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

Follow-up study: Microbiota Transfer Therapy's behavior, GI benefits still evident after two years

A new study reports that the positive behavioral and gastrointestinal (GI) changes seen in children with autism spectrum disorders (ASD) following fecal transplants appear to be lasting.

Fecal transplants are currently used as a treatment for *C. difficile* infection and inflammatory bowel disease. A research team headed by James Adams at Arizona State University has been investigating the potential of this approach for treating children with ASD, who have a high rate of diarrhea, constipation, and other bowel problems that may be connected to their behavioral issues.

In their initial study (see ARRI 31/1, 2017), led by Dae-Wook Kang, 18 participants with ASD and GI problems underwent Microbiota Transfer Therapy, or MTT. Participants first received two weeks of antibiotic treatment and a bowel cleanse to prepare the GI tract. Next, they received one high dose of microbiota administered either orally or rectally, followed by a lower oral daily maintenance dose for 7 to 8 weeks. The researchers used a standardized product containing more than 99% bacteria obtained from healthy individuals and tested to ensure safety. The children also took an acid pump inhibitor to reduce stomach acidity and increase the survival rate of the microbes.

> The researchers say that at their follow-up two years after the initial study, "gastrointestinal symptoms were significantly reduced compared with the beginning of the original trial, and autism-related symptoms improved significantly after the end of treatment."

In the initial study, the researchers followed up on the children for eight weeks after treatment ended. Among their findings:

- The average score on the Gastrointestinal Symptom Rating Scale (GSRS) dropped 82% from the beginning to the end of treatment. At the eight-week follow-up, it remained 77% lower than at baseline.
- Only two of the 18 children with ASD showed less than a 50% reduction in the average GSRS score.
- There was a significant decrease in the number of days with abnormal or no stools, and this improvement also was maintained at the eight-week follow-up.
- The Parent Global Impressions-III (PGI-III) scale revealed significant improvements in behavior, and there was a significant correlation between GSRS scores and PGI-III scores.
- Scores on the Childhood Autism Rating Scale, which measures core autism symptoms, decreased by 22% from the beginning to the end of the study, and were 24% lower than baseline at the eight-week follow-up.
- Participants with ASD also showed improvements on the Social Responsiveness Scale and the Autism Behavior Checklist.
- On the Vineland Adaptive Behavior Scale II, the average developmental age of participants with ASD increased by 1.4 years and improved across all domain areas.

The researchers also detected significant changes in the gut bacteria of the children with ASD. While these children initially had significantly less diverse gut bacteria than controls, the researchers noted that "median richness at week 18 was statistically indistinguishable between the ASD and control groups."

In the new study, led by Rosa Krajmalnik-

continued on page 2

U.S., Finnish researchers implicate insecticide DDT in autism

Children with elevated exposure before birth to the insecticide DDT have increased rates of autism, according to a large-scale, multinational study.

DDT was banned decades ago in the United States and many other countries, including Finland, but it persists in the environment. To see if the insecticide plays a role in autism, researchers in the U.S. and Finland reviewed data from 778 cases of autism identified through the Finnish Maternity Cohort. They matched the mother-child pairs to mothers of children who did not develop autism, analyzing blood samples taken during pregnancy for the presence of the DDT metabolite DDE. In addition, they analyzed the samples for the presence of PCBs, another class of chemicals that persists in the environment.

The researchers found that the odds of having a child diagnosed with both autism and intellectual disability more than doubled for mothers with DDE levels in the highest quartile. The odds of having a child with any form of autism were nearly one-third higher for the highest-exposure group than for controls. The researchers found no association between PCBs and autism.

Lead author Alan Brown says, "We think of these chemicals in the past tense, relegated to a long-gone era of dangerous 20th century toxins. Unfortunately, they are still present in the environment and are in our blood and tissues. In pregnant women, they are passed along to the developing fetus. Along with genetic and other environmental factors, our findings suggest that prenatal exposure to the DDT toxin may be a trigger for autism."

The researchers speculate that DDE may increase autism risk because it increases the odds of preterm birth—a risk factor for autism—and because it inhibits androgen receptor binding, a finding also seen in a rat model of autism.

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"Association of maternal insecticide levels with autism in offspring from a national birth cohort," Alan S. Brown, Keely Cheslack-Postava, Panu Rantakokko, Hannu Kiviranta, Susanna Hinkka-Yli-Salomäki,, Ian W. McKeague, Heljä-Marja Surcel, and Andre Sourander, *American Journal of Psychiatry*, August 16, 2018 (online). Address: Alan Brown, asb11@cumc.columbia.edu.

—and—

"First biomarker evidence of DDT-autism link," news release, Columbia University Mailman School of Public Health, August 16, 2018.

Babies' early responses to peek-a-boo, other social stimuli may point to later ASD diagnosis

Babies with lower levels of brain activity in response to social stimuli have an increased likelihood of receiving a later diagnosis of autism spectrum disorder (ASD), according to a new study.

In the study, Sarah Lloyd-Fox and colleagues used a neuroimaging technology called functional near-infrared spectroscopy to study the brain activity of 20 infants at elevated risk for autism (because they had at least one older sibling with ASD) and 16 low-risk infants, all between four and six months of age. The researchers explored how the brain activity of the infants changed in response to videos showing social scenes (for instance, people playing peek-a-boo) and non-social images of cars and other objects. In addition, they studied the infants' responses to human sounds such as coughing or laughing and to non-human sounds such as bells or running water.

The researchers report that compared to low-risk infants, babies later diagnosed with ASD showed reduced activation to visual social stimuli across the inferior frontal and posterior temporal regions of the cortex. In addition, compared to either low-risk infants or high-risk infants who did not develop ASD, the children later diagnosed with ASD showed reduced activation to vocal sounds and enhanced activation to non-vocal sounds within the left lateralized temporal regions. Moreover, the researchers say, "The degree of activation to both the visual and auditory stimuli correlated with parent-reported ASD symptomology in toddlerhood."

Lloyd-Fox comments, "We have found an early indication of different patterns of brain activity in infants who go on to develop ASD from an early age. Given the importance of responding to others in our social world, it is possible that different attentional biases may particularly impact the development of social brain responses, which can continue to affect the child's developmental trajectory as they get older. Identifying early patterns of altered development which may later associate with ASD is important because it will allow doctors to offer earlier interventions and provide families with earlier avenues for support. This might mean giving the child and parents new strategies to reengage their attention toward important social cues and learn different ways of interacting."

The researchers caution that their findings are preliminary, but note that they "highlight the need for further work interrogating atypical processing in early infancy and how it may relate to later social interaction and communication difficulties characteristic of ASD."

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"Cortical responses before 6 months of life associate with later autism," S. Lloyd-Fox, A. Blasi, G. Pasco, T. Gliga, E. J. H. Jones, D. G. M. Murphy, C. E. Elwell, T. Charman, and M. H. Johnson, *European Journal of Neuroscience*, Vol. 47, pp. 736-49, 2018 (free online). Address: Sarah Lloyd-Fox, Centre for Brain and Cognitive Development, Birkbeck, University of London, Malet St., WC1E 7HX, London, UK, s.fox@bbk.ac.uk.

—and—

"First signs of autism appear in infancy," news release, University College London, August 23, 2018.

Significant association detected between food allergies, ASD

Children with food, respiratory, or skin allergies are significantly more likely to have an autism spectrum disorder (ASD) than children without allergies, according to a new study that adds to evidence implicating immune dysfunction in autism.

In the study, Guifeng Xu and colleagues reviewed data collected by the U.S. National Health Interview Survey between 1997 and 2016. Their analysis included nearly 200,000 children between 3 years and 17 years of age. Of these, 1,868 had an ASD diagnosis.

The researchers report that children with ASD were more likely to have food allergies (11.25% vs. 4.25%), respiratory allergies (18.73% vs. 12.08%), and skin allergies (16.81% vs. 9.84%) than children without ASD. The likelihood of having ASD more than doubled among children with food allergies compared to those without food allergies. Skin and respiratory allergies were also associated with elevated odds of having an ASD diagnosis, although to a lesser degree.

The researchers note, "The association between food allergy and ASD was consistent and significant in all age, sex, and racial/ethnic subgroups." However, boys with ASD were more likely than girls with ASD to have respiratory and skin allergies.

The researchers say it is interesting that the link between food allergies and ASD was the most robust, noting that the prevalence of both conditions has increased over the past two decades. They speculate, "Food allergy may involve alterations in the gut microbiome, allergic immune activation, and impaired brain function through neuroimmune interactions, which may finally affect the enteric nervous system and central nervous system leading to neurodevelopmental abnormalities."

Commenting on the study in a separate article, autism specialist Christopher McDougle says, "From a clinical perspective, patients with ASD who are minimally verbal to nonverbal may be unable to describe the pain and discomfort they experience secondary to food allergy and subsequent inflammation in the gastrointestinal (GI) tract. Instead, their physical distress may manifest as irritability, aggression, and/or self-injury. It is important to underscore the need for healthcare professionals to conduct a thorough history and physical examination to rule out identifiable medical causes of aberrant behavior, including food allergy and secondary GI inflammation, before proceeding with treatments designed to reduce behavior problems."

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"Association of food allergy and other allergic conditions with autism spectrum disorder in children," Guifeng Xu, Linda G. Snetselaar, Jin Jing, Buyun Liu, Lane Strathearn, and Wei Bao, *JAMA Pediatrics*, June 2018 (open access). Address: Wei Bao, Department of Epidemiology, College of Public Health, University of Iowa, 145 N. Riverside Dr., Room S431 CPHB, Iowa City, IA 52242, wei-bao@uiowa.edu.

—and—

"Another step toward defining an immune-mediated subtype of autism spectrum disorder," Christopher J. McDougle, *JAMA Pediatrics*, June 2018 (open access). Address: Christopher J. McDougle, Lurie Center for Autism, Massachusetts General Hospital, Department of Psychiatry, Harvard Medical School, One Maguire Road, Lexington, MA 02421, cmcdougle@mgh.harvard.edu.

Microbiota Transfer Therapy's behavior, GI benefits still evident after two years

(continued from page 1)

Brown, the researchers followed up with all 18 participants two years after treatment stopped. "Notably," they say, "gastrointestinal symptoms were significantly reduced compared with the beginning of the original trial, and autism-related symptoms improved significantly after the end of treatment." In addition, they say, "DNA-sequencing analyses revealed that changes in gut microbiota at the end of treatment still remained at follow-up, including significant increases in bacterial diversity and relative abundances of Bifidobacteria, Prevotella, and Desulfovibrio."

They conclude, "Our observations demonstrate the long-term efficacy of MTT for treating children with ASD who have GI problems. The microbiota transfer therapy performed in this trial thus is a promising approach for sustainably altering the gut bacterial communities, and improving gastrointestinal and behavioral symptoms associated with ASD."

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

EDITORIAL: Stephen M. Edelson, Ph.D.

The National Prevalence Rate of Autism: Is 1 in 59 a Reasonable Estimate?

Many in the autism community consider the prevalence rate reported by the Centers for Disease Control and Prevention (CDC) to be a reasonable estimate of the size of the autistic community in the United States. Researchers often cite this national statistic in their grant proposals, usually in the opening paragraph, and many published research studies also refer to this estimate.

The Autism and Developmental Disabilities Monitoring Network, a division of the CDC, is responsible for determining the national autism rate in the United States. This year's rate, 1 in 59, is the highest ever reported by them. The report was based on data collected in 2014 and involved a review of health and education records of eight-year-olds diagnosed with autism. Similar to earlier reports, the researchers collected data from 11 communities throughout the United States.

In my view, the 1-in-59 rate needs to be viewed as historical data. It would be more accurate to preface all citations of the 1-in-59 statistic as representing the population of eight-year-olds with autism in 2014. Furthermore, parents who are planning a family should not assume that the chances are 1 in 59 (or 1.7%) of having a child with autism. This rate actually applies to the risk in 2006, because the participants in the 2014 survey were born eight years earlier.

As noted above, the 2006 national birthrate of autism was 1 in 59 (or 1.7%). At that time, the reported national statistic regarding eight-year-olds was approximately 1 in 150 (based on the CDC's 2007 report). The latter statistic indicates that the national birthrate of autism eight years earlier (1994) was 1 in 150 (or 0.67%). Given the logarithmic increases in the prevalence of autism that the CDC has reported over the past 12 years, the birthrate of autism today is undeniably significantly higher than 1.7%.

Also, while one might assume that the 11 communities selected by the CDC represent a cross-section of America, the CDC's April 26, 2018 press release stated that the reported rate "is not a representative sample of the United States." Instead, the release stated, the report provides a "detailed look at autism in these specific communities."

The regional prevalence rates reported by the CDC were based on data from Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin. Note that there were no communities on the west coast or in the lower Midwest regions, and only Georgia was included in the southeast. All three of these geographic areas include centers of large populations in the United States.

Regarding minority populations, the CDC noted that the rate of diagnosed autism in black and Hispanic children "is approaching that of white children." The CDC spokesperson also stated that "autism is still more likely to be identified in white children than in black or Hispanic children." Regarding sex differences, the National Autistic Society in the United Kingdom published a study in 2015 indicating that females with autism are under-diagnosed, in part because their social and core autistic impairments are often less severe than those of males with autism. Thus, at least three rather large segments of the population in the United States are not properly represented in this national prevalence statistic.

It is important to mention that the 1-in-59 prevalence estimate is inconsistent with another government-funded survey on autism. The National Health Interview Survey (NHIS) reported a rate of 1 in 44 in 2014—the same year the CDC collected the data for its current report— and a rate of 1 in 37 in 2016.

Moreover, the CDC reported a wide range of prevalence rates across regions in the U.S. Interestingly, New Jersey had the highest estimated rate of 1 in 34, and Minnesota had the second highest rate of 1 in 42. These rates are almost 40% and 30% higher, respectively, than the national statistic. If autism truly varies greatly across regions, it would be more appropriate to cite prevalence estimates for each region than to rely on a single national statistic.

As many in the autism community are aware, the official definition of autism was broadened in 2013 by a task force sponsored by the American Psychiatric Association. However, the data from the CDC report was collected one year after the new definition of autism was formalized. Thus, the records from the eight-year-olds were based mostly on the previous diagnostic criteria for autism.

Furthermore, the CDC acknowledged in their press release that there were differences in how these individuals were diagnosed and documented. Thus, the current national estimate of autism, 1 in 59, is not based on the current diagnostic criteria for autism, and more importantly, *there was no standard method used to determine whether or not an individual was appropriately diagnosed with autism.*

It is important to mention that the 1-in-59 prevalence estimate is inconsistent with another government-funded survey on autism. The National Health Interview Survey (NHIS), which collects information for the U.S. Census Bureau, conducted structured interviews with caregivers to confirm a diagnosis of autism. As described in their 2017 published report, they collected data from 2014 to 2016 on 3- to 17-year-olds with autism spectrum disorder, intellectual disability, and other developmental delays. Regarding autism, NHIS reported a rate of *1 in 44 in 2014*—the same year the CDC collected the data for its current report— and a rate of 1 in 37 in 2016.

In summary:

- The CDC report is based on historical data collected in 2014.
- It does not reflect a cross-section of the autism population throughout the U.S.
- It relies on non-standardized collection procedures.
- It is based on outdated diagnostic criteria.
- It is at odds with the U.S. Census Bureau, another government-funded agency.

Given the magnitude of the decisions that are made based on the CDC's estimate, these concerns raise significant questions:

- Should local, state, and federal governments rely on this estimate to determine policy as well as funding for autism research and services?
- Should the scientific, medical, and autism communities consider this estimate as relevant today?
- Should countries around the world, many of whom rely upon the CDC's report to estimate the prevalence of autism in their own countries, accept the estimate unquestioningly?

In short, should we simply concede that this is the best that we can do—or should we have an active dialogue about the national prevalence statistic with representatives from various vested communities and discuss ways to best calculate the present (or very recent) rate of autism? I strongly vote for the latter.

Research Updates

Drivers with ASD are as good as neurotypical drivers, but need more time to master basic skills

Many individuals with autism spectrum disorders (ASD) are obtaining driver's licenses, and a new study indicates that while they take longer than neurotypical peers to master driving skills, they eventually perform equally well.

Kristina Patrick and colleagues compared 50 participants with ASD and 50 matched neurotypical peers who underwent a driving assessment using a virtual-reality simulator that included increasingly complex demands. The researchers measured differences in mean speed as well as speed and lane variability, factoring in both an ASD diagnosis and driving experience.

They report, "Young adults with ASD demonstrated increased variability in speed and lane positioning compared with controls, even during low demand tasks. When driving demands became more complex, group differences were moderated by driving experience such that licensed drivers with ASD drove similarly to typically developing licensed drivers for most tasks, whereas unlicensed drivers with ASD had more difficulty with speed and lane management than typically developing drivers."

The researchers conclude that individuals with autism may benefit from a "slow and gradual" approach to driver training.

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"Driving comparisons between young adults with autism spectrum disorder and typical development," Kristina E. Patrick, Felicia Hurewitz, Mark D. McCurdy, Frederic Taylor Agate, Brian P. Daly, Reem A. Tarazi, Douglas L. Chute, and Maria T. Schultheis, *Journal of Developmental & Behavioral Pediatrics*, May 18, 2018 (epub prior to print version). Address: Kristina E. Patrick, Department of Pediatric Psychology and Neuropsychology, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, kristina.patrick@nationwidechildrens.org.

Study supports accuracy of metabolite test for ASD

Researchers who reported last year on the results of a blood test for autism say that a new study confirms its efficacy.

The test, developed by Juergen Hahn and colleagues, involves analyzing 24 metabolites in blood samples in order to detect any significant differences between metabolites of children with ASD and neurotypical controls. These differences, the researchers say, allow them to predict whether an individual is on the autism spectrum.

In the initial study (see ARRI 31/2, 2017), the researchers analyzed data from 149 individuals, focusing on metabolites relevant to two cellular pathways linked to ASD: the methionine cycle and the transsulfuration pathway. About half of the children had ASD, while the other half were neurotypical. The researchers deliberately omitted data for one individual at a time, subjected the remaining data to advanced analysis techniques, and used the results to generate an algorithm to predict the data from the omitted individual. Repeating this process for all 149 children, the researchers correctly identified 96.1% of neurotypical children and 97.6% of children with ASD.

In the new study, the researchers used existing datasets from three studies involving a total of 154 children with autism. The datasets included only 22 of the metabolites used to create the original predictive algorithm. The researchers recreated their algorithm using data from the initial group of 149 children but limiting their analysis to these 22 metabolites. They then applied the algorithm to the new group of 154 children. This time, the algorithm predicted autism with 88% accuracy. Hahn says that the lower accuracy rate in the new study can most likely be attributed to the fact that two of the metabolites—both strong predictors in the initial study—were unavailable in this dataset.

"The most meaningful result." Hahn says, "is the high degree of accuracy we are able to obtain using this approach on data collected years apart from the original dataset."

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"Multivariate techniques enable a biochemical classification of children with autism spectrum disorder versus typically-developing peers: A comparison and validation study," Daniel P. Howsmon, Troy Vargason, Robert A. Rubin, Leanna Delhey, Marie Tippett, Shannon Rose, Sirish C. Bennuri, John C. Slattery, Stepan Melnyk, S. Jill James, Richard E. Frye, and Juergen Hahn, *Bioengineering & Translational Medicine*, June 2018 (open access). Address: Juergen Hahn, 110 Eighth St., Rensselaer Polytechnic Institute, CBIS #4213, Troy, NY 12180, hahnj@rpi.edu.

—and—

"Success of blood test for autism affirmed," news release, Rensselaer Polytechnic Institute, June 19, 2018.

—see also—

"Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation," Daniel P. Howsmon, Uwe Kruger, Stepan Melnyk, S. Jill James, and Juergen Hahn, *PLOS Computational Biology*, March 16, 2017 (open access). See address above.

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Children of mothers with type 1 diabetes are more likely to get ASD diagnosis

Women with type 1 diabetes have significantly elevated odds of having a child with an autism spectrum disorder (ASD), according to new research.

To determine the potential influence of any type of maternal diabetes on the risk for ASD, Anny Xiang and colleagues analyzed data collected on more than 400,000 children born in Kaiser Permanente Southern California hospitals over a 17-year period. The researchers used electronic medical records to identify children later diagnosed with ASD. In addition, they used an algorithm developed for electronic health records data to identify mothers with type 1 diabetes, type 2 diabetes, or gestational diabetes that developed either early or late in pregnancy. They confirmed diabetes diagnoses for the mothers by looking for the prescription of insulin during pregnancy.

Adjusting their data to control for a wide range of factors, the researchers found that mothers with type 1 diabetes had more than double the odds of having a child with ASD compared to non-diabetic mothers. Mothers with type 2 diabetes or early gestational diabetes (diagnosed by 26 weeks of pregnancy) also had a higher risk, but it was significantly less than for mothers with type 1 diabetes. Late gestational diabetes (diagnosed after 26 weeks) was not associated with any increase in ASD in children. Within the gestational diabetes group, maternal exposure to antidiabetic medication during pregnancy did not affect children's ASD risk.

Xiang says the findings emphasize that "it is important for both patient and clinician to monitor glucose control as carefully as possible and make sure it is normal right from the time of conception."

Commenting on the findings, physician Peter Damm, who was not involved in the study, says, "The finding that type 1 diabetes in pregnancy has a higher hazard ratio for autism than type 2 diabetes, and more so again than gestational diabetes, reflects the degree of maternal hyperglycemia and seems reasonable. Likewise, the finding that women diagnosed with gestational diabetes early as opposed to late have a higher risk, showing us a dose-response relationship with regard to different types of diabetes and autism risk."

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"Type 1 diabetes in pregnancy doubles risk for autism in offspring," Becky McCall, Medscape, June 25, 2018. Xiang et al. reported their findings at the 2018 conference of the American Diabetes Association in June 2018.

Research UpdatesUpdates:

Gene linked to subtype of autism affects cells that insulate axons in the CNS

A gene linked to a subset of autism spectrum disorders (ASD) plays a key role in the development of cells that form protective insulation around nerves in the central nervous system, a new study reveals.

Mutations of the CHD8 gene affect a small minority of individuals with autism, causing ASD symptoms, abnormalities in the brain's white matter, and significant gastrointestinal disturbances (primarily constipation). Individuals with CHD8 mutations typically have unusual features including a large head circumference, a prominent forehead, and wide-set eyes.

Chuntao Zhao and colleagues studied the role of the CHD8 gene using mice genetically engineered to not express the CHD8 protein in oligodendrocytes, which are cells that provide support and insulation to axons in the central nervous system (CNS). The researchers found that loss or mutation of CHD8 reduces the function of histone methyltransferase, which helps to activate genes needed for oligodendrocytes to develop. Using an experimental compound that inhibits a different molecule linked to CHD8, the researchers were able to "rescue" the development of oligodendrocytes, reversing white matter defects in the mice and reducing their neurological problems.

Senior study coauthor Q. Richard Lu comments, "So far, no treatment is available for autism patients with mutations in CHD8, one of the highest risk-susceptibility genes for autism. Current studies are still at a very early stage in terms of therapeutic agents, but our findings present a potential strategy to restore the function of faulty CHD8-dependent processes."

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"Dual requirement of CHD8 for chromatin landscape establishment and histone methyltransferase recruitment to promote CNS myelination and repair," Chuntao Zhao, Chen Dong, Magali Frah, Yaqi Deng, Corentine Marie, Feng Zhang, Lingli Xu, Zhixing Ma, Xinran Dong, Yifeng Lin, Scott Koenig, Brahim Nait-Oumesmar, Donna M. Martin, Laiman N. Wu, Mei Xin, Wenhao Zhou, Carlos Parras, and Q. Richard Lu, *Developmental Cell*, Vol. 45, No. 6, pp. 753-68, June 2018. Address: Chuntao Zhao, Key Laboratory of Birth Defects, Children's Hospital of Fudan University, Shanghai 201102, China, chuntao.zhao@cchmc.org.

—and—

"Scientists learn more about how gene linked to autism affects brain; study suggests modulating CHD8 might help some people with complex condition," news release, Cincinnati Children's Hospital Medical Center, June 18, 2018.

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Fathers' antidepressant use during conception not associated with ASD

Children of fathers who take antidepressant medications around the time of conception do not appear to have an increased risk for autism spectrum disorders (ASD), a new study indicates.

Alexander Viktorin and colleagues note that while researchers have extensively studied women's use of antidepressants during this time, few studies have looked into the possible effects of paternal use. Because some research suggests that antidepressant use may reduce sperm concentration and motility, cause morphological changes in sperm, and increase DNA fragmentation damage, the researchers wondered whether paternal use of these drugs around the time of conception might increase children's risk for preterm birth, malformations, autism, or intellectual disability.

Using the Swedish Medical Birth Register and the Swedish Prescribed Drug Register, the researchers analyzed the records of more than 170,000 children born in 2006 or 2007 and followed up to 2014. The group included nearly 4,000 children born to fathers receiving antidepressant prescriptions during the conception period (four weeks before to four weeks after conception). The researchers compared the children of these men to children of men who did not take antidepressants, and to children of men who began taking antidepressants after the conception period.

The researchers found no association between paternal antidepressant use during the conception period and preterm birth, malformations, or intellectual disability. (They actually found a reduced risk for intellectual disability in this group when they compared them to fathers who began taking antidepressants after the conception period.) They did find an association with autism, but this association disappeared when they adjusted for other factors.

The researchers conclude, "Paternal intake of antidepressants during the period around conception is safe with respect to the risk of the four major adverse outcomes in offspring—preterm birth, malformation, autism, or intellectual disability."

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"Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study," Alexander Viktorin, Stephen Z. Levine, Margret Altemus, Abraham Reichenberg, and Sven Sandin, *British Journal of Medicine*, June 8, 2018 (open access). Address: Sven Sandin, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, sven.sandin@ki.se.

Simple positive intervention leads to better compliance with toenail and fingernail clipping

A simple reinforcement procedure can reduce the resistance of individuals with autism spectrum disorders (ASD) to having their fingernails and toenails cut, according to a small new study.

Art Dowdy and colleagues note that "escape extinction" (preventing an individual from escaping a demand) is a common approach used during grooming tasks. However, they point out that this can be dangerous when these tasks involve sharp objects such as nail clippers. In addition, escape extinction can temporarily cause a behavior to escalate.

In their study, Dowdy and colleagues tested an approach involving positive reinforcers but not escape extinction. Participants were two nonverbal male teenagers with ASD, attention deficit hyperactivity disorder, and intellectual disability.

During baseline testing, a therapist told each participant, "I am going to cut your nails," and moved the clippers toward a nail. The therapist allowed five seconds of escape response (for instance, pulling the hand away) before re-presenting the nail clippers.

During the intervention, the therapist told each participant, "For each nail I cut, you will earn a snack." The therapist placed preferred snacks in view and provided immediate access to them following each successful nail trimming. As during baseline, the therapist allowed five seconds of escape response before re-presenting the clippers. The researchers clipped the toenails of one child ("Jackson") and the fingernails of the other ("Steven").

During baseline sessions, Jackson engaged in a mean of 5.4 escape responses per minute, and the therapist was unable to cut any of his toenails. Steven engaged in a mean of 4.5 escape responses per minute, and the therapist was able to cut an average of only 31% of his nails.

During intervention sessions, the therapist was able to cut a mean percentage of 91% of Jackson's toenails (and succeeded in cutting 100% during the final three sessions), and he engaged in only 1.7 escape responses per minute. In follow-ups at one and two months, the therapist was able to cut all of his toenails.

In Steven's case, the therapist was able to cut a mean percentage of 92% of his fingernails during the intervention sessions, and his escape responses dropped to 1.1 per minute. (Because he left the residential treatment facility, the researchers could not conduct follow-up visits.)

Dowdy and colleagues cite other research showing that an intervention using reinforcers without escape extinction can be effective in increasing compliance with toothbrushing, haircuts, and blood glucose monitoring. They conclude that "when compared to escape-extinction procedures, which may initially increase problem behavior and create potentially unsafe situations, treatments that do not require escape extinction are more practical for caregivers to implement and are likely to be less prone to producing untoward side effects."

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"Effects of reinforcement without extinction on increasing compliance with nail cutting: a systematic replication," Art Dowdy, Matt Tincani, Timothy Nipe, and Mary Jane Weiss, *Journal of Applied Behavior Analysis*, June 17, 2018 (epub prior to print publication). Address: Art Dowdy, Melmark Pennsylvania, 2600 Wayland Rd., Berwyn, PA 19312, arthur.dowdy@gmail.com.

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Medical and psychiatric comorbidities frequently affect individuals with ASD, researchers find

Medical and psychiatric comorbidities are very common in teens and young adults with autism spectrum disorders (ASD), according to a new study.

Meghan Davignon and colleagues analyzed data collected from Kaiser Permanente Northern California members, all between 14 years and 25 years of age and all enrolled in the health care delivery system from 2013 to 2015. The researchers compared more than 4,000 individuals with ASD to three control groups:

- More than 20,000 peers with attention-deficit/hyperactivity disorder (ADHD), who served as a neurobehavioral control group.
- More than 2,000 individuals with diabetes mellitus (DM), who served as a medical control group.
- More than 20,000 controls not diagnosed with ASD, ADHD, or DM.

The researchers report that more than one-third of individuals with ASD had co-occurring psychiatric conditions. In addition, individuals with ASD had a high rate of medical conditions. The researchers say, "The most common medical conditions in transition-aged individuals with ASD included infections (42%), obesity (25%), neurologic conditions (18%), allergy and/or immunology conditions (16%), musculoskeletal conditions (15%), and GI conditions (11%)."

Psychiatric conditions were more common in individuals with ASD than in any of the control groups, although there were two exceptions: Drug abuse was less common in the ASD group than in any control group, and depression, while elevated in ASD, was less common than in ADHD. One finding of particular concern, the researchers say, was that the suicide rate was nearly four times higher in the ASD group than in neurotypical controls. Most medical conditions were more common in the ASD group than in the ADHD and typical control groups, although individuals with diabetes had similar or higher rates.

Commenting on the high rate of medical and psychiatric issues in individuals with ASD, Davignon and colleagues conclude, "Although more research is needed to identify the intrinsic and extrinsic factors that contribute to this excess burden, there is a pressing need for all clinicians, particularly general pediatricians and adult physicians, to approach ASD as a chronic health condition requiring regular follow-up and routine screening and treatment of medical and psychiatric issues, as is the standard of care for other chronic medical conditions."

—

"Psychiatric and medical conditions in transition-aged individuals with ASD," Meghan N. Davignon, Yinge Qian, Maria Massolo, and Lisa A. Croen, *Pediatrics*, Vol. 141, No. s4, April 2018 (online). Address: Meghan N. Davignon, Kaiser Roseville Medical Center, 1600 Eureka Rd, Building C, Roseville, CA 95661, meghan.davignon@kp.org.

ARRI 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 our online survey at:

https://www.autism.com/adult_survey

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) 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.

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.

For individuals with ASD, spotting lies is more challenging

Individuals with autism spectrum disorders (ASD) and neurotypical individuals with many autistic traits may have more difficulty spotting deception than their peers do, according to a new study involving two separate experiments.

In the first experiment, David Williams and colleagues asked 216 neurotypical adults to complete the Autism Spectrum Quotient (AQ), which measures autistic traits, and to undergo tests evaluating "mindreading" ability (the ability to understand that other people have thoughts, feelings, and perspectives). The researchers then asked the participants to watch videos of people either telling the truth or lying about whether they had cheated on a test. The people shown in the videos were categorized as "transparent"—that is, it was easy to tell if they lied or told the truth—or "nontransparent" and thus more difficult to evaluate.

The researchers found that neurotypical individuals with higher rates of autism traits had significantly more difficulty determining whether the transparent people in the videos were lying or telling the truth. However, AQ scores did not correlate with the accuracy of judgments about the nontransparent people (an area in which both groups performed poorly) or with "truth bias"—in other words, the tendency to believe that people were telling the truth. They also did not correlate with mindreading ability.

In the second experiment, the researchers asked 27 adults with ASD and 27 neurotypical controls to perform the same task. In this experiment, the participants with ASD were far less able than controls to detect lies told by transparent individuals. The researchers say, "This shows that even when people provide clear behavioral cues about their honesty or deceit, individuals with ASD nonetheless have significant difficulty making accurate judgments." Again, ASD diagnosis did not correlate with the accuracy of judgments about the nontransparent people or with "truth bias."

The researchers say it is interesting that the ability to detect lies did not correlate directly with mindreading ability. They speculate, "Rather, lie detection ability might develop as a function of the degree to which one engages with others socially, and attends to and learns from behavioral cues."

Regardless of the reason for impaired lie detection in ASD, the researchers say it might be beneficial to train individuals with ASD to detect behavioral indicators of lying. They note that such training has shown some success when used with neurotypical adults.

—

"Can you spot a liar? Deception, mindreading, and the case of autism spectrum disorder," David M. Williams, Toby Nicholson, Catherine Grainger, Sophie E. Lind, and Peter Carruthers, *Autism Research*, May 2018 (open access). Address: David M. Williams, School of Psychology, Keynes College, University of Kent, Canterbury CT2 7NP, United Kingdom, D.M.Williams@kent.ac.uk.

Medical marijuana may significantly improve ASD symptoms

Researchers in Israel report that medical marijuana may be highly effective in treating behavior problems and other symptoms of autism spectrum disorders (ASD).

Adi Aran and colleagues administered the marijuana constituents cannabidiol and tetrahydrocannabinol orally at a ratio of 20:1 to 60 children with ASD, using multiple scales to evaluate the results. They report that following treatment, behavioral outbreaks lessened significantly in 61% of participants. Anxiety and communication problems improved significantly in 39% and 47% of participants respectively. In addition, parents reported less stress as a result of their children's behavior. Side effects included sleep disturbances in 14% of children, irritability in 9%, and loss of appetite in 9%.

The researchers conclude, "This preliminary study supports the feasibility of cannabidiol based medical cannabis as a promising treatment option for refractory behavioral problems in children with ASD." They are now conducting a large, double blind, placebo controlled cross-over trial to see if they can replicate their results.

—

"Cannabidiol based medical cannabis in children with autism-a retrospective feasibility study," Adi Aran, Hanoch Cassuto, and Asael Lubotzky, *Neurology*, April 24, 2018 (free online). Address: Adi Aran, Pediatric Neurology, Shaare Zedek Medical Center, Jerusalem, Israel.

—IN MEMORIAM—

Tristram Smith, PhD, who passed away recently at the age of 57, was a pioneer in applied behavior analysis. Working alongside Dr. Ivar Lovaas, Dr. Smith helped to conduct much of the early research on ABA and early intervention for children with autism, greatly advancing the field. At the time of his death, Dr. Smith was serving as the Haggerty-Friedman Professor in Developmental/Behavioral Pediatric Research at the University of Rochester Medical Center (URMC).

Differences seen in social reward pathway in ASD

A new study reveals that individuals with autism spectrum disorders (ASD) have structural and functional differences in a brain pathway that makes social behavior rewarding.

In their study, Kaustubh Supekar and colleagues focused on the mesolimbic reward pathway, which connects two brain regions associated with reward—the ventral tegmental area (VTA) and the nucleus accumbens (NAc). The researchers note, "The mesolimbic reward pathway, which evaluates, regulates, and reinforces appetitive behaviors through dopaminergic signaling, is a core brain system for processing reward value."

The researchers investigated structural and functional connectivity of the mesolimbic reward pathway in the brains of children with and without ASD, using a technique called high angular resolution diffusion-weighted imaging along with functional MRI data. They analyzed brain wiring in 24 children with autism and 24 controls, and examined functional connections in the brain in 16 children with autism and 20 controls as they looked at social or nonsocial images (pictures of faces or scenery). The team also performed scans on an additional 17 children with ASD and 17 controls to see if they could replicate their results.

The researchers found that the density of nerve-fiber tracts in the mesolimbic reward pathway was lower in children with ASD than in controls. In comparison, they found no differences between the two groups when they examined an emotion-related brain pathway as a control. Among the children with ASD, lower density of nerve-fiber tracts correlated with greater social deficits. The researchers replicated these results in the second group of children they studied.

In addition, children with ASD had weaker functional connections in the mesolimbic reward pathway than controls, and the degree of functional deficit correlated with the degree of social impairment.

The researchers say their findings support the social motivation theory of autism, which proposes that social interaction is inherently less appealing to people with ASD than it is to their neurotypical peers. "It's the first time we have had concrete brain evidence to support this theory," Supekar says.

—

"Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism," Kaustubh Supekar, John Kochalka, Marie Schaer, Holly Wakeman, Shaozheng Qin, Aarthi Padmanabhan, and Vinod Menon, *Brain*, July 17, 2018 (open access). Address: Kaustubh Supekar, 401 Quarry Road, Stanford, CA 94305, ksupekar@stanford.edu.

—and—

"Key social reward circuit in the brain impaired in kids with autism," Stanford News Center, July 16, 2018.

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ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (more than $200,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

•

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

•

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

•

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

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

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