam Karami, Roxana Koushki, Fariba Arabgol, Maryam Rahmani, and Abdol-Hossein Vahabie, *Frontiers in Psychiatry*, June 23, 2021 (free online). Address: Behnam Karami, School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran.

### “Extreme male brain” theory investigated

According to the “extreme male brain” theory of autism, individuals with autism spectrum disorders (ASD) have a masculinized brain. However, a new study indicates that the reality may be more complex.

ASD is much more common in males than females, and studies indicate that it is associated with behaviors considered typical for males. Study coauthor Liza van Eijk

notes, “Men score on average lower on empathy tasks than women, while adults with ASD, irrespective of their sex, score the lowest. Conversely, men score on average higher than women on an attention-to-detail task, while individuals with ASD score the highest.”

To explore variations in brain structure that might shed light on these differences, van Eijk and colleague Brendan Zietsch developed a data-derived measure of individual differences in subcortical brain shape along a male-female continuum. They then used this tool to analyze data from 1,060 individuals with ASD and 1,166 neurotypical individuals, in order to determine the “maleness” of their brains.

“Consistent with the extreme male brain hypothesis,” van Eijk says, “we found a higher mean brain maleness score in the ASD group than in controls.” In addition, brain “maleness” scores were positively associated with autistic symptoms.

However, the researchers considered that their finding might be due to the larger brain size in the ASD group. “Indeed,” they say, “after adjusting for differences in brain size, the brain maleness difference between the ASD group and controls disappeared, and no association with autistic symptoms remained... suggesting greater maleness of the autistic brain is driven by brain size.”

“Testing the extreme male brain hypothesis: Is autism spectrum disorder associated with a more male-typical brain?”, Liza van Eijk and Brendan P. Zietsch, *Autism Research*, May 19, 2021 (online). Address: Liza van Eijk, Department of Psychology, College of Healthcare Sciences, Division of Tropical Health and Medicine, James Cook University, Douglas, QLD, Australia, liza.vaneijk@jcu.edu.au.

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“Is autism linked to a more ‘male’ brain?”, news release, James Cook University, June 16, 2021.

### Individuals with ASD rate phone calls as worst communication mode

A new study indicates that when communicating with other people, the option least liked by adults with autism spectrum disorders (ASD) is the telephone.

Philippa Howard and Felicity Sedgewick enrolled 245 adults with ASD in their study, asking them to complete a questionnaire in which they ranked six communication modes in order of preference across seven different scenarios. The researchers found that “email ranked highly when accessing services, seeking customer support, and communicating about research.”

When individuals with ASD communicated with family or friends, in employment, and in education, the researchers found, “both face-to-face and written modes (email or text message) were preferred.” Participants commented that written communication in particular provides structure, increases thinking time, and reduces sensory issues and anxiety.

In contrast, the researchers say, “The pattern that was clearest among all participants and scenarios was that autistic people are highly averse to making or receiving phone calls.” The reasons cited included difficulties with auditory processing, anxiety, the unpredictability of phone calls, and difficulty in interpreting callers’ tones or intentions.

The researchers also asked participants to complete the Autism Quotient, the Generalised Anxiety Disorder scale, and the Camouflaging Autistic Traits Questionnaire. “Notably,” they say, “few individual differences were found to influence mode preference selection,” with little variance in the data when they controlled for age, age at diagnosis, anxiety level, or camouflaging behaviors (that is, behaviors used to disguise the person’s ASD diagnosis).

The researchers conclude, “The findings suggest that services should move away from a reliance on phone calls for communication. They should make sure that access to support is not dependent on the phone, and instead offer written options such as email and live messaging, which are more accessible.”

“‘Anything but the phone!’ Communication mode preferences in the autism community,” Philippa L. Howard and Felicity Sedgewick, *Autism*, June 25, 2021 (free online). Address: Philippa L. Howard, Centre for Psychological Approaches to Studying Education, School of Education, University of Bristol, 35 Berkeley Square, Bristol BS8 1JA, UK, philippa.howard@bristol.ac.uk.

#### ARI Survey: Seniors with Autism Spectrum Disorder

[https://www.autism.org/adult\\_survey](https://www.autism.org/adult_survey)

If you or a person you care for is on the autism spectrum and is 50 years of age or older, we would appreciate it if you could complete this online form.

We hope the results from this survey will provide insight into the needs and challenges faced by seniors with autism and their support providers.

## Imbalance of inhibitory, excitatory brain signaling linked to sensory issues

The majority of individuals with autism spectrum disorders (ASD) exhibit hyper- or hyporeactivity to stimuli, and a new study adds to evidence that this altered reactivity may result from an imbalance of excitatory and inhibitory signaling in the brain.

Jason He and colleagues used a technique called spectral-edited magnetic resonance spectroscopy to analyze GABA and glutamate levels in two brain regions specifically involved in tactile processing: the primary sensorimotor cortex (SMI) and the thalamus. GABA is an inhibitory neurotransmitter, while glutamate is excitatory. Because there are challenges involved in measuring GABA and glutamate, the researchers actually measured GABA+ (GABA plus macromolecules) and Glx (glutamate plus glutamine).

Studying 73 children with ASD and 92 controls, the researchers report that they found region-specific elevations of Glx in the SMI of the children with ASD. Higher levels of Glx were associated with more parent-reported issues involving sensory hyper- or hypoactivity. In addition, during tactile perception, higher levels of Glx in the thalamus in individuals with ASD were associated with reductions in “feed-forward” inhibition—a mechanism critical for preventing over-excitation and reducing task-irrelevant noise during signal processing. The researchers detected no differences between individuals with ASD and controls in GABA+ in either the SMI or the thalamus.

“Collectively,” the researchers say, “our findings provide strong evidence in support of the altered excitation-inhibition balance theory of ASD.”

“Region-specific elevations of glutamate + glutamine correlate with the sensory symptoms of autism spectrum disorders,” Jason L. He, Georg Oeltzschner, Mark Mikkelsen, Alyssa Deronda, Ashley D. Harris, Deana Crocetti, Ericka L. Wodka, Stewart H. Mostofsky, Richard A. E. Edden, and Nicolaas A. J. Puts, *Translational Psychiatry*, July 2021 (free online). Address: nicolaas.puts@kd.ac.uk.

The Johnson Center for Child Health and Development is conducting a study of Eye Movement Desensitization and Reprocessing (EMDR) for addressing anxiety and post-traumatic stress. Participants will be ages 18 or older, have an autism diagnosis, and have experienced traumatic or adverse events. Participants must be within traveling distance of the research location in Austin, TX.

For more information, call (512)732-8400 or email the study coordinators at info@johnson-center.org.

## Feedback, “feed-forward” loop impairments detected in ASD

(continued from page 1)

over time. Feed-forward systems, in contrast, carry out rapid actions that happen too quickly for sensory feedback to be processed in the brain.

“For example, when you reach out to grab a cup of coffee, a feed-forward situation, you don’t think about it,” Unruh says. “The brain initiates this movement based on the many times you reached for the coffee before. Conversely, feedback systems are responsible for monitoring to see if any adjustments needed to be made to that plan—maybe it’s a little further away than you thought, or the mug is heavier than you expected. Both of these systems work together to make precise, accurate, and effective movements that allow you to pick up your coffee without spilling it.”

The researchers found that when motor adjustments needed to be made very rapidly, individuals with ASD exhibited more pronounced deficits. When motor processes occurred over a longer period of time, these deficits were smaller. The researchers say this suggests that people with ASD may rely more heavily on slower feedback processes than neurotypical individuals do.

In addition, the researchers found that precision motor deficits in ASD varied across ages and types of grips. For example, they discovered that precision grip movements at very low force (similar, for instance, to holding a pencil) were significantly impaired in very young children with ASD. This suggests, they say, that measuring precision grip variability at a low force level could help to differentiate children

with ASD from typically developing children.

The study also detected differences in “handedness” between the ASD and control groups. Neurotypical individuals typically exert stronger force with the dominant hand. However, in participants with ASD, the researchers detected a smaller differ-

Unruh and colleagues found that when motor adjustments needed to be made very rapidly, individuals with ASD exhibited more pronounced deficits. When motor processes occurred over a longer period of time, these deficits were smaller. The researchers say this suggests that people with ASD may rely more heavily on slower feedback processes than neurotypical individuals do.

ence between the dominant and non-dominant hand. They say this suggests reduced specialization between hemispheres of the brain, which could impact development of language and other skills that are impaired in autism.

“Initial action output and feedback-guided motor behaviors in autism spectrum disorder,” Kathryn E. Unruh, Walker S. McKinney, Erin K. Bojanek, Kandace K. Fleming, John A. Sweeney, and Matthew W. Mosconi, *Molecular Autism*, July 10, 2021 (free online). Address: Matthew W. Mosconi, mosconi@ku.edu.

—and—  
“Differences in rapidly processing sensory feedback among people with autism spectrum disorder,” news release, Jen Humphrey, University of Kansas, August 12, 2021.

## Perinatal stroke significantly increases risk for ASD diagnosis

Children who suffer strokes around the time of birth have an increased risk of developing autism spectrum disorders (ASD), according to a new study. The study also found that these children receive an ASD diagnosis later than children in the general population.

Using a stroke registry maintained by a medical facility, Taralee Hamner and colleagues identified patients with a history of perinatal stroke. They then performed a retrospective chart review of 201 cases to analyze the children’s outcomes.

The researchers say that 23 children, or more than 11%, were formally diagnosed with ASD. “First concerns were noted in toddlerhood,” they say, “yet the average age of diagnosis was 6.26 years.” The children diagnosed with ASD were more likely than other children with a history of perinatal stroke to have earlier diagnoses of intellectual disability, global developmental delay, or a mixed

receptive-expressive language disorder, but there was no difference between the groups when it came to diagnoses of cerebral palsy, hemiplegia (one-sided paralysis), or epilepsy. The risk for ASD increased with accumulating diagnoses.

The researchers also found that children with a history of perinatal stroke received an autism diagnosis almost two years later than children in the general population and three and a half years after parents first expressed concerns. They comment, “Clinicians must be aware of increased prevalence and implement screening as part of routine care for all pediatric patients with perinatal stroke.”

“Children with perinatal stroke are at increased risk for autism spectrum disorder: Prevalence and co-occurring conditions within a clinically followed sample,” Taralee Hamner, Evelyn Shih, Rebecca Ichord, and Lauren Krivitzky, *The Clinical Neuropsychologist*, July 24, 2021 (online ahead of print publication). Address: Lauren Krivitzky, krivitzky@email.chop.edu.

## Attention training may improve children's academic skills

Attention training may lead to significant improvements in academic skills in children with autism spectrum disorders (ASD), according to a new study.

In the double-blind study, Mayra Spaniol and colleagues worked with 26 children with ASD in a special children's treatment unit in Brazil. The children participated in 45-minute training sessions twice a week for eight weeks.

Half of the children used a computer program called CPAT (Computerised Pro-

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Spaniol and colleagues found that children with ASD who underwent attention training did better in reading, writing, and math afterward.

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gressive Attentional Training), while the other half played regular computer games. The CPAT program includes games targeting different types of attention with activities that increase in difficulty.

Immediately after completing the sessions, the CPAT group showed significant improvements in the number of isolated words they could correctly identify and read and the number of words they could copy. They also improved their math scores by more than 50 percent. All of the improvements were maintained when the children

were re-tested three months later. In contrast, the control group participants showed no evidence of improvement.

The researchers note that their pilot study was small and their results need to be replicated in a larger population. However, they say their findings are similar to those of an earlier pilot study they conducted.

Senior study author Carmel Mevorach comments, "It's only recently that we have started to focus on the way autistic people pay attention in addition to, for example, how they interact and socialize. Attention is a fundamental cognitive process and better controlling it can have an impact on other behaviors, as well as on learning ability."

"Attention training in children with autism spectrum disorder improves academic performance: A double-blind pilot application of the computerized progressive attentional training program," Mayra Muller Spaniol, Carmel Mevorach, Lilach Shalev, Maria Cristina T. V. Teixeira, Rosane Lowenthal, and Christiane Silvestre de Paula, *Autism Research*, July 2021 (free online). Address: Mayra Muller Spaniol, Developmental Disorders Program, Mackenzie Presbyterian University, R. da Consolação, 930 Consolação, São Paulo SP, 01302-907, Brazil, mayramspaniol@gmail.com.

—and—

"Autistic children can benefit from attention training, study finds," news release, University of Birmingham, July 6, 2021.

## Study finds early-onset dementia risk is elevated in individuals with ASD

Individuals with autism spectrum disorders (ASD) have a significantly elevated risk of being diagnosed with early-onset dementia, according to a new study.

Using Medicaid data collected from 2008 through 2012, Giacomo Vivanti and colleagues analyzed data for four groups of 30- to 64-year-old adults: those who had a diagnosis of ASD only, those who had a diagnosis of ASD with co-occurring intellectual disability (ID), those who had a diagnosis of ID without ASD, and those with no ASD or ID diagnosis.

The researchers report, "The 5-year prevalence of dementia was 4.04% among adults with ASD only, and 5.22% for those with ASD and co-occurring ID. This prevalence was higher compared to the prevalence of dementia in individuals with no ASD and no ID (0.97%), but lower compared to individuals with ID only (7.10%)." After adjusting for variables that could affect the risk for dementia, the researchers found that "adults with ASD under the age of 65 were approximately 2.6 times more likely to be diagnosed with dementia compared to the general population in our study."

"The prevalence and incidence of early-onset dementia among adults with autism spectrum disorder," Giacomo Vivanti, Sha Tao, Kristen Lyall, Diana L. Robins, and Lindsay L. Shea, *Autism Research*, August 11, 2021 (epub prior to print publication). Address: Lindsay L. Shea, A. J. Drexel Autism Institute, Drexel University, 3020 Market Street, Suite 560, Philadelphia, PA 19104, lj142@drexel.edu.

## Puppets may be a useful tool for teaching social skills (continued from page 2)

less severe symptoms, children with mild and severe symptoms paid similar attention to the puppet.

The researchers conclude, "Since puppets can engage in back-and-forth interactions and model social interactions and communication, they may play a promising role in therapeutic efforts for young children with ASD."

"Puppets facilitate attention to social cues in children with ASD," Suzanne Macari, Xinyuan Chen, Ludivine Brunissen, Eukyung Yhang, Emma Brennan-Wydra, Angelina Verneti, Fred Volkmar, Joseph Chang, and Katarzyna Chawarska, *Autism Research*, August 2021 (online) Address: Katarzyna Chawarska, Yale Child Study Center, 300 George Street, Suite 900, New Haven, CT 06511, katarzyna.chawarska@yale.edu.

—and—

"Study finds children with autism respond well to puppets," news release, Mike Cummings, Yale University, August 5, 2021.

## 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.

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ABCs OF ABA IN 2021  
Melissa Olive, Ph.D., BCBA-D

—October 20, 2021—

1 p.m. Eastern Time (U.S.)  
BULLYING AND ASD:  
ADDRESSING VICTIMIZATION  
Ryan E. Adams, Ph.D.

—November 3, 2021—

1 p.m. Eastern Time (U.S.)  
BEHAVIORAL SUPPORT—  
BEYOND EARLY INTERVENTION  
Melissa Olive, Ph.D., BCBA-D

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