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

Transcranial magnetic stimulation may improve symptoms in autism spectrum disorder

Repetitive transcranial magnetic stimulation (rTMS) may improve symptoms of autism, according to studies conducted by two separate groups of researchers. rTMS, a noninvasive procedure, involves creating magnetic pulses over the scalp via a magnetic coil.

The first group of researchers, headed by Manuel Casanova, used rTMS to treat individuals younger than 18 years of age who were diagnosed with autism spectrum disorders (ASD). The researchers note, "Recent evidence suggests the symptoms of autism spectrum disorder may be related to an increased ratio of cortical excitation to inhibition." Treatment with low-frequency rTMS has been shown to increase cortical inhibition by activating inhibitory circuits.

The study involved approximately 200 individuals who received rTMS. The researchers measured the participants' symptoms using neuropsychological questionnaires administered before and after rTMS. Using electroencephalographic (EEG) and event-related potential (ERP) tests, they also assessed participants' selective attention and executive function skills. (Selective attention is the ability to focus on something without being distracted, while executive function is a term for skills including planning, impulse inhibition, and cognitive flexibility.)

The researchers report, "Our preliminary findings in experimental studies using 6-, 12-, or 18-session long, low frequency rTMS in children with ASD indicate significant improvement in EEG and ERP measures of selective attention and executive functioning, and also showed significant improvement in measures of irritability and repetitive/stereotyped behavior."

They conclude, "rTMS has the potential to become an important therapeutic tool in research and treatment and may play an important role in improving the quality of life for many individuals with ASD."

In separate research, Peter Enticott and colleagues treated adults with ASD using high-frequency rTMS to stimulate the dorsomedial prefrontal cortex. The first of two studies they conducted involved 28 individuals with ASD who received either active or sham deep rTMS each weekday for two weeks. The second study was an open label study in which 20 individuals with ASD received 16 active treatments over four weeks.

The researchers assessed the results in both studies using clinical and cognitive tests, and performed positron emission tomography (PET) scans on participants in the second study to assess brain glucose metabolism before and after treatment. They report that in the first study, participants in the active condition, but not those in the sham condition, reported a significant decrease in social impairment. Participants in the second trial also reported a decrease in social impairment, and PET scans showed evidence of enhanced glucose metabolism.

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"Transcranial magnetic stimulation treatment: Focusing on core pathological features of autism spectrum disorders," Manuel F. Casanova, presentation to the May 2016 International Meeting for Autism Research (IMFAR).

—and—

"Clinical trials of deep repetitive transcranial magnetic stimulation (rTMS) to bilateral dorsomedial prefrontal cortex in autism spectrum disorder," Peter Enticott, presentation to the May 2016 International Meeting for Autism Research (IMFAR).

—and—

"Repetitive TMS may help core features of autism," Pam Harrison, *Medscape*, May 18, 2016.

Intensive job training, internships prove highly successful

Intensive on-the-job training for high school-aged students with ASD (autism spectrum disorders) can lead to high employment rates, a new study reports.

Between 2009 and 2012, Paul Wehman and colleagues enrolled 54 individuals with ASD into a program called Project SEARCH plus Autism Spectrum Disorder Supports (PS-ASD). This program is a modification of Project SEARCH, a job training program for individuals with developmental disabilities. In addition to the basic Project SEARCH protocol, PS-ASD incorporates applied behavioral analysis and more intensive social communication skills training.

Participants, 49 of whom completed the program, were between the ages of 18 and 21. Thirty-one of them participated in PS-ASD rather than attending high school, while the remainder served as controls and continued to attend school.

The PS-ASD program is an intensive nine-month program that involves embedding participants in job settings. Participants rotate through three 10- to 12-week internships, accumulating around 720 hours of experience. In addition, they participate in 180 hours of classroom activity on site. A number of agencies collaborate to help participants find jobs when they complete the program.

During their internships, participants received supported employment services, working with job coaches who helped them determine their goals, prepare for interviews, and train on the job. Coaches also provided long-term support, which was phased out over time.

The researchers report that 87% of PS-ASD participants were competitively employed 12 months after graduation, compared to 12% of controls. In addition, PS-ASD participants worked longer hours over time, indicating that their employers appreciated their value. The researchers add, "Possibly the most exciting part of these findings is that each year students became increasingly independent at work. They required less help and less support."

The researchers say that the internships were a major key to participants' success. "These intensive internships," they say, "essentially acted as the vocational training equivalent of intensive early intervention," allowing participants to repeatedly practice critical work skills.

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"Effects of an employer-based intervention on employment outcomes for youth with significant support needs due to autism," Paul Wehman, Carol M. Schall, Jennifer McDonough, Carolyn Graham, Valerie Brooke, J. Erin Riehle, Alissa Brooke, Whitney Ham, Stephanie Lau, Jaclyn Allen, and Lauren Avellone, *Autism*, May 5, 2016 (epub prior to print publication). Address: Carol M. Schall, School of Education, Virginia Commonwealth University, Box 842011, Richmond, VA 23284-2011, cmschall@vcu.edu.

High maternal folate, B_{12} linked to increased autism risk—but supplements reduce risk

Very high plasma levels of maternal folate and vitamin B_{12} are associated with an increased risk for autism in children, a new study suggests.

Ramkripa Raghavan and colleagues analyzed data from 1,391 mother-child pairs participating in an ongoing study, focusing on the mothers' maternal plasma biomarkers of folate and vitamin B_{12} measured 24-72 hours after delivery. (The researchers were not able to determine whether these levels correlated with dietary supplementation.)

Study coauthor Daniele Fallin says, "When we looked at the vitamin supplementation evidence, we saw what our colleagues see—that indeed, women who took vitamin supplementation during pregnancy had a lower risk of autism in their children and that is very consistent with the literature." Maternal multivitamin supplementation three to five times per week was associated with significantly lower risk of autism spectrum disorders (ASD) in offspring across all trimesters.

However, Fallin says, "When we looked at women who had excessively high levels of folate, we saw that very high levels of folate in the mother were responsible for about a twofold increased risk for autism in their child, and when we looked at B_{12}, women who had excessively high levels of B_{12} had a threefold increased risk for their child to have autism, while women who had extreme levels of both folate and vitamin B_{12} had a 17.6 times greater risk of having their child diagnosed with an ASD later on."

She concludes that for now, "the public health message is, supplementation is good, but there may be a subset of women whose levels are extremely high, and these extreme levels may be harmful."

Fallin also notes that blood levels of folate are not just a function of supplement intake. "They are also a function of diet," she says, "and a genetic makeup that can change dramatically how easily a person retains or clears folate."

Editor's note: See related article below.

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"Maternal plasma folate, vitamin B_{12} levels and multivitamin supplement during pregnancy and risk of autism spectrum disorders in the Boston Birth Cohort," R. Raghavan, A. Riley, D. M. Caruso, X. Hong, G. Wang, B. Ajao, J. Zhang, Y. Ji, M. Li, H. He, Z. Chen, M. C. Wang, C. Pearson, L. K. Hironaka, L. Sices, M. D. Fallin, and X. Wang. Dr. Raghavan and colleagues presented their findings at the 2016 International Meeting for Autism Research (IMFAR) in May 2016.

—and—

"Excessive folate, B_{12} in pregnancy dramatically ups autism risk," Pam Harrison, M*edscape Multispecialty*, May 12, 2016.

Editor's note: *ARRI asked researcher Richard Deth, Professor of Pharmaceutical Sciences at Nova Southeastern University in Fort Lauderdale, Florida, to comment on these findings. Here is his reply:*

"At first glance these findings seem contradictory, with consumption of a multivitamin decreasing ASD risk while elevated folate and vitamin B12 increases the risk. However, the study did not establish that the women with very elevated folate and B12 levels were taking multivitamins, so these are two separate issues.

"Interpretation of the increased ASD rates with very high maternal folate and B12 levels is challenging. High maternal plasma levels do not necessarily mean that the developing fetus was exposed to the high levels since transport across the placenta intervenes. Moreover, high maternal levels might indicate a problem with the folate and B12 transport systems of genetic origin that translates into higher ASD rates in offspring. Dr. Jill James and colleagues previously demonstrated that antioxidant and methylation pathway metabolites are abnormally skewed in mothers of ASD children, so it may not be surprising that folate and B12 levels are abnormal as well. Indeed, the well-recognized genetic influence in ASD may reside within methylation, transsulfuration and glutathione synthesis pathways.

"This scientific meeting presentation was only preliminary and further details may become available when the work is published in a peer-reviewed journal."

Maternal streptococcal infection may play role in autism spectrum disorder

A common bacterium may play an important role in the genesis of autism, a new study suggests.

Marie-Julie Allard and colleagues note that Group B Streptococcus (GBS), a bacterium found in the lower genital tract of 15% to 30% of healthy pregnant women, is the leading cause of chorioamnionitis (an infection of the fetal membranes) and cerebral injuries in newborns. However, they say, little is known about the effect of maternal GBS exposure on children's brain development. The researchers hypothesized that maternal infection and inflammation due to GBS may negatively impact the neurodevelopment of uninfected offspring.

Studying rats, Allard and colleagues found that GBS-exposed placentas exhibited chorioamnionitis, with more prominent abnormalities in male offspring. GBS-exposed male offspring also exhibited reduced thickness of periventricular white matter. "In addition," the researchers say, "they exhibited autistic-like behaviors, such as abnormal social interaction and communication, impaired processing of sensory information, and hyperactivity."

The researchers conclude, "Overall, these data show for the first time that gestational exposure to GBS plays an important role in the generation of neurodevelopmental abnormalities reminiscent of human autism spectrum disorders."

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"A sexually dichotomous, autistic-like phenotype is induced by Group B Streptococcus maternofetal immune activation," M. J. Allard, J. D. Bergeron, M. Baharnoori, L. K. Srivastava, L. C. Fortier, C. Poyart, and G. Sébire, *Autism Research*, May 25, 2016 (epub prior to print publication). Address: Guillaume Sébire, Research Institute of the McGill University Health Centre, 1001-Decarie Boulevard, Glen Site, Block E, M0.3211, Montreal, QC H4A 3J1, Canada, guillaume.sebire@mcgill.ca.

Injected methyl B_{12} may improve symptoms of autism

Injections of vitamin B_{12} may benefit children with autism, a new study reports.

In a double-blind study, Robert Hendren and colleagues randomly assigned 57 children with autism spectrum disorders (ASD) to receive injections of methyl B_{12} (75 µg per kilogram) or saline placebo every three days for eight weeks. Before and after treatment, they measured the children's scores on the Clinical Global Impressions-Improvement (CGI-I) Scale, the Aberrant Behavior Checklist (ABC), and the Social Responsiveness Scale (SRS).

Fifty children completed the study. The researchers report, "The primary outcome measure—the clinician rated CGI-I score—was statistically significantly better (lower) in the methyl B_{12} group than in the placebo group." This scale measures overall autism severity. However, the children's scores on the ABC and SRS, which measure changes in specific autism symptoms, did not change. Improvement occurred primarily in children who exhibited blood changes indicating an improvement in cellular methylation capacity.

"Although these findings are preliminary," the researchers say, "this is an exciting finding that suggests that treating a known metabolic abnormality—impaired methylation capacity—holds the potential to improve [autism] symptoms."

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"Randomized, placebo-controlled trial of methyl B_{12} for children with autism," Robert L. Hendren, S. Jill James, Felicia Widjaja, Brittany Lawton, Abram Rosenblatt, and Stephen Bent, *Journal of Child and Adolescent Psychopharmacology*, February 18, 2016. Address: Stephen Bent, Stephen.Bent@ucsf.edu.

—and—

"Small study finds B_{12} injections ease autism symptoms in some children," Autism Speaks Science News, March 23, 2016.

GUEST EDITORIAL:

Autism, water, and constipation

Kelly M. Barnhill, MBA, CN, CCN, The Johnson Center for Child Health and Development, Austin, Texas
and
Harland Winter, M.D., Harvard Medical School, MassGeneral Hospital for Children, Boston, Massachusetts

The parents of most children we serve within our clinic report that their children have some gastrointestinal symptoms and concerns. The most common issues that parents raise are constipation, diarrhea, abdominal distention, and pain. Parents also note several behaviors that may or may not be related to gastrointestinal health, including self-injurious behaviors (slapping or hitting the chest, for example), posturing (such as bending over an arm chair or table edge), and hyperactivity prior to a bowel movement. These behaviors should trigger concerns about an underlying gastrointestinal problem. To address the patient's overall health status and assess the impact of nutritional status, a full evaluation is essential. Much attention is given to nutrient intake—protein, fat, carbohydrate—but other components of the diet are also relevant.

One of the most underestimated and misunderstood (and easiest to remedy, frankly) deficits in our children's (and our own) diets is water and fluid intake. Water accounts for almost 60% of body weight in children (over 75% in infants less than one year of age), and comprises 77-78% of brain volume (McIlwain and Bachelard, 1985). Simply put, water is foundational nutrition and we need to take adequate intake seriously. Bodily functions rely on water, and being well hydrated is essential for overall health. Water helps maintain constant body temperature and maintains appropriate blood volume. Water carries nutrients (and oxygen) to cells and also removes waste products. We have two organs in our bodies that are designed to preserve water. The kidneys pull water from the urine that is filtered from the blood and return it to the circulation. The colon's main role is to reabsorb water. If we are dehydrated, colonic motility slows down so that more water can be absorbed. This results in not only a decreased number of bowel movements, but also stools that are harder, more dense, and drier. For many children with constipation, merely increasing their intake of water significantly helps the problem.

The first question at hand is just how much water is recommended or required for pediatric patients. While we have solid information on most nutrients, recommendations for water intake are lacking. Research is limited and the few formal guidelines for pediatric water intake can provide conflicting information. A 2015 study by researchers at Harvard University (Kenney et al., 2015) indicates that the majority of school-age children in the United States were dehydrated to some extent. Also compounding the issue of assessing both the need for water and hydration status is the body's ability to adapt to a variety of hydration levels—so we can and do adjust to a dehydrated state and still manage to function. But there are consequences to constant dehydration. Research indicates that constipation and cognitive function are two key impacts of this chronic state (Arnaud, 2003; Bar-David, Y, 2005; Fadda R et al., 2008; Gisolfi and Lamb, 1989; Manz & Wentz, 2005; Popkin et al., 2010; Schroeder et al., 2002; Young et al., 1998). For pediatric patients in particular, the data support the belief that dehydration may impact mood, focus, attention, ability to learn, and fatigue levels.

The Institute of Medicine (IOM) of the National Academy of Science issued Dietary Reference Intakes (DRIs) for the U.S. population in 2005. These recommendations are based on water intake assessments alone, and they did not include any assessment for hydration status. This is largely because we have no accepted research or clinical measurements for accurately determining hydration status. DRIs for water intake range from 1.7 to 3.3 liters of water daily for children 4-18. Children living in hot or dry environments (such as in the winter), or children who exercise and lose water by sweating, may require much more water. Specific intake recommendations based on age, size, and sex can be found below.

DRI Water Intake for Children

Age/ Gender	Intake in Liters/day	Intake in Cups/Day
4-8 years, male and female	1.7 L/day	7.2 c/day
9-13 years, male	2.4 L/day	10 c/day
9-13 years, female	2.1 L/day	9 c/day
14-18 years, male	3.3 L/day	14 c/day
14-18 years, female	2.3 L/day	9.75 c/day

Source: *Institute of Medicine of the National Academy of Science. Dietary Reference Intakes (DRIs) Tables. Recommended Daily Allowance and Adequate Intake Values: Total Water and Macronutrients. 2005.*

Most families are shocked by the volume of water intake recommended each day, and many indicate that their children consume much lower amounts. To put this in perspective, over 40% of Americans do not consume adequate water, and over 25% of US children consume no water whatsoever! (Drewnowski et al., 2013). While it is true that water content of foods also contributes to total daily intake, our experience is that the children we serve eat few high water content foods such as fruits and vegetables, so intake from those sources is negligible as well.

In our clinic, we recommend 1 ounce of water per pound of body weight per day. This is an easy calculation for most parents, and equates roughly to the overall DRI recommendations published by the IOM. Some clinicians encourage 6-8 glasses (cups) of water each day for children up to adolescence, and then make additional recommendations based on age, size, and activity level.

The next question we face is how to get a child to consume more water. Two basic answers: Make it available and make it appealing. Water has a lot of competition from juices and sodas and other sweet drinks, so de-emphasizing (or eliminating) those attractive nuisances is a good step in the correct direction.

These are the suggestions we share with our clients on a daily basis:

First and foremost, don't keep things in your home that you don't want your children to drink.

Teach water consumption from a behavioral perspective as you remove the juice and soda or other preferred beverages.

Make water available to your children at all times. Place a glass or bottle of water next to the bed every night. Remind children in the morning as soon as they awaken to drink the water. They will be thirsty after an overnight fast and are more likely to drink all the water. Speak to the school about allowing your child to keep a bottle of water on the desk during the day.

Help your child choose fun water bottles. Look for something that is stainless steel or wrapped glassware, not plastic. Decorate and personalize it for your child. If necessary choose multiple bottles for home, school, and afterschool activities. Encourage your child to keep a water bottle at hand (and drink) at all times; build in a reward system if necessary.

Serve water with all meals—nothing else. The constant exposure to water as the option will go a long way in reinforcing its acceptance and consumption.

Enhance the flavor of the water to make it fun. Try citrus fruits, berries, and cucum-

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Research Updates

Close pregnancy spacing may up risk of ASD in children

A new research review adds to evidence that closely spaced pregnancies are a risk factor for autism spectrum disorders (ASD).

Agustín Conde-Agudelo and colleagues examined data from seven studies containing data on more than one million children. The researchers found that compared with children born to women with interpregnancy intervals of 36 months or longer, children born to women with intervals under 12 months had nearly twice the risk of receiving any ASD diagnosis and had more than double the risk for developing "classical" autism. The researchers speculate that women who have closely spaced pregnancies may have depleted levels of folic acid, which is necessary for proper brain development.

Three of the studies also found an association between interpregnancy intervals greater than five years and a greater risk for ASD—particularly Asperger's syndrome and pervasive developmental disorder. The researchers say that low fertility, unintended pregnancy, or maternal inflammation may play a role in this phenomenon.

"Based on the current best available evidence," Conde-Agudelo says, "it appears that the ideal interpregnancy interval—the time elapsed between the birth of the immediate older sibling and the conception of the younger sibling—is two to five years, in order to reduce the risk of autism."

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"Birth spacing and risk of autism and other neurodevelopmental disabilities: A systematic review," Agustín Conde-Agudelo, Anyeli Rosas-Bermudez, and Maureen H. Norton, *Pediatrics*, May 2016. Address: Agustín Conde-Agudelo, World Health Organization Collaborating Center in Human Reproduction, University of Valle, Cali, Colombia.

—and—

"Short gap between pregnancies tied to higher autism risk?," HealthDay, April 7, 2016.

Adults with ASD respond similarly to human, artificial singing

Adults with autism spectrum disorders (ASD) do not detect differences in "humanness" between human and artificial singing, a new study from Japan reports.

Shinji Kuriki and colleagues asked 14 adults with high-functioning ASD and 14 adults without ASD to listen to 24 song segments presented in random order. Half of the song segments were sung by a human voice, while the other half were sung by an artificial voice created by software.

The researchers report that for people without ASD, the songs sung by a human voice evoked more impressions of "humanness" and more positive feelings than those sung by the artificial voice. "In contrast," they say, "people with ASD had similar impressions of humanness and positive feelings for the songs sung by the human and artificial voices." The two groups did not differ in their perception of musical characteristics such as complexity, regularity, and brightness.

The researchers conclude, "The present study demonstrates that human beings seem to have a unique sense of humanness in auditory processing and that this sense may be impaired in individuals with ASD. This could be a reasonable explanation for some characteristics typical of ASD, such as the low orientation to social stimuli and the tendency to prefer robots to humans."

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"Similar impressions of humanness for human and artificial singing voices in autism spectrum disorders," Shinji Kuriki, Yuri Tamura, Miki Igarashi, Nobumasa Kato, and Tamami Nakano, *Cognition*, Vol. 153, 2016, 1-5. Address: Tamami Nakano, Graduate School of Frontiers Biosciences, Osaka University, 1-3, Yamadaoka, Suita, Osaka 565-0871, Japan, tamami_nakano@fbs.osaka-u.ac.jp.

ARI Survey: Seniors with Autism Spectrum Disorder

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 the online form.

We invite you to complete the survey on quality of life issues associated with senior adults on the autism spectrum. We hope the results from this survey will provide much insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers. We anticipate that this study will also inspire others as well as better inform the autism community, government agencies, and other welfare and health-related organizations about such quality of life issues.

Once the data from this survey are collected and analyzed, we will contact those who completed the questionnaire and send them a summary report of the findings.

Website: ASDSeniorSurvey.com

Individuals with ASD have more oncogene mutations, less cancer

Individuals with autism have an elevated number of mutations in genes associated with cancer but are less likely than other people to develop the disease, a new study reports.

In the study, Benjamin Darbro and colleagues analyzed large genomic databases containing information on individuals with autism. They found that these individuals had significantly higher rates of DNA variation in cancer-promoting oncogenes than people without autism.

Next, the researchers used the University of Iowa Hospitals and Clinics' electronic medical record (EMR) to compare 1,837 patients with autism spectrum disorders (ASD) to 9,336 patients with other diagnoses. They found that only 1.3% of patients with ASD had received a cancer diagnosis, compared to 3.9% of the controls.

The difference was even more marked in younger patients: The odds of having cancer were reduced by 94% in individuals with ASD under 14 years of age compared to controls in the same age range. This protective effect held true for both males and females.

Darbro comments, "The overlap in genes between those known to promote cancer and those implicated in syndromic neurodevelopmental disorders is not new, but what we've shown is that this overlap is much broader at the genetic level than previously known and that, somehow, it may translate into a lower risk of cancer."

He and his team conclude, "Neurodevelopment and oncogenesis are multi-step processes, and it is possible that signaling through the same cellular proliferation pathways can have different effects depending on embryological timing, as well as cell type and mitotic status."

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"Autism linked to increased oncogene mutations but decreased cancer rate," Benjamin W. Darbro, Rohini Singh, M. Bridget Zimmerman, Vinit B. Mahajan, and Alexander G. Bassuk, *PLOS ONE*, March 2, 2016 (online). Address: Benjamin Darbro, benjamin-darbro@uiowa.edu.

—and—

"Patients with autism have increased mutations in genes that drive cancer but decreased rates of cancer," news release, University of Iowa, April 7, 2016.

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

Research Updates

"Autism genes" affect neurotypical behavior

Gene variants associated with autism spectrum disorders (ASD) are widespread throughout the neurotypical population and influence behavior and development in this population, according to a new study.

Elise Robinson and colleagues analyzed data collected on more than 5,600 children by the Avon Longitudinal Study of Parents and Children, as well as data from other studies involving more than 13,000 children with autism and more than 16,000 controls. The researchers say their data strongly suggest that both inherited and spontaneously occurring gene variants associated with ASD influence a range of behavioral and developmental traits across the entire population, with individuals diagnosed with ASD representing a severe presentation of these traits.

Study coauthor George Davey Smith says, "Many traits that relate to disease risk—like blood pressure or cholesterol levels—demonstrate a similar continuum of risk, with contributions from common and rare genetic variants, plus environmental and chance events. The present study demonstrates how this continuum applies to a condition generally thought of as either existing or not."

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"Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population," Elise Robinson et al., *Nature Genetics*, March 21, 2016 (online). Address: erobinson@atgu.mgh.harvard.edu.

—and—

"Autism genes are in all of us, new research reveals," news release, University of Bristol, March 21, 2016.

—and—

"Autism genes may be in all of us, researchers say," Shaun Heasley, *Disability Scoop*, April 12, 2016.

Mind-body therapy aids stressed parents

Therapists are increasingly incorporating mind-body therapies such as mindful meditation and breathing exercises into their practices, and a new study from Jordan indicates that these interventions can improve the quality of life of parents caring for children with autism spectrum disorders (ASD).

Ahmad Rayan and Muayyad Ahmad enrolled 104 parents of children with ASD in their study. Half of the participants served as controls while the other half participated in a five-week mindfulness-based intervention (MBI). In this intervention, the parents learned the principles of mindfulness, which include observing, describing, and participating; nonjudgmental acceptance; distancing from thoughts; staying present; and being effective. They also learned breathing techniques.

The researchers found that compared to controls, participants exhibited significant improvements in measures of psychological health, social relationships, mindfulness, and positive stress reappraisal (the ability to reframe an experience in a positive way—for instance, "I think I can become a stronger person as a result of what happened."). They conclude, "MBI is a culturally adaptable, acceptable, and effective method to improve quality of life and positive stress reappraisal in parents of children with ASD."

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"Effectiveness of mindfulness-based interventions on quality of life and positive reappraisal coping among parents of children with autism spectrum disorder," Ahmad Rayan and Muayyad Ahmad, *Research in Developmental Disabilities*, Vol. 55, 2016, 185-96. Address: ahmad.rayan87@yahoo.com.

Case study compares gut microbes in sibs

In a single-case study, researchers report finding significant differences between the gut microbes of a child with autism and those of the child's neurotypical sibling.

Ruth Ann Luna and colleagues took daily stool samples from the child with autism over a two-week period, as well as one sample from the sibling. They report that all of the daily stool samples from the child with autism, but not the sample from the sibling, contained three organisms previously associated with autism: *Sarcina ventriculi*, *Barnesiella intestihominis*, and *Clostridium bartlettii.*

In addition, the bacterium *Haemophilus parainfluenzae* appeared in the stool of the child with autism during a three-day period in which the child experienced GI pain, diarrhea and an increase in behavior problems. During a separate two-day period, an increase in *H. parainfluenzae* correlated with another increase in self-injurious behavior, but without any change in stool consistency or evidence of GI pain. The researchers say the appearance of *H. parainfluenzae* in the child's stool is surprising because it normally resides in the respiratory tract.

Luna and colleagues plan to characterize the gut microbiomes of additional children with autism, saying the results may open up new treatment pathways.

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"A case study of the gut microbiome in ASD: Correlation of microbial profiles with GI and behavioral symptoms," R. A. Luna, A. Magee, J. K. Runge, A. Venkatachalam, M. RubioGonzales, and J. Versalovic. The researchers reported their findings at the May 2016 International Meeting for Autism Research (IMFAR).

Mild autism traits may add to challenges of age

Adults with mild traits of autism may experience more difficulties as they age than their neurotypical peers do, a small study suggests.

Gregory Wallace and colleagues enrolled 66 individuals in their study. Forty-six were controls, while 20 exhibited mild, subclinical autism traits as measured by the Broad Autism Phenotype Questionnaire (BAPQ). The BAPQ assesses whether individuals have social problems (aloof personality), pragmatic language difficulties, or a rigid personality. Participants also completed tests measuring their level of social support, their executive function (a term that refers to cognitive skills such as cognitive flexibility and shifting, inhibitory control, and working memory), and their levels of depression and anxiety.

After controlling for age, education level, sex, and health problems, the researchers found that individuals with the broad autism phenotype (BAP) exhibited more problems than controls in executive function. In addition, they had lower levels of social support and higher levels of depression and anxiety.

The researchers note that as people age, executive function typically declines, as do levels of social support. At the same time, individuals become more vulnerable to depression and anxiety. BAP traits, they say, may compound the risk for these problems.

The study reported three additional findings:

- Seven of the individuals with BAP had a relative with ASD, which the researchers say "supports BAP traits existing across a continuum during late life, consistent with numerous studies documenting variance in these traits in childhood and adolescence."
- Levels of BAP traits did not correlate with age, suggesting that these traits remain stable across older adulthood.
- There were equal numbers of men and women in the BAP group, which the researchers say is consistent with previous findings indicating that while ASD affects far more males than females, BAP traits are as common in females as in males.

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"Aging and autism spectrum disorder: Evidence from the broad autism phenotype," Gregory L. Wallace, Jessica Budgett, and Rebecca A. Charlton, *Autism Research*, March 11, 2016 (epub prior to print publication). Address: Rebecca A. Charlton, Department of Psychology, Goldsmiths University of London, London, SE14 6NW, U.K., r.charlton@gold.ac.uk.

Gastrointestinal problems common in autism linked to gene mutation that affects behavior

A new study suggests that the gastrointestinal problems common in autism may stem from gene mutations that are also linked to the behavioral symptoms of the condition.

Kara Gross Margolis and colleagues studied mice carrying a mutation also seen in some individuals with autism. The mutation reduces the activity of the neurotransmitter serotonin by increasing the activity of the serotonin reuptake transporter (SERT), which ferries serotonin back into neurons after it is released.

While serotonin transmits signals in the brain, the brain contains only 5% of the body's serotonin. Most of the remainder is active in the GI system, and the researchers note that gene mutations that affect serotonin activity will affect the gut as well as the brain.

Previously, the researchers found that mice with the SERT mutation exhibited behaviors very similar to those seen in children with autism—for instance, repetitive behaviors, avoidance of contact with other mice, and reduced vocalizations. In the new study, they found that mice with the mutation have fewer gut neurons, a badly maintained gut lining, and slow gut activity. These changes persisted throughout the mice's lives.

"Basically," study coauthor Michael Gershon says, "the gut goes slower and the mice were constipated, which is a common complaint in kids with autism."

The researchers also found that GI changes related to the SERT mutation could be prevented during prenatal development if the mothers of the mice received the drug prucalopride, which mimics the ability of serotonin to stimulate nerve cell development.

Study coauthor Kara Gross Margolis says, "We see that we can prevent gastrointestinal changes in mice with the SERT mutation, but we still need to learn if we can reverse these changes once they appear."

Margolis says that parents and doctors need to be aware that GI problems are common in autism. She notes, "The difficulty is that these kids present in a different way. Often they're not verbal or they have sensory issues so they can't pinpoint where the pain is coming from. So it's important that when these patients present with distress or behavioral problems, a gastrointestinal source is considered."

Margolis says that parents and doctors need to be aware that GI problems are common in autism. She notes, "The difficulty is that these kids present in a different way. Often they're not verbal or they have sensory issues so they can't pinpoint where the pain is coming from. So it's important that when these patients present with distress or behavioral problems, a gastrointestinal source is considered."

The researchers conducted a separate experiment to see how increasing serotonin levels in the mice before birth would affect their development. When they did this by giving the mothers of the mice Prozac during pregnancy or knocking out the SERT gene, they found that the offspring had too many neurons, a gut that moved too fast, and a gut lining that was too thick. The researchers say that while they are not recommending that pregnant women stop taking SSRIs, these women need to be aware of their potential effects.

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"Serotonin transporter variant drives preventable gastrointestinal abnormalities in development and function," Kara Gross Margolis, Zhishan Li, Korey Stevanovic, Virginia Saurman, Narek Israelyan, George M. Anderson, Isaac Snyder, Jeremy Veenstra-VanderWeele, Randy D. Blakely, and Michael D. Gershon, *Journal of Clinical Investigation*, April 25, 2016 (online). Address: Kara Gross Margolis, Morgan Stanley Children's Hospital, Columbia University College of Physicians and Surgeons, Department of Pediatrics, Division of Pediatric Gastroenterology, 620 West 168th Street, New York, New York 10032, kjg2133@cumc.columbia.edu.

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"GI problems in autism may originate in genes, study suggests," news release, Columbia University Medical Center, April 25, 2016.

New Study: Autism Treatment Effectiveness Survey Gauges Improvements, Side Effects

Researchers at Arizona State University are conducting a survey to evaluate the effectiveness of treatments for autism, including medications, nutritional supplements, diets, therapies, and education. The investigators hope to learn which treatments are most effective for different symptoms (language, anxiety, sleep, GI, etc.). Survey results will be posted online for families and clinicians, and published in a scientific journal.

Share your experiences—take the survey here:

https://autism.asu.edu

Editorial: Autism, water, and constipation

(continued from page 3)

ber in water for subtle flavors. Consider sparkling mineral waters with added flavor in this fashion as well for meals or other special treats.

Finally, remember foods can be rich in water status, too. Encourage consumption of healthy fruits, vegetables, soups, and broths as a form of water intake.

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Mouse study: Restoring one species of gut bacteria can correct social impairments

Researchers at Baylor University report that mice lacking one specific species of bacteria in their guts exhibit social deficits similar to those seen in autism, and that restoring this species can reverse some of their behavior problems.

Noting that children of obese mothers are at higher risk for autism and that children with autism often suffer from gastrointestinal problems, Shelly Buffington and colleagues explored the possible relationship between gut microbes, obesity, and social behavior. The researchers first fed about 60 female mice a high-fat diet equivalent to eating fast food. They then bred the mice and weaned their offspring onto a normal diet. After a month, the offspring exhibited behavioral abnormalities including spending less time with their peers and failing to initiate social interactions.

The researchers then compared the gut bacteria of these "fast food" mice to those of mice born to mothers fed a normal diet. Buffington reports that the differences were so consistent "that by looking at the microbiome of an individual mouse we could predict whether its behavior would be impaired."

Next, the researchers housed both groups of mice together so that they would acquire each other's gut microbes by eating feces (a typical mouse behavior). As a result, the mice in the high-fat group quickly developed a normal microbiome. When this happened, their social behavior became more normal as well. Fecal transplant experiments involving mice with no gut bacteria (which also are socially impaired) were consistent with these results.

Finally, the researchers determined that one specific bacterial species—*Lactobacillus reuteri*—was responsible for the behavioral deficits of the "fast food" group. "We found that treatment with this single bacterial strain was able to rescue their social behavior," Buffington says. The researchers discovered that the mice deficient in this bacterial species exhibited a lack of synaptic potentiation in a key reward area of the brain in response to social interaction, and that providing them with the bacteria corrected this anomaly. They also note that *Lactobacillus reuteri* boosts levels of the hormone oxytocin, which plays a powerful role in social behavior.

Senior study author Mauro Costa-Mattioli comments, "Other research groups are trying to use drugs or electrical brain stimulation as a way to reverse some of the behavioral symptoms associated with neurodevelopmental disorders—but here we have, perhaps, a new approach. Whether it would be effective in humans, we don't know yet, but it is an extremely exciting way of affecting the brain from the gut."

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"Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring," Shelly A. Buffington, Gonzalo Viana Di Prisco, Thomas A. Auchtung, Nadim J. Ajami, Joseph F. Petrosino, and Mauro Costa-Mattioli, *Cell*, Vol. 165, June 16, 2016, 1762-75. Address: Mauro Costa-Mattioli, costamat@bcm.edu.

—and—

"A single species of gut bacteria can reverse autism-related social behavior in mice," news release, Cell Press, June 16, 2016.

Self-injurious behavior may not stem from pain insensitivity

A large number of children with autism spectrum disorders (ASD) exhibit self-injurious behavior (SIB). A new study casts doubt on the prevailing theory that these children are insensitive to pain, instead suggesting that the opposite may be true.

James Bodfish and colleagues evaluated 30 adolescents with ASD and cognitive impairment and 41 with ASD only. They found that 63% of the participants with ASD and intellectual disability exhibited SIB, compared to only 24% of the participants with ASD only. Participants with intellectual disability also exhibited more severe SIB.

The researchers then compared 34 adolescents with ASD and severe SIB to 17 with ASD only, taking skin samples to evaluate epidermal nerves and saliva samples to analyze biological markers associated with pain and stress. In addition, they tested the participants' responses to sensory stimuli including heat, cold, pin prick, and deep pressure, evaluating their facial responses to these stimuli.

The researchers report that the participants with SIB exhibited a significant increase in nonverbal responses to painful stimuli. "We also saw marked differences in nerve morphology in terms of density and distribution between the two groups," Bodfish says. In addition, the researchers detected changes in immune system markers in the SIB group indicating heightened inflammatory response.

"Taken together," the researchers say, "our work suggests that at least a subgroup of individuals with chronic repetitive SIB may be in a physiological state similar to neuropathic pain/hyperalgesia associated with alterations in inflammatory, immune, and nociceptive [pain sensing] systems."

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"Severe self-injury in persons with autism and related neurodevelopmental disorders: Differences in sensory, autonomic, and immune markers suggest hyperalgesia," J. W. Bodfish, M. Garrett, G. Wendelschafer-Crabb, W. Kennedy, and F. J. Symons, presentation to the May 2016 International Meeting for Autism Research (IMFAR).

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"Self-injury linked to altered pain processing in autism," Pam Harrison, *Medscape News*, May 18, 2016.

TOLL-FREE CALLING CENTER:

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

866-366-3361

If you are a parent struggling to find help, our volunteers can help you locate the information and resources you need.

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Conducting and sponsoring research on the causes of and best treatments for autism ($300,000 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.

•

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•

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