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# Autism Research Review INTERNATIONAL

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

## New animal research offers insights into the effects of the microbiome on social deficits in ASD

A new study provides additional clues about the role the gut microbiome may play in autism spectrum disorders (ASD).

In earlier research (see ARRI 2019, Volume 1), Mauro Costa-Mattioli and colleagues found that in several different mouse models of ASD, administering a specific strain of gut microbes called *Lactobacillus reuteri* ameliorated social deficits. The researchers found that the microbe reversed social deficits in all models tested—whether the autism was environmentally caused, genetically caused, or idiopathic (meaning that the cause was unknown).

The researchers also found that the effects of *L. reuteri* did not result from changes to the composition of the gut microbiome, which was altered in all of the models tested. Instead, they discovered that *L. reuteri* promotes social behavior via the vagus nerve, a nerve that bidirectionally connects the gut and the brain and the oxytocin-dopamine reward system. When this nerve was severed or when the researchers blocked oxytocin uptake, *L. reuteri* could no longer restore social behavior in ASD-model mice.

> The researchers found that housing the Cntnap2 knockout mice with regular mice led to the disappearance of gut microbiome differences, which in turn led to increased sociability in the knockout mice. Once again, they found that L. reuteri alone was sufficient to restore normal social behavior in the knockout mice.

In the new study, the researchers (including first author Shelly Buffington) worked with mice lacking a gene called *Cntnap2*, which is loosely associated with autism. The mice had abnormal microbiomes and exhibited hyperactivity and autistic-like deficits. However, the researchers found that when they housed regular mice and *Cntnap2* knockout mice together after weaning, the gut microbiomes and social behaviors of the knockout mice normalized (although the mice remained hyperactive). Once again, the researchers found that *L. reuteri* alone was sufficient to restore normal social behavior in the knockout mice.

The researchers also discovered that tetrahydrobiopterin, which is used in the biosynthesis of dopamine, was deficient in isolated knockout mice but was restored by *L. reuteri.* Administration of tetrahydrobiopterin alone proved to be sufficient to restore social behavior in the knockout mice. Finally, the researchers found evidence that both *L. reuteri* and tetrahydrobiopterin improve social reward-mediated synaptic transmission in these mice.

The researchers conclude, "[G]iven the current brain-centric view of genetic neurological disorders, we believe that our results widen our understanding of how a genetic mutation leads to behavioral abnormalities. In addition, they suggest that both brain and gut microbiota may need to be targeted to fully and effectively reverse the core symptoms associated with some neurological disorders."

Buffington adds, "Our work strengthens an emerging concept of a new frontier for the development of safe and effective therapeutics that target the gut microbiome with selective probiotic strains of bacteria or bacteria-inspired pharmaceuticals." Costa-

*continued on page 7*

## Alzheimer's drug appears to benefit adult men with fragile X

A drug intended to help people with Alzheimer's disease may also be beneficial for individuals with fragile X syndrome, according to a new study.

Fragile X syndrome is the most common known genetic cause of autistic-like symptoms and the most common cause of inherited intellectual disability. It affects about 1 in 4,000 males and 1 in 8,000 females.

In a 24-week randomized, placebo-controlled, two-way crossover study, Elizabeth Berry-Kravis and colleagues tested the Alzheimer's drug, called BPN14770, on 30 adult male patients with fragile X syndrome. Study coauthor Mark Gurney became interested in the drug when he learned that both autism and Alzheimer's affect a substance called cyclic AMP (cAMP), which helps transmit messages inside cells and plays a critical role in memory formation. Researchers in Germany had developed BPN14770 to inhibit the activity of an enzyme called PDE4D, increasing the levels of cyclic AMP in the brain.

The drug was first tested on animals before being tested on humans. Unlike several other drugs that worked well in animal models but were ineffective in people with fragile X syndrome, BPN14770 appears to be effective for both animals and humans.

The researchers found that cognitive scores increased by about 10% in participants receiving the drug, and language and daily functioning skills improved significantly. Moreover, no differences in side effects were seen between the active and placebo groups.

Berry-Kravis says, "The majority of clinical outcome measures were in favor of the drug. These measures included performance-based assessments, biomarkers, and parent and physician-rated scales, which in combination suggest a meaningful impact on the global [fragile X] disease process." She adds that it is exciting that the drug "potentially addresses a core biochemical deficit in [fragile X], a deficiency of cAMP," which has been documented in individuals with fragile X syndrome. The researchers note, however, that larger trials are needed.

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"Inhibition of phosphodiesterase-4D in adults with fragile X syndrome: a randomized, placebo-controlled, phase 2 clinical trial," Elizabeth M. Berry-Kravis, Mark D. Harnett, Scott A. Reines, Melody A. Reese, Lauren E. Ethridge, Abigail H. Outterson, Claire Michalak, Jeremiah Furman, and Mark E. Gurney, *Nature Medicine*, April 29, 2021 (online). Address: Elizabeth Berry-Kravis, Department of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center, Chicago, IL 60612.

—and—

"Treatment found to improve cognitive function in patients with fragile X syndrome," news release, Rush University Medical Center, April 29, 2021.

—and—

"An Alzheimer's drug may boost cognition in people with fragile X syndrome," Jon Hamilton, NPR, April 30, 2021.

## Researchers find clues to inconsistent microbiome findings in ASD, see longitudinal effects

A new study suggests that changes occurring over time in the behavior of individuals with autism spectrum disorders (ASD) may be related to their gut microbiomes. In addition, it offers insights into the inconsistent findings of studies investigating the role of the gut microbiome in ASD.

In the study, Jennifer Fouquier and colleagues compared fecal samples from individuals with ASD and controls in Arizona and Colorado, using standardized DNA extraction and sequencing methods. The Arizona participants included 36 children with ASD and 38 age-matched neurotypical controls who did not have first-degree relatives with autism. The Colorado participants included 13 children with ASD and 16 matched neurotypical controls; five of the controls had siblings with ASD.

The researchers found that gut microbiomes differed between individuals in Arizona and those in Colorado. Moreover, in Arizona but not Colorado, gastrointestinal symptoms were higher in individuals with ASD than in controls. Gut microbiome composition was significantly associated with ASD when the researchers controlled for study site location but not when they controlled for gastrointestinal symptoms.

"Taken together," the researchers say, "these results suggest that geographical differences in gut microbiome composition and differences in levels of gastrointestinal symptoms in autistic individuals at different study sites may contribute to inconsistent results in the literature."

The researchers found that changes in levels of lethargy and social withdrawal measured in individuals at different times correlated with the degree of change in gut microbiome composition. In addition, they say, "a worsening of inappropriate speech between time points was associated with decreased gut microbiome diversity."

The researchers also studied seven children with ASD and nine neurotypical controls over time, evaluating the gut microbiome's relationship to behavioral severity, diet, and gastrointestinal symptoms. All of these children were from the Colorado group.

The researchers contacted participants in the longitudinal study every three months and asked them to fill out a number of questionnaires including the Aberrant Behavior Checklist. In addition, they asked participants to fill out a food frequency questionnaire and to describe any GI symptoms they were experiencing. They also obtained fecal samples.

The researchers say the results indicated that changes in levels of lethargy and social withdrawal at different times correlated with the degree of change in gut microbiome composition. In addition, they say, "A worsening of inappropriate speech between time points was associated with decreased gut microbiome diversity."

"We need more research," says study coauthor Catherine Lozupone, "but our work shows that the gut microbiome is playing a role in the provocation of symptoms in kids with autism spectrum disorder. This further supports the fact that the gut microbiome could be a valuable therapeutic target for children with autism spectrum disorders."

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"The gut microbiome in autism: Study-site effects and longitudinal analysis of behavior change," Jennifer Fouquier, Nancy Moreno Huizar, Jody Donnelly, Cody Glickman, Dae-Wook Kang, Juan Maldonado, Rachel A. Jones, Kimberly Johnson, James B. Adams, Rosa Krajmalnik-Brown, and Catherine Lozupone, *mSystems*, March/April 2021 (free online). Address: Catherine Lozupone, Catherine.lozupone@cuanschutz.edu.

—and—

"Gut microbiome plays role in autism," news release, American Society for Microbiology, April 6, 2021.

## New study: Epidural anesthesia during labor not linked to ASD

Exposure to epidural anesthesia during delivery does not increase a child's risk for developing autism spectrum disorder (ASD), according to a new, large-scale study.

In earlier research (see ARRI 2020, Volume 4), Chunyuan Qiu and colleagues examined data on 147,895 children delivered vaginally either with or without epidural labor analgesia (ELA). The researchers found that 1.9% of the children exposed to ELA were diagnosed with ASD, compared to 1.3% of unexposed children. They concluded, "This study suggests that exposure to epidural analgesia for vaginal delivery may be associated with increased risk of autism in children."

The new study, by Elizabeth Wall-Wieler and colleagues, included 123,175 children born between 2005 and 2016 and followed until 2019. All of the children in the study were born via vaginal delivery and were single births. The researchers identified all children at least 18 months of age with at least one inpatient or outpatient diagnosis of ASD.

Overall, 38.2% of the children were exposed to ELA. Of the children exposed to epidurals during labor, 2.1% later received a diagnosis of ASD, compared with 1.7% of children not exposed to epidurals. However, this study controlled for a far greater number of factors than the previous study, and the researchers note, "There were substantial differences in maternal sociodemographic, preexisting, pregnancy-related, and birth-specific covariates between births who were exposed vs nonexposed to ELA." When the researchers controlled for these factors, senior study author Alexander Butwick says, "We did not find evidence for any genuine link between having an epidural and putting your baby at increased risk of autism spectrum disorder."

Examining sibling pairs, the researchers found that the ASD risk in exposed children was slightly higher than in unexposed children. Again, however, when the researchers controlled for sociodemographic, pre-pregnancy, and perinatal factors, they found no association between ASD and epidural exposure.

They conclude, "Results of this population-based cohort study, including an analysis of exposure-discordant siblings, found no association between ELA and offspring risk of ASD."

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"Association of epidural labor analgesia with offspring risk of autism spectrum disorders," Elizabeth Wall-Wieler, Brian Bateman, Ana Hanlon-Dearman, Leslie Roos, and Alexander Butwick, J*AMA Pediatrics*, April 19, 2021 (free online). Address: Elizabeth Wall-Wieler, Department of Community Health Sciences, University of Manitoba, 408-727 McDermot Ave, Winnipeg, MB R3E 3P5, Canada, elizabeth.wall-wieler@umanitoba.ca.

—and—

"Epidural use at birth not linked to autism risk, study finds," news release, Stanford University Medical Center, April 19, 2021.

**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

***GUEST EDITORIAL***

# Notes on exosomes and autism

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While a great many biological processes take place within cells, proper functioning of an organ, or indeed an entire organism, depends heavily on what takes place between cells as well. It is becoming clear that cells affect each other by means of extracellular vesicles (EVs) that they secrete. Exosomes, the smallest of the three types of EVs, have been the focus of most research. (A vesicle is a self-contained structure consisting of fluid containing biological material, referred to as its cargo, surrounded and enclosed by an outer membrane called the lipid bilayer.)

Exosomes are about 40 to 150 nanometers in size, around the same sizes as most viruses. All types of cells produce them. Exosomes are extremely plentiful—normal human blood is estimated to carry two quadrillion ($2x10^{15}$) exosomes—and are found in abundance in all bodily fluids.

Exosomes vary greatly in their cargos, which include proteins, lipids, RNAs, and DNA. In many cases, it is possible to determine the type of cell that produced a particular exosome, based on its cargo.

Currently, most exosome research has addressed their role in cancers and to a somewhat lesser extent, HIV. Many in vitro and in vivo studies have shown that cancerous cells produce exosomes with certain proteins and microRNAs (miRNAs) being overexpressed with respect to healthy cells of the same type. Furthermore, abnormal cells produce many more exosomes than healthy cells do.

Exosome research has been focusing on several different roles that exosomes can and do play in the progression and treatment of diseases and other abnormal conditions. In cancer research, some exosomes have been found to promote tumor growth, while others act to suppress it. In HIV studies, exosomes that have been hijacked by HIV have been implicated in the spread of HIV to healthy T-cells—the so-called "Trojan Exosome Hypothesis." In any case, the ubiquity of exosomes in many biological fluids and the potential to tie them to the cell types they originated from makes them ideal candidates for non-invasive diagnostic tools that can act as disease-specific biomarkers. Furthermore, since the number of exosomes a cell produces and the cargos they carry vary with health status of the cell, the effectiveness of a treatment could be monitored by regularly analyzing blood serum or some other relevant fluid.

Our understanding as to how exosomes act to achieve communication and influence between cells is still in its infancy. Many scientists believe that as progress is made on this front, it will be possible to engineer the contents of exosomes so as to deliver therapeutic materials to diseased cells.

Exosomes have also caught the attention of psychiatrists and neurologists, for several reasons. First, miRNAs, many of which can only be easily obtained from exosomes, have been implicated in several brain disorders such as depression, schizophrenia, anxiety, and bipolar disorder, as well as affecting more general brain functions such as neuroinflammation, neurogenesis, interneuronal communication, and transcriptional regulation. Both the number of exosomes and their cargos can differ significantly between normal brains and those with impairments. As some studies have shown, miRNAs extracted from exosomes in plasma can function very effectively as biomarkers that can, for example, differentiate among controls, people with schizophrenia, and bipolar patients.

Second, exosomes can cross the blood-brain barrier (BBB) bi-directionally and tend to be ignored by the immune system. This implies that, in concept, exosomes can be engineered to deliver therapeutic drugs to the brain.

To date, there have been just a few studies looking specifically at autism and exosomes, and they have had limited scopes. One study reported that compared to 40 controls, 40 children with autism carried significantly more EVs in their serum and that these EVs contained greater amounts of mitochondrial DNA (mtDNA). The authors also reported that in vitro EVs from the subjects with ASD stimulated human-cultured microglia to secrete the pro-inflammatory cytokine IL-1β.

However, several of the more general studies of the roles exosomes can and do play in brain disorders would seem to include autism without explicitly saying so. This is especially the case for studies that focus on neuroinflammation. Some studies have shown that exosomes not only cross the blood-brain barrier, but they can also affect the barrier resulting in a leaky BBB.

There are several avenues and opportunities for introducing exosomes into autism research. It seems reasonable that exosomes should initially be used to confirm and extend findings already established by other means. Existing banks of stored brain tissue and bodily fluids from controls and individuals with autism should be able to provide abundant sources of exosomes for such studies. Interested researchers can read the references below and do their own web searches for methodological details. It is critically important that any initial research using exosomes be carried out using data that has been properly truthed. Once the effectiveness of exosome-based research has been established, then we can turn to their diagnostic and therapeutic uses.

Suggested further readings are listed below. There are many other articles on the net that delve more deeply into the biology of EVs and their functions.

- "The biology and function of exosomes in cancer," R. Kalluri, *J Clin Invest.* 2016; 126(4):1208-1215, https://doi.org/10.1172/JCI81135. This review article provides an overview of exosomes, and then gets more specific about how the many roles that exosomes play can be used to detect cancers and to understand the biogenesis and microenvironments of tumors, and can perhaps be used in chemotherapy and immunotherapy.
- "The emerging role of exosomes in mental disorders," S. Saeedi et al., *Translational Psychiatry* (2019) 9:122, https://doi.org/10.1038/s41398-019-0459-9. This review article describes the state of the art in our knowledge of how exosomes are involved, in many ways, in synaptic plasticity, neuronal stress response, neuroinflammation, cell-to-cell communication, and neurogenesis. It describes, with excellent graphics, the many implications of exosomes being able to freely cross the blood-brain barrier. Much of what this article discusses applies to autism as well as the disorders addressed in the paper.
- "Differential expression of exosomal microRNAs in prefrontal cortices of schizophrenia and bipolar disorder patients," M.G. Banigan et al., (2013). *PLoS ONE* 8(1): e48814. doi:10.1371/journal.pone.0048814. This article describes in great detail the process of extracting exosomes from stored brain tissue and their role in distinguishing controls from schizophrenia or bipolar disorder.
- "Extracellular vesicles are increased in the serum of children with autism spectrum disorder, contain mitochondrial DNA, and stimulate human microglia to secrete IL-1β," I. Tsilioni and T. Theoharides *Journal of Neuroinflammation* (2018) 15:239 https://doi.org/10.1186/s12974-018-1275-5. This article, referred to above, provides an excellent example of an experimental design using exosomes in autism research.
- "Stem cell-derived exosomes in autism spectrum disorder," N. Alessio et al, *Int J Environ Res Public Health*, http://dx.doi.org/10.3390/ijerph17030944. To quote from the abstract, "This review article describes the potential role of exosomes in alleviating ASD symptoms." It claims, "Neuroinflammation and neuro-immune cross-talk are specific hallmarks of ASD." Like other papers that examine the role of exosomes in all aspects of autism, this one is long on prediction and short on data. Nonetheless, it provides some useful biological information and some references that might be worth following.

# Research Updates

## Symptoms are similar in young boys, girls with ASD

Research indicates that in school-aged children, teenagers, and adults with autism spectrum (ASD), symptoms differ significantly between males and females. Because of this, there are concerns that the skewed male-to-female ratio of individuals diagnosed with ASD may be due in part to a failure to diagnose females. However, a new study concludes that any differences between the sexes are not evident early in life, when autism is typically diagnosed.

Lisa Wiggins and colleagues identified 1,480 children between two and five years of age who were classified as having ASD, as well as 593 with subthreshold characteristics of ASD. Looking at the children's behavior problems, developmental abilities, performance on screening and diagnostic tests for ASD, and parental reports, they found no significant difference between girls and boys. "Males in both study groups had more parent reported restricted interests and repetitive behaviors than females," they say, "but these differences were small in magnitude and not clinically meaningful."

They conclude, "Preschool males and females who showed risk for ASD were more similar than different in the outcomes assessed in our study."

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"Evaluation of sex differences in preschool children with and without autism spectrum disorder enrolled in the study to explore early development," Lisa D. Wiggins, Eric Rubenstein, Gayle Windham, Brian Barger, Lisa Croen, Nicole Dowling, Ellen Giarelli, Susan Levy, Eric Moody, Gnakub Soke, Victoria Fields, and Laura Schieve, *Research in Developmental Disabilities*, Vol.112, May 2021 (online). Address: Lisa Wiggins, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway NE S106-4, Atlanta, GA 30341, lwiggins@cdc.gov.

## Observers may incorrectly rate people with ASD as being less truthful

Adults with autism spectrum disorders (ASD) may be incorrectly perceived by other people as being deceptive and lacking credibility, according to a new study.

Alliyza Lim and colleagues asked 30 individuals with ASD and 29 neurotypical individuals to participate in video-recorded interviews and measured their levels of five behaviors related to autism: gaze aversion, repetitive body movements, literal interpretation of figurative language, poor reciprocity, and flat affect. The researchers then asked 1,410 people to each view one video and rate their perception of the individual's credibility and truthfulness.

The researchers say that while individual behaviors associated with autism did not directly contribute to a person being judged as lacking credibility or being untruthful, people with autism overall were rated as less reliable than their neurotypical peers.

Study coauthor Robyn Young says, "It's unfortunate that many of the behaviors that are believed to be portrayed by people who are being deceptive, often erroneously, are also commonly seen among people on the autism spectrum." The study's authors say this can disadvantage an individual with ASD who interacts with the criminal justice system, noting that their findings are consistent with statistics suggesting that people with ASD tend to receive higher sentences than non-autistic individuals who commit similar offenses. In addition, they say, it may make it more difficult for individuals with ASD to successfully interview for jobs.

The researchers also note that in this study, individuals with ASD were rated as less deceptive and of higher character when observers were given information about their ASD diagnosis. "This suggests," they say, "that appropriate disclosure of an ASD diagnosis, in conjunction with relevant education on autistic behaviors, may be an effective way to reduce the negative bias toward people on the autism spectrum."

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"Autistic adults may be erroneously perceived as deceptive and lacking credibility," Alliyza Lim, Robyn L. Young, and Neil Brewer, *Journal of Autism and Developmental Disorders*, March 17, 2021 (free online). Address: Alliyza Lim, alliyza.lim@flinders.edu.au.

—and—

"Poor judgment of autistic adults," news release, Flinders University, April 1, 2021.

## Study offers insights into large head size in ASD

Severe forms of autism spectrum disorder (ASD) are often associated with large head size, and many individuals with ASD and a large head size have a deletion in a small piece of chromosome 16 known as 16p11.2. (See related article on page 6). A new study casts light on the association of this chromosome deletion with ASD and enlarged head size.

Jingling Li and colleagues studied two types of neural stem cells—neural progenitor cells and oligodendrocyte progenitor cells—derived from individuals with the 16p11.2 deletion and control subjects. The researchers found that CD47, a protein that signals "don't eat me," was overexpressed in both types of cells from people with 16p11.2 deletion syndrome. As a result, unhealthy cells were eliminated at lower rates by the immune system.

The researchers also found that the neural cells of people with 16p11.2 duplication syndrome exhibited increased cell surface expression of calreticulin, an "eat me" signal. However, this signal appears to be overridden by the high levels of CD47.

The researchers discovered that blocking CD47 restored the normal elimination of unhealthy neural cells. They conclude, "These findings suggest that targeting the CD47 pathway may be helpful in identifying treatments for psychiatric disorders associated with brain overgrowth."

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"Overexpression of CD47 is associated with brain overgrowth and 16p11.2 deletion syndrome," Jingling Li, Thomas Brickler, Allison Banuelos, Kristopher Marjon, Anna Shcherbina, Sravani Banerjee, Jing Bian, Cyndhavi Narayanan, Irving L. Weissman, and Sundari Chetty, *Proceedings of the National Academy of Sciences*, April 2021 (free online). Address: Sundari Chetty, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, chettys@stanford.edu.

**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.

# Research Updates

## Insulin resistance studied in children, teens with ASD

Some abnormalities seen in autism spectrum disorder (ASD) may be caused by insulin resistance affecting the brain and central nervous system, according to a new study from Italy.

Melania Manco and colleagues note that a number of metabolic anomalies are associated with ASD—for instance, low-grade inflammation, enhanced oxidative damage, low levels of carnitine, high levels of lactate, and high levels of branched-chain amino acids (which are toxic to the central nervous system in excess). The researchers speculate that these abnormalities may be associated with reduced glucose metabolism at the level of the central nervous system, caused by insulin resistance. Insulin resistance occurs when cells do not respond correctly to insulin, a hormone that ferries glucose into the cells, and as a result cannot obtain sufficient glucose for energy.

The researchers used a test called HOMA-IR to investigate insulin resistance in 60 individuals with ASD between 4 and 18 years of age, comparing them to 240 controls. All of the individuals with ASD were newly diagnosed and had no exposure to psychiatric medications, which can worsen insulin resistance. The researchers note that the HOMA-IR test, in addition to measuring peripheral insulin resistance (for instance, insulin resistance in the muscles), provides an estimate of insulin resistance in the brain.

When the researchers adjusted for sex, age, body mass index, and lipids that are known to influence HOMA-IR, they found that HOMA-IR scores were significantly higher in individuals with ASD.

In addition, they note, 47% of individuals with ASD exhibited elevated levels of branched-chain amino acids, low levels of acetyl carnitine, high levels of lactate, or other metabolic abnormalities. HOMA-IR correlated significantly with levels of BCAAs.

The researchers say the high levels of lactate and low levels of acetyl carnitine seen in individuals with ASD are consistent with dysfunctional activity of the mitochondria (which are the "power plants" of cells). Mitochondrial defects are a common finding in ASD, and the researchers say their findings suggest that brain insulin resistance may impair mitochondrial functioning.

They conclude, "Our study must be intended as [a] provocative attempt at investigating autism as [a] 'metabolic' condition in which IR is in some patients the marker of more profound metabolic disturbances that deserve investigation toward a more personalized medicine approach."

The researchers caution that their study sample was small and that HOMA-IR is a less accurate measure of insulin resistance than "gold standard" measures such as an intravenous glucose tolerance test. Thus, they say, "Findings of this preliminary study suggest it is worth investigating brain glucose metabolism in [a] larger population of patients with ASD by using gold standard technique."

They conclude, "The recognition of a reduced glucose metabolism in some areas of the brain as a marker of autism might have tremendous impact on our understanding of the pathogenic mechanisms of the disease and in terms of public health." They also note that a number of interventions that benefit neurotypical individuals with insulin resistance—for instance, dietary interventions, exercise, and drugs such as metformin—might prove to be beneficial for individuals with ASD and insulin resistance.

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"Cross-sectional investigation of insulin resistance in youths with autism spectrum disorder. Any role for reduced brain glucose metabolism?", Melania Manco, Silvia Guerrera, Lucilla Ravà, Marta Ciofi degli Atti, Silvia Di Vara, Giovanni Valeri, and Stefano Vicari, *Translational Psychiatry*, 2021 (free online). Address: Melania Manco, Research Area for Multifactorial Diseases and Complex Phenotypes, Bambino Gesù, Children's Hospital, IRCCS, Rome, Italy, melania.manco@opbg.net.

## Lifestyle issues play role in shorter life expectancy

Individuals with autism spectrum disorders (ASD) have a shorter life expectancy than people in the general population, and a new study suggests that lifestyle issues play a large role in shortening their lifespans.

Elizabeth Weir and colleagues collected data from 1,183 adults with ASD and 1,203 individuals without ASD who completed an anonymous online survey asking about their lifestyle, daily habits, personal medical history, and family medical history. The researchers found that the individuals with ASD were less likely than other participants to meet even minimal recommendations for diet, exercise, and sleep. They also were more likely to have atypical eating patterns and sleep disturbances, and to be underweight or obese. The researchers note that for males with ASD, lifestyle factors had a greater impact on the risk of cardiovascular disease than family history.

Simon Baron-Cohen, a coauthor of the study, says, "The wider picture suggests that autistic adults experience vulnerability in a variety of contexts, and this is just one new area that we should consider. Seeing that autistic adults are having such a hard time comparatively with healthy lifestyle habits has clear healthcare and policy implications: We need to create new and better support systems tailored to the specific needs of autistic people."

The researchers note that their study results may not be generalizable to all individuals with ASD, as all respondents had access to the internet and only 2% of respondents had developmental or intellectual disabilities. In addition, the sample was heavily weighted toward individuals who were white and female.

However, they conclude, "Although the present study can only provide preliminary, correlational evidence, our findings suggest that diet, exercise, and sleep should be considered and further investigated as key targets for reducing the now widely reported and dramatically increased risks of health comorbidity and premature death among autistic individuals compared to others."

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"An investigation of the diet, exercise, sleep, BMI, and health outcomes of autistic adults," Elizabeth Weir, Carrie Allison, Ken K. Ong, and Simon Baron-Cohen, *Molecular Autism*, May 2021 (free online). Address: Elizabeth Weir, Autism Research Centre, Department of Psychiatry, University of Cambridge, Douglas House, 188 Trumpington Road, Cambridge, England CB2 8AH, emw60@medschl.cam.ac.uk.

—and—

"Diet, exercise and sleep linked to high risk of cardiovascular disease in autistic people," news release, University of Cambridge, May 10, 2021.

### Participants needed for ASD microbiome study

Researchers at Massachusetts General Hospital, Harvard Medical School, and the Autism Research Institute are investigating whether the reason why boys are more affected than girls is related to differences in intestinal bacteria.

We are seeking families to participate in this study who have boy and girl siblings with autism. These families will be mailed stool kits with instructions and will be asked to collect samples. A brief medical history will be taken.

For additional information and enrollment details, please contact Harland Winter, MD by phone, 617-724-2004, or by email at GenderDimorphism@autism.org.

## Time-release melatonin effective in improving sleep in children with ASD, does not alter puberty

A new study, in addition to adding to evidence that time-release melatonin may improve sleep in individuals with autism, indicates that administering the hormone does not have any adverse effect on development during puberty.

An earlier double-blind, placebo-controlled study by Paul Gringras and colleagues (see ARRI 2018, Volume 2) involved 119 children between 2 and 17 years of age. The children's parents first received instruction on behavioral interventions to improve their children's sleep. Children who did not respond to these interventions then received prolonged-release melatonin, in doses beginning at 2 mg per day and increasing to 5 mg if needed, for 13 weeks. At the end of the study, the researchers reported, 68.9% of children taking melatonin slept better, compared to only 39.3% of children taking the placebo.

Malow and colleagues say they detected no effects on puberty in children taking extended-release melatonin for two years.

In the new study by Gringras and colleagues (including lead author Beth Malow), 80 children from the original study continued to take time-release melatonin for an additional 91 weeks, for a total of two years. Dosages were increased as needed, up to 10 mg.

The researchers report, "Improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep, and quality of life were maintained throughout the 104-week treatment period." Moreover, while concerns have been raised about the possible effects of supplemental melatonin on puberty (because melatonin levels typically drop during puberty), the researchers say, "Changes in mean weight, height, body mass index, and pubertal status… were within normal ranges for age with no evidence of delay in body mass index or pubertal development." Adverse effects, including sleepiness, fatigue, and mood swings, were few and generally mild, and no withdrawal symptoms were seen during a two-week washout period.

The researchers conclude, "Nightly doses [of time-release melatonin] at optimal dose (2, 5, or 10 mg nightly) is safe and effective for long-term treatment in children and adolescents with autism spectrum disorder and insomnia." They caution, however, that unlike their original study, this study was open label, with no children receiving a placebo.

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"Sleep, growth, and puberty after 2 years of prolonged-release melatonin in children with autism spectrum disorder," Beth A. Malow, Robert L. Findling, Carmen M. Schroder, Athanasios Maras, John Breddy, Tali Nir, Nava Zisapel, and Paul Gringras, *Journal of the American Academy of Child & Adolescent Psychiatry*, Vol. 60, No. 2, February 2021, 252-261. Address: Beth Malow, Sleep Division, Department of Neurology, Vanderbilt University Medical Center, 1161 21st Avenue South, Room A-0116, Nashville, TN 37232, beth.malow@vumc.org.

**Need help or information?**

The Autism Research Institute maintains a toll-free calling center:

**833-281-7165**

## Study offers insights into motor delays in children with ASD

Children with autism spectrum disorders (ASD) exhibit delays in learning motor skills, and a new study points to one possible cause of this problem.

Xuming Yin and colleagues studied mice missing one copy of a chromosome region called 16p11.2. This deletion is also seen in many individuals with autism. (See related article on page 4.)

The researchers put normal mice and mice with the 16p11.2 deletion through two tests of motor learning. In one, the mice had to balance on the top of a rotating rod. In the other, they had to spin a disk with their feet.

The researchers found that both groups of mice eventually mastered the tasks, but it took the 16p11.2 mice significantly longer.

Chen and colleagues found that in mice with the 16p11.2 deletion, significantly less noradrenaline was released into the primary motor cortex during learning.

In addition, they found that in mice with the deletion, reduced amounts of the neurotransmitter noradrenaline were released into the primary motor cortex of the brain during learning.

The researchers determined that the deficit in noradrenaline originated in a separate region of the brain called the locus coeruleus. Examining the brains of the mice, they found that compared to control mice, the 16p11.2 mice had fewer axons extending from the locus coeruleus into the motor cortex.

Senior study author Simon Chen says, "The locus coeruleus is the area in the brain that releases noradrenaline—or adrenaline—which makes you more alert. In the mouse model of autism, we found that in the motor cortex there is a lack of adrenaline's innervation to the area which caused them to have delayed motor learning."

Chen says, "The implication is similar for kids with autism. They normally behave the same whether reaching to grab something or playing ball or catch—they learn at a slower pace compared to kids of the same age, which could cause them to feel more distant and perhaps prefer not to play with them."

He adds, "With autistic kids, we sometimes think that an aspect of this delayed motor learning is a result of social deficits and dysfunction: that they simply don't want to play with the other kids. But it might be because they're learning how to play these games slower than the other kids, which is why they're distancing themselves from them."

The researchers also found that neurons in the motor cortex of the 16p11.2 mice were more active during the initial stages of learning, and that there was a delay in removing unnecessary synapses in the motor cortex while forming new ones. Chen says, "When you are not removing the unnecessary synapses (old memories) you have higher noise, and we think the brain doesn't know what signal to process because of its delay of removing the unnecessary synapses."

He adds, "Think of it as you and I go play golf and we hit the ball many times. With a good signal-to-noise ratio in the brain, I will remember the movement when I hit the ball far. But if I have high noise and low signal-to-noise ratio, I'll hit the ball many times without knowing which movement is good for me, meaning it will take me longer to differentiate what's the right movement for a good golf swing."

The researchers also found that boosting noradrenaline in the motor cortex successfully reestablished motor learning in the mice. This finding, Chen suggests, could possibly lead someday to treatments to help children with ASD learn motor skills more easily.

—

"Delayed motor learning in a 16p11.2 deletion mouse model of autism is rescued by locus coeruleus activation," Xuming Yin, Nathaniel Jones, Jungwoo Yang, Nabil Asraoui, Marie-Eve Mathieu, Liwen Cai, and Simon X. Chen, *Nature Neuroscience*, March 22, 2021 (online). Address: Simon Chen, schen2@uottawa.ca.

—and—

"Researchers close in on root of slow motor learning in autism," news release, University of Ottawa, March 22, 2021.

—and—

"Circuit flaw underlies motor learning issues in autism mouse model," Peter Hess, Spectrum News, April 12, 2021.

## TV, videos affect language skills in young kids with ASD

A new study raises concerns about the effects of extensive television and video watching on the development of receptive language in children with autism spectrum disorders (ASD).

The study, by Elisabeth Fridberg and colleagues, collected data on the development of 3,227 two- to five-year-old children with ASD. The researchers asked parents to assess the children's development quarterly for three years.

Using this data, the researchers assessed both expressive and receptive language. Expressive language involved such skills as using one or two words at a time or carrying on a conversation. Receptive language, in contrast, was defined as "complex language that uses modifiers, spatial prepositions, and fictitious situations, which require visuospatial mental integration rather than memorization." (As an example, they cite the ability to understand the meanings of the phrases "cat on a mat," "mat on a cat," and "big black cat on a tiny wet mat.") This ability to combine and recombine novel mental images at will is called *prefrontal synthesis*, or PFS.

The researchers report, "Longer video and television watching were associated with better development of expressive language but significantly impeded development of complex language comprehension." On an annual basis, they say, "low TV users [40 min or less of videos and television per day] improved their language comprehension 1.4 times faster than high TV users [2 hours or more of videos and television per day]." At the same time, they note, "high TV users improved their expressive language 1.3 times faster than low TV users." However, they say, the difference in expressive language between the two groups was not statistically significant.

Comparing the development of PFS to the development of motor skills, the researchers say, "Just like it is impossible to acquire muscle control from the passive watching of sports programs, it is equally impossible to develop PFS from the passive watching of cartoons and fairytales." Much as children need to be physically active to develop motor control skills, the researchers say, they need to actively develop PFS through such activities as conversations and storytelling.

They conclude, "The results of this study complement existing evidence in neurotypical children: Passive video and television watching does not develop PFS. Critically, passive video and television watching may be particularly detrimental for young children with ASD who may have a shorter critical period for PFS acquisition."

—

"Watching videos and television is related to a lower development of complex language comprehension in young children with autism," Elisabeth Fridberg, Edward Khokhlovich, and Andrey Vyshedskiy, *Healthcare*, 2021 (free online). Address: Andrey Vyshedskiy, Biology Department, Boston University, Boston, MA 02215, vysha@bu.edu.

## Free Autism Continuing Education and Webinars

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

**—September 8, 2021—**
1 p.m. Eastern Time (U.S.)
**PANS AND AUTISM—2021 UPDATES**
Jennifer Frankovich, MD

**—October 6, 2021—**
1 p.m. Eastern Time (U.S.)
**ABCs OF ABA IN 2021**
Missy Olive, PhD, BCBA-D

**—October 20, 2021—**
1 p.m. Eastern Time (U.S.)
**BULLYING AND ASD: ADDRESSING VICTIMIZATION**
Ryan E. Adams, PhD

Space is limited—watch your email or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars at https://www.autism.com/webinars.

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## New animal research offers insights into the effects of the microbiome on social deficits in ASD

**(continued from page 1)**

Mattioli notes that *L. reuteri* is already being tested in Italy as a treatment for children with autism, and he plans to conduct a trial himself.

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"Dissecting the contribution of host genetics and the microbiome in complex behaviors," Shelly A. Buffington, Sean W. Dooling, Martina Sgritta, Cecilia Noecker, Oscar D. Murillo, Daniel F. Felice, Peter J. Turnbaugh, and Mauro Costa-Mattioli, *Cell Press*, Volume 184, Issue 7, P1740-P1756, April 1, 2021. Address: Mauro Costa-Mattioli, Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX 77030, costamat@bcm.edu.

—and—

"Microbes may hold the key for treating neurological disorders," news release, Baylor College of Medicine, March 10, 2021.

—and—

"Bugs R Us: Restoring sociability with microbiota in autism," Camilla Bellone and Christian Lüscher, *Cell Press*, April 20, 2021 (free online). Address: Camilla Bellone, camilla.bellone@unige.ch.

—and—

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

—and—

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

—and—

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

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

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, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population's quality-of-life issues.

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•

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•

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