

# 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

## Microbiota therapy may lead to lasting beneficial changes in the gut health of children with ASD

Microbiota transfer therapy (MTT) may lead to long-term improvements in the gut health of children with autism spectrum disorders (ASD), according to a recent study by Khemlal Nirmalkar and colleagues at Arizona State University.

Interest in MTT as a potential therapy for ASD has been growing due to research indicating that many children with ASD have gastrointestinal (GI) problems such as chronic constipation, diarrhea, and/or abdominal pain. In addition, studies indicate that the gut microbiota of individuals with ASD may differ significantly from the microbiota of neurotypical individuals. Nirmalkar and colleagues note as well that “the gut–brain axis is bidirectional; gut microbiota, metabolic function, and metabolites play an important role in establishing GI and central nervous system (CNS) connections.”

The researchers’ new study on MTT builds on two earlier studies conducted by their group in 2017 and 2019. In the original study, 18 participants with ASD and GI problems underwent MTT. The researchers found that the treatment reduced gastrointestinal (GI) symptom severity by approximately 80 percent and ASD symptoms by approximately 24 percent, as well as increasing the abundance of several beneficial types of gut bacteria (*Bifidobacterium*, *Prevotella*, and *Desulfovibrio*). A two-year follow-up study of the children showed reductions of approximately 59 percent in GI symptoms and approximately 47 percent in ASD symptoms compared to baseline, and levels of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* remained higher than at baseline.

In the new study, the researchers used a technology called “shotgun metagenomics” to obtain detailed data on more than 5,000 bacterial species found in the guts of the children with ASD before and after MTT. They then compared these bacterial populations with those of neurotypical children.

The researchers found that MTT increased the abundance of beneficial bacteria and also helped to normalize levels of bacterial genes involved in pathways that play roles in folate biosynthesis, sulfur metabolism, and protection against oxidative

stress—all processes known to be altered in autism. They note, however, that “over the time (two years) the abundance of *Prevotella* and *Bifidobacterium* decreased, which suggests a longer MTT treatment time or a booster after a certain time might be needed for the retention of these bacteria.”

Nirmalkar comments, “This study highlights altered levels of important bacterial species and metabolic genes in children with autism and improvements after MTT. Our long-term goal is to understand the functional role of the gut microbiome, fill the knowledge gap of the gut–brain axis in autism, and identify therapeutic targets to improve GI health and behavior in children with autism.”

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“Shotgun metagenomics study suggests alteration in sulfur metabolism and oxidative stress in children with autism and improvement after microbiota transfer therapy,” Khemlal Nirmalkar, Fatir Qureshi, Dae-Wook Kang, Juergen Hahn, James B. Adams, and Rosa Krajmalnik-Brown, *International Journal of Molecular Sciences*, November 3, 2022 (free online). Address: Khemlal Nirmalkar, Biodesign Center for Health Through

Microbiomes, Arizona State University, Tempe, AZ 85287, [khem@asu.edu](mailto:khem@asu.edu).

—and—

“Study finds microbiota transfer therapy provides long term improvement in gut health in children with autism,” news release, Richard Harth, Arizona State University, December 14, 2022.

—and—

“2-year follow-up study reveals consistent benefits of microbiota transfer therapy in autism and gut symptoms,” Rosa Krajmalnik-Brown, Dae-Wook Kang, Devon Coleman, Elena L. Polard, Juan Maldonado, Sharon McDonough-Means, J. Gregory Caporaso, and James B. Adams. The researchers’ findings were presented at the Beneficial Microbes Conference on July 10, 2018.

—and—

“Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study,” Dae-Wook Kang, James B. Adams, Ann C. Gregory, Thomas Borody, Lauren Chittick, Alessio Fasano, Alexander Khoruts, Elizabeth Geis, Juan Maldonado, Sharon McDonough-Means, Elena L. Pollard, Simon Roux, Michael J. Sadowsky, Karen Schwarberg Lipson, Matthew B. Sullivan, J. Gregory Caporaso, and Rosa Krajmalnik-Brown, *Microbiome*, January 2017 (free online). Address: Matthew B. Sullivan, [mbsulli@gmail.com](mailto:mbsulli@gmail.com).

## Could treating moms’ periodontal disease lower odds of ASD?

Mothers who receive periodontal treatment during pregnancy may reduce the odds of their children developing autism spectrum disorders (ASD), according to a new study.

Carl Bose and colleagues collected data on 306 two-year-old children whose mothers had participated in the Maternal Oral Therapy to Reduce Obstetric Risk Study (MOTOR). The mothers were assigned to either a periodontal treatment arm, consisting of scaling and root planing early in the second trimester, or a delayed treatment arm in which they received periodontal care after delivery. At two years of age, the children were categorized as being at high or low risk for neurodevelopmental disorders (children categorized as “high-risk” were premature or small for gestational age).

The researchers administered the Modified Checklist for Autism in Toddlers (M-CHAT) to all of the children, and found that children whose mothers received periodontal care only after delivery were more likely

to have a positive M-CHAT score (indicating a higher likelihood of being autistic) than children of mothers who received care during pregnancy. This effect was larger for low-risk children than for high-risk children. The severity of periodontal disease proved to be a key factor, with children of mothers with severe periodontal disease—but not children of mothers with mild or moderate disease—having significantly higher odds of a positive M-CHAT score.

The researchers also analyzed levels of the pro-inflammatory cytokine IL-6 in cord blood samples as well as in blood samples taken from the mothers at baseline and after delivery. They found that children with positive M-CHAT scores had higher IL-6 cord blood measurements at birth, and that their mothers’ IL-6 levels rose between baseline and delivery. This suggests, they say, that increased inflammation during pregnancy is associated with higher odds for ASD-like

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## Study investigates responses to pain in individuals with ASD

A new study offers insights into the responses of adults with autism spectrum disorders (ASD) to painful stimuli.

Tseela Hoffman and colleagues investigated pain perception in 104 adults, 52 of whom were diagnosed with ASD. The participants with ASD, who ranged in age from 18 to 55, were matched with neurotypical controls for age and sex, and both groups had similar scores on a cognitive test.

The researchers found that participants with ASD were more likely than controls to use psychiatric medications. In addition,

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The researchers say, "This evidence demonstrating enhanced pain sensitivity warrants changing the common belief that autistic individuals experience less pain. This misinterpretation can lead to late diagnosis and poor treatment causing suffering and exacerbating the autistic symptoms, e.g., sleep disorders, restlessness, and aggressive behaviors."

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they rated themselves as being more anxious and having a higher sensitivity to pain and other environmental stimuli.

On sensory tests, participants with ASD and controls had similar thermal and pain detection thresholds, a finding that suggests normal functioning of the peripheral nervous system in ASD. However, when participants were exposed to various stimuli above their pain threshold, those with ASD consistently rated their pain as higher compared to controls—an indication of hypersensitivity to pain. The researchers also found that individuals with ASD were able to successfully inhibit short pain stimuli but not long-lasting pain stimuli.

Overall, the researchers say, their findings suggest that individuals with ASD have a "pro-nociceptive" pain modulation pro-

file, meaning that their brains appear more active in facilitating the experience of pain and less active in inhibiting continuous pain. This profile, they say, may increase these individuals' risk of developing chronic pain. They also note that their findings are consistent with the theory that ASD involves an imbalance between excitation and inhibition in the brain.

The researchers conclude, "This evidence demonstrating enhanced pain sensitivity warrants changing the common belief that autistic individuals experience less pain. This misinterpretation can lead to late diagnosis and poor treatment causing suffering and exacerbating the autistic symptoms, e.g., sleep disorders, restlessness, and aggressive behaviors."

*Editor's Note: Mounting evidence indicates that the perception of pain by individuals with ASD can vary from person to person, and may involve hypersensitivity to pain, hyposensitivity to pain, or an inability to identify the location of pain.*

"Indifference or hypersensitivity? Solving the riddle of the pain profile in individuals with autism," Tseela Hoffman, Tami Bar-Shalita, Yelena Granovsky, Eynat Gal, Merry Kalingel-Levi, Yael Dori, Chen Buxbaum, Natalya Yarovinsky, and Irit Weissman-Fogel, *PAIN*, November 2022 (free online). Address: Irit Weissman-Fogel, Department of Physical Therapy, Faculty of Social Welfare and Health Sciences, University of Haifa, Abba Khoushy Ave 199, Haifa 3498838, Israel, ifogel@univ.haifa.ac.il.

—and—  
 "New evidence questions the assumptions about pain in autism," news release, Wolters Kluwer Health, November 30, 2022.

### Need help or information?

The Autism Research Institute maintains a toll-free calling center:  
**833-281-7165**

## MYT1L mutations may play a role in some cases of autism

Some cases of autism may involve mutations in a gene called MYT1L, according to new research by Bettina Weigel and colleagues.

Weigel and her team studied the role of MYT1L—called the "guardian of neuronal identity," because it is one of three genes needed to turn stem cells into neurons rather than other types of cells—by exploring the effects of MYT1L deficiency both in mice and in human nerve cells derived from reprogrammed stem cells in the laboratory.

The researchers found that mice deficient in MYT1L had a thinner cerebral cortex. The mice also exhibited several behavioral changes similar to those seen in autism, including social deficits (seen only in male mice) and hyperactivity.

Additionally, the neurons of MYT1L-deficient mice produced an excess of sodium channels, leading to electrophysiological hyperactivation and impairing nerve function. Treatment with lamotrigine, an anti-epileptic drug that blocks sodium channels, returned the cells' electrophysiological activity to normal, and MYT1L-deficient mice given the drug no longer exhibited hyperactivity or anxiety-like behaviors.

The researchers discovered that in the MYT1L-deficient mouse neurons, as well as in human nerve cells engineered to be deficient in MYT1L, genes that prompt cells into becoming muscle or heart tissue were still active. This indicates, Mall says, that "[t]he cells cannot jump from the progeni-

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## Functional somatic problems are common in adolescents with elevated autistic traits

Teenagers with autistic-like traits often experience functional somatic symptoms (FSS)—in other words, physical symptoms that cannot be readily explained medically. In a new study, Elske Hogendoorn and colleagues examined the relationship over time between autistic traits and FFS in a large adolescent population.

The researchers analyzed data collected on 2,772 teenagers participating in the Tracking Adolescents' Individuals Lives Survey (TRAILS). Of the teens, 543 had received referrals for clinical treatment for mental health problems, and 264 had formal diagnoses of autism spectrum disorder (ASD). The researchers say that autistic-like traits were higher in the clinical group than in the general TRAILS group, which allowed them to explore a wide range of these traits.

Data on the adolescents were analyzed for four separate time periods or "waves," covering the ages between 11 and 19 years. Parents contributed information on the children's autistic traits, while the children themselves reported on somatic complaints including aches and pains, headaches, nausea, stomach pain, vomiting, fatigue, and dizziness.

"In our sample," the researchers report, "adolescents who experienced many autistic symptoms also experienced many unexplained somatic symptoms." There was a consistent relationship with FSS for three domains of autistic traits: social and communication behaviors, repetitive behaviors, and self-regulatory behaviors. Analyzing the relationship between FFS and autistic traits over time, the researchers found that changes in autistic-like features in one wave did not contribute to changes in FSS in a subsequent wave, and changes in FSS in one wave did not contribute to changes in autistic-like traits in a subsequent wave.

They comment, "The results of this study may alert clinicians to coexisting autistic-like features and FSS.... Treatment focusing on FSS may be adapted to better suit adolescents with autistic-like features. In turn, more attention could be paid to FSS in treatment focusing on autistic-like features."

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 "Longitudinal relations between autistic-like features and functional somatic symptoms in adolescence," Elske Hogendoorn, Catharina A. Hartman, Sarah M. Burke, Marijn W.G. van Dijk, and Judith G.M. Rosmalen, *Autism*, January 2023 (free online). Address: Elske Hogendoorn, Interdisciplinary Center Psychopathology and Emotion Regulation, University of Groningen, University Medical Center Groningen, CC 72, P.O. Box 30001, 9700 RB Groningen, The Netherlands, e.hogendoorn@umcg.nl.

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

## —Introducing the National Autism History Museum—

### Part I: Highlighting Bernard Rimland's Vision and Contributions to the Autism Field

To mark nearly a century of written history of autism, the Autism Research Institute (ARI) recently opened the National Autism History Museum—the first historical museum dedicated to autism. The four-room museum is located in the Kensington district in San Diego, California, adjacent to ARI's main office.

Many of the materials and artifacts in the museum were collected by Dr. Bernard Rimland, one of the true pioneers in research and parent advocacy. In addition to these, the museum displays a great deal of fascinating facts, as well as timelines of important milestones in the field.

The museum describes many groundbreaking issues such as the recognition of autism by the professional community, changes in the criteria for autism since 1961, reported prevalence rates from 1966 through 2022, and the origins of behavioral therapy (or Applied Behavior Analysis).

One exhibit focuses on Dr. Temple Grandin's efforts to help the autism community as well as to create humane ways of handling animals in livestock facilities. Another exhibit is dedicated to movies with popular actors and actresses linked to autism in some way, including Elvis Presley, Brooke Shields, Leonardo DiCaprio, and Dustin Hoffman.

#### ARI's contributions to the field of autism

In honor of the opening of the new museum, this editorial will describe many of the contributions of Bernard Rimland and the Autism Research Institute during the more than 50 years since its founding. Future issues will describe other historical highlights in the autism community.

Previously, I have described how Dr. Rimland played a pivotal role in the autism field by exposing the complete lack of evidence for the then-accepted belief that autism was caused by bad parenting. Soon after his son, Mark, was diagnosed with autism, Rimland set out to do everything he could to help his son. He read every article he could find on autism and hired interpreters to translate numerous articles. Quickly, Rimland realized that the entire professional community was blaming him and his wife for emotionally neglecting Mark.

These professionals initially included Dr. Leo Kanner, an eminent scholar and well-respected child psychiatrist credited with writing the first article on autism published in a major scientific journal [1]. (To his credit, Kanner later abandoned the

parent-blaming theory.) Bruno Bettelheim expanded on Kanner's initial negative descriptions of parents, blaming them directly in his 1959 *Scientific American* article [2] and his 1967 book titled *The Empty Fortress* [3]. At that time, parents were told to attend marriage counseling sessions and have their children participate in play therapy.

Rimland began writing a paper to disprove the parental-neglect theory and to make the case that genetics, neurology, and/or the environment play an instrumental role in autism. Over a five-year period, the article grew into a book, which was published in 1964 [4]. Rimland's thesis received immediate international acclaim and ushered in a new era of research and treatment focused on biological and behavioral interventions.

A year later, Rimland participated in a one-year think tank associated with Stanford University. During this time, he recognized the need to create a nationwide network in order to share information on effective treatments with families throughout the country. Along with Dr. Ruth Sullivan, he started the National Society for Autistic Children (NSAC), known today as the Autism Society (of America). Around this time, he visited Dr. Ivar Lovaas at UCLA, and soon afterward he instructed NSAC to share information about behavior therapy with its members.

In 1967, Rimland established the Institute for Child Behavior Research, known today as the Autism Research Institute. The aim was, and continues to be, to encourage and share scientific knowledge about understanding and supporting autistic people with researchers as well as the entire autism community.

In the late 60s and early 70s, there was an effort to establish a scientific journal dedicated to autism. At that time, the *Diagnostic and Statistical Manual*, version 2 (DSM-2) used the terms "autistic, atypical and withdrawn behavior" as part of the criteria for childhood schizophrenia [5]. After being approached by many scientists, Scripta Publishing Corporation in Washington, D.C. agreed to publish a quarterly journal titled the *Journal of Autism and Childhood Schizophrenia*. Kanner (who by then had abandoned his earlier parent-blaming views) was named as its first editor, and the editorial board included the Who's Who in the autism field at that time. You can view an image of the cover of the first issue, the list of editorial board members, and the table of contents at [www.autism.org/JACS](http://www.autism.org/JACS).

When Kanner stepped down as editor in

1974, he asked Rimland to be the journal's next editor. Because Rimland had a full-time job working as a civilian for the Navy, he declined. The editorship was then given to Eric Schopler, who held this position for the next 24 years.

In the 1980s, Rimland was an outspoken supporter of Ivar Lovaas' work on behavior therapy, which is known today as Applied Behavior Analysis or ABA. He wrote many letters to support Lovaas' research grants, wrote editorials promoting ABA, and lectured on its effectiveness to audiences worldwide. Through the years, ABA has evolved to become more person-centered, natural, and child-directed.

In the mid-1980s, the Hasbro toy company received much criticism for creating a GI Joe action figure described as an "extreme paranoid schizophrenic." Soon after, Hasbro recalled the toy and donated money to support mental health research. Rimland saw an opportunity and requested a start-up grant to publish a quarterly science newsletter for parents and professionals, summarizing the current and most relevant findings on autism. ARI continues to publish this quarterly hardcopy newsletter, the *Autism Research Review International*.

Another major highlight in the 1980s was the release of the Academy Award-winning movie *Rain Man*. As many of you know, Rimland was asked to review an early draft of the script since he had published several articles on savant abilities including a popular one in a 1978 issue of *Psychology Today* [6]. Interestingly, Raymond was initially slated to be intellectually challenged. While giving his input on the script, Rimland suggested that Raymond have autism, even though autism was not very well known in those days. The producer took Rimland's advice, and history was made.

During the 1990s, I began working closely with Rimland after completing graduate school and teaching for several years. During this time, we began studying sensory processing, an area of research largely inspired by Grandin's descriptions of discomfort and even pain as a result of her sensory sensitivities. For more than a decade, we studied sensory-related treatments including auditory integration training, ambient vision therapy, and Grandin's Hug Machine.

Since Rimland's passing in 2006, ARI continues to maintain many of the programs he started. As a continuation of his vision, we currently fund many more biologically based research studies. In addition, we have

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# Research Updates

## Individuals with ASD are at significantly elevated risk for cardiometabolic issues

Individuals with autism spectrum disorders (ASD) have a significantly elevated risk of developing cardiometabolic problems, according to a new meta-analysis.

Chathurika Dhanasekara and colleagues reviewed 34 studies involving more than 276,000 participants with autism and more than 7,733,000 participants without autism. They report, “[I]ndividuals with autism had a higher associated risk of developing diabetes, dyslipidemia, and heart disease, but not hypertension or stroke. The associated risks of developing diabetes and hypertension were even higher among children with autism.”

The researchers conclude, “Results suggest that the associated increased risk of cardiometabolic diseases should prompt clinicians to vigilantly monitor individuals with autism for potential contributors, signs of cardiometabolic disease, and their complications.”

Commenting on the study, researcher Elizabeth Weir says there is a need for more research into the elevated mortality rate in individuals with ASD. “In particular,” she says, “there is a paucity of research on the chronic physical health problems among autistic people as they age, with only a handful of studies assessing chronic health burden among those older than 35 years.”

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“Association between autism spectrum disorders and cardiometabolic diseases: a systematic review and meta-analysis,” Chathurika S. Dhanasekara, Dominic Ancona, Leticia Cortes, Amy Hu, Afrina H. Rimu, Christina Robohm-Leavitt, Drew Payne, Sarah M. Wakefield, Ann M. Mastergeorge, and Chanaka N. Kahathuduwa, *JAMA Pediatrics*, January 30, 2023 (online). Address: Chathurika S. Dhanasekara, Department of Laboratory Science and Primary Care, School of Health Professions, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

—and—

“Autism, physical health conditions, and a need for reform,” Elizabeth M. Weir, *JAMA Pediatrics*, January 30, 2023 (online). Address: Elizabeth Weir, Autism Research Centre, Department of Psychiatry, University of Cambridge, Douglas House, 18B Trumpington Road, Cambridge, CB2 8AH, UK, sb205@cam.ac.uk.

## Breastfeeding does not impact severity of ASD

The severity of symptoms in children with autism spectrum disorder (ASD) is not influenced by whether or not mothers breastfeed or by the length of breastfeeding, according to a new study.

Marianne Peries and colleagues collected data on 243 children who were part of the ELENA study, a long-term study investigating the developmental trajectories of children with ASD. They note, “The frequency of the initiation of breastfeeding was comparable to that of the general population and the rate of children still being breastfed at six months of age was higher.”

Using multiple assessments, the researchers measured the clinical severity of ASD symptoms for each child. They report, “Our results did not indicate a contribution of initiation or duration of breastfeeding to the prevention of clinical severity of ASD.” In addition, they say, “The evidence of a positive association between breastfeeding duration and IQ in the general population was not found in our sample of children with ASD.”

They conclude that although there is some evidence from previous studies that longer duration of breastfeeding and/or predominant breastfeeding are significantly associated with lower odds of a child developing ASD, “our results do not support a protective role against greater clinical severity in ASD.”

The researchers note, however, that their study was fairly small, and that the children they studied—who were selected from the full ELENA cohort because their parents had provided complete information on their breastfeeding history—had higher IQs and levels of adaptive skills than other participants in the ELENA cohort, which may limit the generalizability of their results.

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“Breastfeeding is not a risk factor for clinical severity in autism spectrum disorder in children from the ELENA cohort,” Marianne Peries, Fanny Duhr, Marie-Christine Picot, Barbara Heude, Jonathan Y. Bernard, and Amaria Baghdadli, *Nature Scientific Reports*, January 2023 (free online). Address: Amaria Baghdadli, rech-clinique-autisme@chu-montpellier.fr.

## Test using single hair strand may help predict ASD

According to a new study, it may be possible to predict autism spectrum disorders (ASD) with 81 percent accuracy using hair samples from infants.

In the study, Christine Austin and colleagues tested the diagnostic accuracy of a new algorithm that analyzes patterns of metal metabolism over time in single strands of hair. The researchers say they developed the algorithm after their earlier research showed that “the dysregulation of the dynamics underlying the metabolism of essential and toxic elements is a critical component of ASD etiology.” The researchers coupled their analyses with machine learning to improve the accuracy of their predictions.

To create their algorithm, the researchers analyzed hair samples from 486 children in three different populations. These included children participating in a nationwide study in Japan; children enrolled in a Swedish study of twins concordant or discordant for ASD; and both neurotypical children and children with ASD in the United States.

Analyzing 97 hair samples in order to validate their algorithm, the researchers found that it correctly predicted ASD in children as young as one month of age with 96.4 percent sensitivity (which refers to the correct identification of positive cases), 75.4 percent specificity (which refers to the correct exclusion of negative cases), and 81.4 percent accuracy. They also found that results did not differ by age or sex.

Austin and colleagues note, however, that their findings are preliminary and need to be replicated by other researchers.

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“Elemental dynamics in hair accurately predict future autism spectrum disorder diagnosis: an international multi-center study,” Christine Austin, Paul Curtin, Manish Arora, Abraham Reichenberg, Austen Curtin, Miyuki Iwai-Shimada, Robert O. Wright, Rosalind J. Wright, Karl Lundin Remnelius, Johan Isaksson, Sven Bölte, and Shoji F. Nakayama, *Journal of Clinical Medicine*, December 1, 2002 (free online). Address: Manish Arora, Environmental Medicine and Public Health, Mount Sinai School of Medicine, New York, NY 10029, manish.arora@mssm.edu.

—see also—

“A new test for autism hopes to help doctors diagnose before symptoms show,” Evan Bush, NBC News, January 5, 2023.

### — AUTISM.JOBS —

#### A Free Resource for Job Seekers, Caregivers, Job Coaches, and Employers

[www.Autism.Jobs](http://www.Autism.Jobs)

At this site, you can discover the advantages of hiring individuals with autism, access practical information designed to help candidates with autism become “job ready,” and learn how to create autism-friendly workplaces.

#### Moving?

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

# Research Updates

## Mainstream, special ed classes lead to similar gains for preschoolers

Many preschoolers with autism spectrum disorders (ASD) are placed in mainstream classrooms, while many others are placed in special education classes. According to a new study from Israel, children in the two different settings display comparable changes in core autistic symptoms over the course of one to two years.

Michal Ilan and colleagues analyzed data on 121 preschoolers with ASD placed in either mainstream or special education classrooms, comparing changes in core ASD symptoms as measured by the Autism Diagnostic Observation Schedule, Version 2 (ADOS-2). The researchers accounted for baseline cognitive scores, age of diagnosis, and parent-reported intensity of intervention. They report, “Longitudinal changes in ADOS-2 scores did not differ significantly across settings over a one- to two-year period.” In contrast, they note, changes in ADOS severity scores were strongly associated with the age of diagnosis, “demonstrating that children diagnosed earlier improved more regardless of educational settings.”

The researchers say, “Special and [mainstream] settings differ dramatically in their structure and cost. Yet there are remarkably small differences in the outcome of preschool children with ASD across settings in terms of their core ASD symptoms and gross spoken language abilities.” They conclude, “This highlights the need to identify specific criteria for establishing meaningful placement recommendations.”

The researchers caution, however, that their findings have limitations. For example, they say, they focused on changes in core ASD symptoms and did not examine other measures of outcome.

“Children with autism exhibit similar longitudinal changes in core symptoms when placed in special or mainstream education settings,” Michal Ilan, Michal Faroy, Ditzza Zachor, Liora Manelis, Danel Waissengreen, Analya Michaelovski, Inbar Avni, Idan Menashe, Judah Koller, Ilan Dinstein, and Gal Meiri, *Autism*, January 11, 2023 (free online). Address: Michal Ilan, Psychology Department, Ben-Gurion University of the Negev, Ben-Gurion 1, Beer Sheva 8410501, Israel, mici83@gmail.com.

**Did you know?** The Autism Research Institute recently received its fifth annual four-star rating—the highest possible rating—from Charity Navigator.

## Parents of children with ASD report high rates of stress, stigmatization

Caregivers of children with autism spectrum disorders (ASD) or other neurological conditions experience high rates of stress, poor mental health, and stigmatization, according to a new study from Australia.

Emily D’Arcy and colleagues surveyed 66 caregivers caring for children with neurological conditions. Nearly all of the children were diagnosed with ASD and/or attention-deficit/hyperactivity disorder (ADHD). The researchers found that almost 80 percent of respondents experienced poor well-being, high levels of stress, and poor mental health. In addition, more than 22 percent reported experiencing stigmatization.

Lead study author Ben Milbourn adds, “Financial stresses were also a major contributor to caregivers’ poor mental health and well-being, with the study finding that caregivers faced significant obstacles in terms of career success and progression and were often required to make personal sacrifices which impacted their personal identity.”

The researchers conclude, “Findings indicate that there is an array of unmet needs amongst this population, including support groups, education and training, respite and financial assistance.” Milbourn adds, “Future caregiver interventions and support services should specifically focus on protecting caregivers from existing stigma, while also educating the general public about what stigma is, how caregivers experience it, and how the general public is contributing to this.”

“The well-being and support needs of Australian caregivers of neurodiverse children,” Emily D’Arcy, Tayah Burnett, Emily Capstick, Catherine Elder, Olivia Slee, Sonya Girdler, Melissa Scott, and Ben Milbourn, *Journal of Autism and Developmental Disorders*, February 9, 2023 (free online). Address: Ben Milbourn, ben.milbourn@curtin.edu.au.

“Stress levels sky high for families of neurodiverse kids,” news release, Curtin University, February 13, 2023.

### 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/>

## Rate of autism spectrum disorders is high in girls with Turner syndrome

Girls with Turner syndrome have a high rate of autism spectrum disorders (ASD), according to a new study.

Turner syndrome occurs when females have only one X chromosome, or when the second X chromosome is partial or abnormal. The syndrome causes a wide range of signs and symptoms including short stature, heart and kidney defects, vision and hearing problems, ovarian failure, and dysmorphic features. While it is well established that many females with Turner syndrome experience difficulties with socialization, this has often been attributed solely to their physical difficulties.

In the new study, Jeanne Wolstencroft and colleagues evaluated 127 girls with Turner syndrome, all between five and 19 years of age, using multiple assessments involving parent and teacher reports and self-reports. The researchers report that 83 percent of the children had experienced significant social communication difficulties, and 61 percent had mild to moderate autistic traits that affected their social interactions; in addition, 23 percent met diagnostic criteria for ASD. “This is equivalent to a 57-fold relative risk of meeting criteria for an ASD in Turner syndrome compared to typically developing girls,” they say, adding that “there is undoubtedly a strong association between Turner syndrome and risk of ASD, despite earlier claims to the contrary.”

The researchers add that 34 percent of the girls they evaluated had at least one mental health or neurodevelopmental condition, and that those with ASD were at greater risk of having a co-occurring emotional disorder and/or attention deficit hyperactivity disorder (ADHD).

They conclude, “Clinicians managing the care of children with Turner syndrome should consider referrals for ASD assessment, in order to facilitate the implementation of social skills support, as [this has] been shown to be effective in young women with Turner syndrome.”

“Mental health and neurodevelopment in children and adolescents with Turner syndrome,” Jeanne Wolstencroft, William Mandy, and David Skuse, *Women’s Health*, December 2022 (free online). Address: Jeanne Wolstencroft, The Great Ormond Street Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK, j.wolstencroft@ucl.ac.uk.

—see also—  
“Turner syndrome tied to autism,” Emmet Fraizer, *Spectrum News*, January 5, 2023.

## New study of voles leads to surprising findings about oxytocin

Because the hormone oxytocin is involved in social bonding, multiple research groups have been testing the effects of oxytocin administration on the social behavior of individuals with autism spectrum disorders (ASD). However, a surprising new study reveals that oxytocin may not play as critical a role in forming social bonds as scientists believed.

Prairie voles are commonly used in research on the social effects of oxytocin because unlike other species of voles, which are promiscuous, these animals are monogamous and form strong social bonds. In addition, they have a higher density of oxytocin binding in several brain regions.

In the new research, Kristen Berendzen and colleagues used CRISPR gene editing to create three different lines of prairie voles with mutations in the oxytocin receptor gene that disrupted its function. The researchers discovered that the voles with the mutated oxytocin receptor genes exhibited the same monogamous mating, attachment, and parenting behaviors as regular voles. (In addition, they gave birth and produced milk, although in smaller quantities than normal female voles.)

Devanand Manoli, a co-senior author of the paper, comments, “The patterns were indistinguishable. The major behavioral traits that were thought to be dependent on oxytocin—sexual partners huddling together and rejecting other potential partners as well as parenting by mothers and fathers—appear to be completely intact in the absence of

its receptor.” He adds, “While oxytocin has been considered ‘Love Potion #9,’ it seems that potions 1 through 8 might be sufficient. This study tells us that oxytocin is likely just one part of a much more complex genetic program.”

The new research may offer insights into the equivocal results of studies investigating the effects of oxytocin on social behaviors in autism. Manoli says, “These behaviors are too important to survival to hinge on this single point of potential failure. There are likely other pathways or other genetic wiring to allow for that behavior. Oxytocin receptor signaling could be one part of that program, but it’s not the be-all end-all.”

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 “Oxytocin receptor is not required for social attachment in prairie voles,” Kristen M. Berendzen, Ruchira Sharma, Maricruz Alvarado Mandujano, Yichao Wei, Forrest D. Rogers, Trenton C. Simmons, Adele M.H. Seelke, Jessica M. Bond, Rose Larios, Nastacia L. Goodwin, Michael Sherman, Srinivas Parthasarthy, Isidoro Espineda, Joseph R. Knoedler, Annaliese Beery, Karen L. Bales, Nirao M. Shah, and Devanand S. Manoli, *Neuron*, January 27, 2023 (free online). Address: Devanand Manoli, devanand.manoli@ucsf.edu.

—and—

“Fresh questions about oxytocin as the ‘love hormone’ behind pair bonding,” news release, University of California, San Francisco, January 27, 2023.

—and—

“‘Mind-blowing’ study upends conventional wisdom on oxytocin,” Angie Voyles Askham, *Spectrum*, January 27, 2023.

## Could treating maternal periodontal disease lower ASD risk?

(continued from page 1)

symptoms in two-year-olds, and that periodontal treatment during pregnancy may reduce the odds of children developing ASD by decreasing inflammation.

The researchers note that their findings are in line with other research showing that periodontal disease during pregnancy is associated with a range of adverse effects including preterm birth, fetal growth restriction, and preeclampsia. They also cite animal studies indicating that exposure to oral pathogens may cause fetoplacental inflammation, which in turn may cause cerebral white matter damage that may lead to neurodevelopmental abnormalities resembling autism in humans. However, they caution that their study has limitations. For example, they note, they relied on the M-CHAT, which has been criticized for its limited predictive value, and did not follow up to see which children actually developed ASD.

—  
 “Antepartum periodontitis treatment and risk of offspring screening positive for autism spectrum disorder,” Carl Bose, Gregory C. Valentine, Kamaira Philips, Kim Boggess, Kevin Moss, Silvana P. Barros, Julie Marchesan, Di Wu, Thomas M. O’Shea, Myriam Peralta-Carcelen, Ricki Goldstein, Rajam Ramamurthy, and James D. Beck, *Journal of Perinatology*, January 25, 2023 (online). Address: Gregory Valentine, gvalent@uw.edu.

## New Jersey Autism Study shows large increase in cases of autism without intellectual disability

A new study reports that diagnosed cases of autism spectrum disorder (ASD) in the New York–New Jersey metro region rose sharply between 2000 and 2016. Additionally, it found that the largest increase occurred among children without intellectual disabilities.

“One of the assumptions about ASD is that it occurs alongside intellectual disabilities,” says lead author Josephine Shenouda. “This claim was supported by older studies suggesting that up to 75 percent of children with autism also have intellectual disability.” However, she says, “What our paper shows is that this assumption is not true. In fact, in this study, two in three children with autism had no intellectual disability whatsoever.”

The researchers used biannual data from the ongoing New Jersey Autism Study to identify 4,661 eight-year-olds with ASD in four New Jersey counties during the study period. Of these, only about 32 percent had an intellectual disability. Further analysis showed that rates of ASD co-occurring with

intellectual disability increased two-fold between 2000 and 2016, while rates of ASD with no intellectual disability increased five-fold.

Senior study coauthor Walter Zahorodny comments, “Better awareness of and

—  
 Shenouda and colleagues say their findings challenge the assumption that autism generally occurs alongside intellectual disability.

—  
 testing for ASD does play a role. But the fact that we saw a 500 percent increase in autism among kids without any intellectual disabilities—children we know are falling through the cracks—suggests that something else is also driving the surge.”

The Rutgers study found that black children with ASD and no intellectual disabilities were 30 percent less likely to be identified compared with white children, and that children in wealthy areas were 80 percent more likely to be identified than children in poorer areas.

Shenouda says, “With up to 72 percent of the ASD population having borderline or average intellectual ability, emphasis should be placed on early screening, early identification and early intervention. Because gains in intellectual functioning are proportionate with intense intervention at younger ages, it’s essential that universal screening is in place, especially in underserved communities.”

—  
 “Prevalence and disparities in the detection of autism without intellectual disability,” Josephine Shenouda, Emily Barrett, Amy L. Davidow, Kate Sidwell, Cara Lescott, William Halperin, Vincent M. B. Silenzio, and Walter Zahorodny, *Pediatrics*, November 2023 (free online). Address: Josephine Shenouda, Department of Pediatrics, Rutgers New Jersey Medical School, 185 South Orange Ave F-511, Newark, New Jersey 07103, shenoujo@njms.rutgers.edu.

—and—

“Study logs five-fold increase in autism in New York–New Jersey region,” news release, Rutgers University–New Brunswick, January 18, 2023.

## New research adds to evidence of unusual responses to “motherese” by toddlers with ASD

A new study adds to evidence that an unusual response to “motherese”—the playful, exaggerated form of speech often used by mothers when talking to infants—may help to identify toddlers with autism spectrum disorders (ASD).

Karen Pierce and colleagues used eye-tracking technology to evaluate 653 toddlers, all between 12 and 48 months of age. The children were presented with two short videos, shown side by side: one of a woman speaking in motherese, and another of either a busy highway or abstract shapes with accompanying electronic music. The direction of the toddlers’ gaze determined the amount of time each video played.

The researchers found that toddlers without ASD consistently showed a great deal of interest in the “motherese” video, spending approximately 80 percent of their time watching this video. Toddlers diagnosed with ASD were far less consistent, with their fixation on the “motherese” video ranging from 0 to 100 percent of the time. The subset of toddlers who fixated on motherese less than 30 percent of the time could be accurately identified as having ASD via this measurement alone. Toddlers who had ASD but still spent most of their time paying attention to the “motherese” video exhibited greater social and language abilities than toddlers with ASD who were less attentive.

Pierce comments, “We know the earlier we can introduce treatment, the more effective it is likely to be, but most children don’t get a formal diagnosis until around age three or four. There is a real need for easy and effective diagnostic tools that can be used on young children, and eye-tracking is a great place to start.” In addition, the researchers say, eye-tracking tests might help to uncover biological subtypes of ASD.

The new research expands on an earlier study by the same researchers (see *ARRI* 2022, No. 1) In that brain imaging study, toddlers with ASD who showed the lowest levels of attention to motherese speech also showed the lowest levels of neural functional activation in speech-processing regions and exhibited lower language abilities than toddlers who paid greater attention to motherese speech. Conversely, typically developing infants and toddlers showed the strongest neural responses and affinity to motherese.

—  
“Level of attention to motherese speech as an early marker of autism spectrum disorder,” Karen Pierce, Teresa H. Wen, Javad Zahiri, Charlene Andreason, Eric Courchesne, Cynthia C. Barnes, Linda Lopez, Steven J. Arias, Ahtziry Esquivel, and Amanda Cheng, *JAMA Pediatrics*, February 8, 2023 (free online). Address: Karen Pierce, De-

partment of Neurosciences, University of California San Diego, 8110 La Jolla Shores Dr., La Jolla, CA 92037, kpierce@health.ucsd.edu.

—and—  
“Toddlers’ attention to ‘motherese’ speech may be used to diagnose autism,” news release, University of California San Diego, February 8, 2023.

—and—  
“Neural responses to affective speech, including motherese, map onto clinical and social eye tracking profiles in toddlers with ASD,” Yaqiong

Xiao, Teresa H. Wen, Lauren Kupis, Lisa T. Eyller, Disha Goel, Keith Vaux, Michael V. Lombardo, Nathan E. Lewis, Karen Pierce, and Eric Courchesne, *Nature Human Behavior*, January 3, 2022 (online). Address: Yaqiong Xiao, Autism Center of Excellence, Department of Neurosciences, University of California, La Jolla, CA 92093, yaq.xiao@gmail.com.

—and—  
“When mom talks, are infants with ASD listening?,” news release, University of California San Diego, January 3, 2022.

## MYT1L mutations may play a role in some cases of autism

(continued from page 2)

tor stage that efficiently to a differentiated neural state.”

Weigel and colleagues note that while lamotrigine reduced hyperactivity and anxiety-related behaviors in mice, it is not yet known if it may be helpful for humans with ASD associated with MYT1L mutations. A 2001 study by Karin Belsito and colleagues found that lamotrigine did not improve the scores of children with ASD on standardized behavior tests.

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“MYT1L haploinsufficiency in human neurons and mice causes autism-associated phenotypes that can be reversed by genetic and pharmacologic intervention,” Bettina Weigel, Jana F. Tegethoff, Sarah D. Grieder, Bryce Lim, Bhuvaneshwari Nagarajan, Yu-Chao Liu, Jule Truberg,

Dimitris Papageorgiou, Juan M. Adrian-Segarra, Laura K. Schmidt, Janina Kaspar, Eric Poisel, Elisa Heinzelmann, Manu Saraswat, Marleen Christ, Christian Arnold, Ignacio L. Ibarra, Joaquin Campos, Jeroen Krijgsveld, Hannah Monyer, Judith B. Zaugg, Claudio Acuna, and Moritz Mall, *Molecular Psychiatry*, February 14, 2023 (free online). Address: Moritz Mall, m.mall@dkfz.de.

—and—  
“Autism-linked MYT1L mutations prompt ‘identify crisis’ in budding brain cells,” Laura Dattaro, *Spectrum News*, February 14, 2023.

—see also—  
“Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial,” Karin M. Belsito, Paul A. Law, Karen S. Kirk, Rebecca J. Landa, and Andrew W. Zimmerman, *Journal of Autism and Developmental Disorders*, April 2001 (online). Address: Karin Belsito, belsito@kenedykrieger.org.

## —Introducing the National Autism History Museum— Part I: Highlighting Bernard Rimland’s Vision and Contributions to the Autism Field

(continued from page 3)

expanded our efforts to include understanding and supporting adults and seniors on the spectrum. We also sponsor numerous free webinars on co-occurring medical issues for the autism community worldwide (for information, visit [ARI.org](http://ARI.org)), and we disseminate science-based information through monthly and bimonthly e-newsletters.

As one would expect, the autism field has progressed quite significantly since Rimland’s initial insights nearly 60 years ago. For example, the publication of the DSM-5 a decade ago made autism a more inclusive diagnosis by integrating those diagnosed with Asperger syndrome and Pervasive Developmental Disorder (or PDD) [7]. More recently, autistic individuals are sharing their voices and becoming active participants in the direction of research as well as co-producing this research.

### Come and visit us!

ARI’s history is just one of the topics explored in the rich collection of documents and artifacts in the National Autism History

Museum. If you are traveling to San Diego for business or pleasure, I hope you will have a chance to stop by the museum, where you can learn about the past—because understanding the past can help us create a framework for the future.

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### —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 \$475,000 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.

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