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Gene linked to autism also shown to affect the gut

Individuals with autism spectrum disorders (ASD) frequently suffer from gastrointestinal problems as well, and new research suggests that these GI problems may stem from the same gene mutations that cause brain and behavioral symptoms.

In a 2003 study, one group of researchers identified a specific gene mutation that causes some cases of ASD. The mutation alters the "Velcro" between neurons that keeps them in close contact. This study involved two brothers with ASD who also had GI problems.

Now, a separate group of researchers has extended this work by conducting a series of studies on the structure and function of the gut in mice that have the same gene mutation. They report that this mutation affects gut contractions, the number of neurons in the small intestine, the speed at which food moves through the small intestine, and the gut's responses to the neurotransmitter GABA. In addition, the researchers detected significant differences in the gut microbiomes of mice with the mutation and control mice, even though both groups were kept in identical environments.

While the specific mutation the researchers studied is rare, they note that more than 150 autism-associated gene mutations alter neuronal connections. Study coauthor Elisa Hill-Yardin says, "The link we've confirmed suggests a broader mechanism, indicating that the mutations that affect connections between neurons could be behind the gut problems in many patients."

Hill-Yardin says the group's discoveries could someday lead to the development of therapies specifically designed to work on neurotransmitters in the gut. She adds, "Another promising path for future research is investigating how gene mutations in the nervous system relate with microbes in the gut. We know these microbes interact with the brain via the gut-brain axis, so could tweaking them improve mood and behavior? While this wouldn't reverse the gene mutation, we might be able to tone down its effects, and make a real difference in the quality of life for people with autism and their families."

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Study points to mutations in "junk" DNA as a factor in autism

A new study indicates that some cases of autism spectrum disorder (ASD) may involve mutations in so-called "junk" DNA—that is, parts of the genome that do not encode proteins.

Jian Zhou and colleagues used artificial intelligence techniques to explore the genomes of 1,790 individuals with autism and their unaffected parents and siblings. The families had no history of autism, indicating that the gene defects in the individuals with ASD probably stemmed from spontaneous mutations.

The researchers created a framework that predicted the specific regulatory effects and harmful impacts of gene variants. They used their model to predict the ramifications of non-inherited, noncoding mutations in each child with autism, and then compared these predictions with the effects of the same (unmutated) strand in the child's neurotypical sibling.

The researchers found that the number of autism cases linked to noncoding mutations was comparable to the number of cases linked to protein-coding mutations that disable gene function. Analysis suggested that noncoding mutations in many of the individuals with ASD altered gene regulation. In addition, it suggested that the mutations affected gene expression in the brain and genes responsible for neuronal development and synaptic transmission.

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Individuals with ASD cite benefits of self-stimulatory actions

While behavioral programs for individuals with autism spectrum disorders (ASD) often attempt to reduce self-stimulatory behaviors (or "stims") such as hand flapping and rocking, a new study shows that many people with ASD believe these behaviors have value and object to treatments that aim to eliminate them.

The researchers say that not all participants reported having voluntary control over their stimming, "but even those who said they could suppress their stims described depleting, effortful costs."

In interviews and focus groups, Steven Kapp and colleagues asked 31 adults with ASD to share their views and experiences involving stimming. The researchers found that most participants described stimming as comfortable or calming, with some specifically saying that it served as a self-regulatory mechanism. The researchers say participants' accounts suggest that stimming creates a feedback loop that helps to regulate responses to overwhelming environments, sensory overload, "noisy" thoughts, or uncontainable positive or negative emotions. They add, "Not all participants reported voluntary control over their stimming, but even those who said they could suppress their stims described depleting, effortful costs."

Participants said that as they aged, stimming became less socially accepted. The researchers say the participants' comments revealed how "stigmatization of stimming infantilizes autistic people, who may fear they come across as 'immature.'" Participants said they felt angry, nervous, frustrated, belittled, shamed, or confused when other people told them to stop stimming. As a result, many suppressed or concealed their stims in public, or altered their stims to appear more socially acceptable. They emphasized the need for neurotypical individuals to understand and accept the value of stimming, while generally agreeing that they wanted to avoid stimming in ways harmful to themselves or others.

The researchers conclude, "The autism field would be best placed to take a more nuanced look at why autistic people perform repetitive motor behaviors so frequently…. Rather than aiming to obliviate all stims, perhaps support for interventions that aid non-harmful stimming and reduce prejudice is the way forward."

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"'People should be allowed to do what they like:' Autistic adults' views and experiences of stimming," Steven K. Kapp, Robyn Steward, Laura Crane, Daisy Elliott, Chris Elphick, Elizabeth Pellicano, and Ginny Russell, *Autism*, February 28, 2019 (free online). Address: Steven K. Kapp, s.k.kapp@exeter.ac.uk.

Highly accurate diagnosis of ASD possible at 14 months

Most children with autism spectrum disorders (ASD) receive a diagnosis after their third birthday, but a new study indicates that trained professionals can make an ASD diagnosis with a high degree of accuracy when children are as young as 14 months of age.

Karen Pierce and colleagues analyzed data on 441 toddlers with ASD and 828 controls without ASD. All of the children had received their first diagnostic evaluation between 12 and 36 months of age and had undergone at least one subsequent evaluation, with all evaluations performed by licensed psychologists. Diagnoses included ASD, features of ASD, language and developmental delay, and other developmental issues.

The researchers report that the overall diagnostic stability for ASD was 0.84, which was higher than for any other diagnostic group. Only 2 percent of children initially diagnosed with ASD were later found to be developing typically. Among children initially diagnosed with ASD, the most common transition was from ASD to ASD features (9 percent).

The diagnostic stability of ASD at 12 to 13 months was only 0.50, but increased to 0.79 by 14 months and 0.83 by 16 months. Twenty-four percent of toddlers did not receive an ASD diagnosis at their initial evaluations but were identified later. The most common transition in this group was an initial designation of developmental delay (25 percent) or language delay (16 percent), transitioning to later-onset ASD.

Study coauthor Karen Pierce notes that early diagnosis is important, saying, "The sooner you can address issues of ASD, the better the outcome for the child." She adds, "Synaptic density, or connections between neurons in the prefrontal and temporal cortex, brain regions centrally involved in higher order social behavior, doubles between birth and one to two years in age. It's conceivable that outcomes for children with autism could be improved if treatment occurred during this period of rapid brain growth, rather than after, which is more commonly the case."

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"Evaluation of the diagnostic stability of the early autism spectrum disorder phenotype in the general population starting at 12 months," Karen Pierce, Vahid H. Gazestani, Elizabeth Bacon, Cynthia Carter Barnes, Debra Cha, Srinivasa Nalabolu, Linda Lopez, Adrienne Moore, Sunny Pence-Stophaeros, and Eric Courchesne, *JAMA Pediatrics*, April 29, 2019 (free online). Address: Karen Pierce, Department of Neurosciences, University of California, San Diego, 8110 La Jolla Shores Dr., La Jolla, CA 92037, kpierce@ucsd.edu.

—and—

"Autism diagnoses prove highly stable as early as 14 months," Scott LaFee, UC San Diego News Center, April 29, 2019.

Researchers in Italy explore links between ASD traits, excessive internet use, and suicide in college-age students

Problematic internet use is rapidly increasing, especially among young people, and research indicates that individuals with autism spectrum disorders (ASD) are particularly vulnerable. In addition, individuals with either ASD or obsessive internet use are at increased risk for suicide. These findings recently led researchers in Italy to investigate the links between problematic internet use, ASD traits, and suicide in the general population.

Liliana Dell'Ossa and colleagues collected information from 178 university students. Participants completed three self-report questionnaires: the Adult Autism Subthreshold Spectrum (AdAS Spectrum), the Autism Quotient (AQ), and selected questions from the Trauma and Loss Spectrum-Self Report (TALS-SR). The AdAS Spectrum includes a question about obsessive internet use.

The researchers report that more than 27% of participants reported problematic internet use, and that this subgroup had higher scores in all domains of the AdAS Spectrum and AQ compared to other participants. For students who admitted to an obsession with the internet, a significant correlation existed between suicide risk and the non-verbal communication domain of the AdAS Spectrum and the social skills domain of the AQ.

The researchers say, "The present study corroborates previous studies showing higher autistic traits in individuals with problematic internet use. These data point out the relationship between autistic features and pathological levels of internet use in a non-clinical population. Consequently, putative problematic internet use should be evaluated by clinicians during the assessment of individuals with high autistic traits."

"Moreover," they add, "investigating ASD symptomatology may be useful when investigating patients with putative problematic internet use. Furthermore, this is the first study to suggest how an impairment in social skills and in non-verbal communication, typical of autism symptomatology, may be correlated to suicide risk in individuals with putative problematic internet use. Autism spectrum features like difficulties in social relationships and isolation might be a warning sign of increased suicide risk in subjects spending most of their time on the internet."

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"Problematic internet use in university students attending three superior graduate schools in Italy: Is autism spectrum related to suicide risk?", Liliana Dell'Osso, Carlo Antonio Bertelloni, Marco Di Paolo, Maria Teresa Avella, Barbara Carpita, Federica Gori, Maurizio Pompili, and Claudia Carmassi, *International Journal of Environmental Research and Public Health*, March 2019 (free online). Addresss: Carlo Antonio Bertelloni, Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy, carlo.ab@hotmail.it.

The Kids First Initiative: Giving Back to Families

The Hartwell Foundation Kids First initiative seeks to help every family who has a child with an autism spectrum disorder. The goal is to create detailed categories that accurately reflect individual behavior and personality, with the expectation of advancing personalized, targeted approaches for care and intervention that will be more successful than what is available today.

The Kids First approach is conducted using IRB-approved confidential survey methodology by prominent universities. Survey questions are simple, focused on basic behavioral and medical information, and can be completed in about 10 minutes. Results will be shared confidentially with all survey participants. The collected data will provide a unique opportunity for researchers to begin classification of ASD, and as new categories are identified, the effort will expand to more sophisticated requests for information.

We invite you to participate in the Kids First confidential survey, joining a growing network of families, clinicians, and scientists involved in this innovative research project to improve the lives of children and families affected by ASD. To learn more and begin your survey, visit kidsfirst.stanford.edu and when asked, type ARI as your referral code.

Study points to mutations in "junk" DNA as a factor in ASD

(continued from page 1)

Study coauthor Olga Troyanskaya comments that the implications of the work extend beyond autism. She says, "This is the first clear demonstration of non-inherited, noncoding mutations causing any complex human disease or disorder."

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"Whole-genome deep-learning analysis identifies contribution of noncoding mutations to autism risk," Jian Zhou, Christopher Y. Park, Chandra L. Theesfeld, Aaron K. Wong, Yuan Yuan, Claudia Scheckel, John J. Fak, Julien Funk, Kevin Yao, Yoko Tajima, Alan Packer, Robert B. Darnell, and Olga G. Troyanskaya, N*ature Genetics*, Vol. 51, May 27, 2019, 973-80. Address: Olga G. Troyanskaya, ogt@cs.princeton.edu.

—and—

"New causes of autism found in 'junk' DNA," news release, Simons Foundation, May 27. 2019.

EDITORIAL: Stephen M. Edelson, Ph.D.

Large-scale studies in autism: What do they show?

Over the past decade, many studies have documented substantial impairments in the gastrointestinal (GI), immunological, and metabolic systems of individuals with autism spectrum disorders (ASD). Although this is well known among researchers in the autism biomedical field, many other professionals have yet to acknowledge the high rate of these medical comorbidities.

The lack of awareness of medical symptoms associated with autism is partly due to the poor lines of communication among researchers, clinicians, and therapists in the autism and general medical communities.

In the past few years, numerous large-scale studies have documented high rates of medical problems in individuals with ASD as compared to the general population. Some of these medical problems have also been shown to be highly related to challenging behaviors.

Another reason for it, which is the theme of this editorial, is that many professionals are unaware of the findings of large-scale research studies, which are a core component of scientific investigation.

Most of the research documenting gastrointestinal, immune, and metabolic impairments in ASD has involved small-to-moderate sample sizes. However, in the past few years, numerous large-scale studies have documented high rates of medical problems in individuals with autism as compared to the general population. Some of these medical problems have also been shown to be highly related to challenging behaviors. A brief summary of several of these studies is described below.

In a study of 300,000 children in the United States, children with ASD were 60% more likely to suffer from irritable bowel disease than neurotypical controls (*Journal of Autism and Developmental Disorders*, 2018).

A meta-analysis, which combines and reanalyzes the data from previously published studies, revealed that children with autism were four times more likely to experience gastrointestinal complaints as compared to controls (*Pediatrics*, 2014).

Based on 17 items on a questionnaire filled out by 131 parents of children with ASD, pediatric gastroenterologists were able to correctly identify GI problems in 84% of the children (*Journal of Autism and Developmental Disorders*, 2018).

A study involving 522 children with ASD and 703 controls revealed that the children with ASD were 75% more likely to suffer from sleep problems than controls (*Pediatrics*, 2019).

Researchers found a strong correlation between sleep problems and aggression in 1,045 children with ASD (*Research in Developmental Disabilities*, 2018).

A moderate-size study involving 81 children with ASD found that sleep problems were associated with aggression, irritability, inattention, and hyperactivity (*Journal of Autism and Developmental Disorders*, 2016).

A study examining the U.S. National Health Interview Survey database analyzed data from 1,868 children with ASD and 197,652 controls. Children with ASD were 7% more likely to suffer from food, respiratory, and skin allergies than controls (*JAMA Network Open*, 2018).

Researchers using the National Survey of Children's Health database studied the prevalence of obesity in autism. Obesity is related directly or indirectly to GI function, immunology, and metabolism. Analyzing data on 875,963 teenagers with ASD and 31,913,657 controls, the researchers found that the individuals with ASD were 7% more likely to be obese than controls (*Autism*, 2018).

A study examined the prevalence rate of obesity in 5,053 children with ASD who were between two and 17 years of age. Thirty-five percent of them were overweight, and 18% were obese (*Pediatrics*, 2015).

Another important component of scientific investigation is referred to as *converging operations*. This means that researchers study a phenomenon in many different ways, providing support to a hypothesis from a multitude of perspectives. Over the past decade, hundreds of studies have investigated medical problems associated with autism, using numerous sample sizes, experimental designs, and assessment measures. Such studies overwhelmingly indicate the presence of several common medical comorbidities in autism, and some of these comorbidities are related to challenging behaviors.

Given the frequent association of medical symptoms with autism, standardized diagnostic assessments (e.g., ADOS-2, ADI-R) and medical evaluations (conducted by pediatricians) should address these common symptoms. If any medical comorbidity is suspected, standard practice should include a referral to a specialist.

Regarding treatment of medical comorbidities, there are many small-to-moderate studies published and underway. However, at this time, only two medical interventions are approved by the Food and Drug Administration (FDA), and they are both psychiatric drugs: risperidone (Risperdal) and aripiprazole (Abilify). There are no FDA-approved interventions to treat common medical problems in autism, such as GI, immune, or metabolic dysfunction. Physicians should consider, at the very least, prescribing treatments that have already been standardized for the general population.

The fact that individuals with ASD often suffer from medical comorbidities should no longer be considered questionable. Professional licensing organizations should require professional training (e.g., CME) about these medical conditions in order to ensure that providers offer patients with ASD optimal care.

One note: Based on many clinical reports, doctors should take caution regarding medication doses. Some individuals with ASD are sensitive to certain medications and, as a result, tend to overreact when given a recommended dose. The opposite effect can also occur, with individuals requiring more than the suggested dose in order to show a response. It would be advisable to start low and increase slowly when prescribing medications.

The fact that individuals with autism often suffer from medical comorbidities should no longer be considered questionable. Professional licensing organizations should require professional training (e.g., CME) about these medical conditions in order to ensure that providers offer patients with ASD optimal care. (Note: ARI offers, in joint providership with the Cleveland Clinic, complimentary AMA PRA Category 1 Credit™ to physicians and the general public.)

Finally, funding agencies should focus more of their attention on supporting research on GI, immunological, and metabolic problems in ASD. They should do this by financing multidisciplinary (i.e., medical, sensory, behavioral) studies.

In recent years, our knowledge about the role of comorbid medical problems in ASD has expanded rapidly. Now it is time for us to translate this knowledge into state-of-the-art research and more effective treatment options, so individuals with ASD can get the help they need.

Research Updates

Biomarker may aid doctors in choosing GI treatments

Researchers say they may have discovered a biomarker that could help gastroenterologists better treat children with ASD and comorbid gastrointestinal (GI) problems.

Stephen Walker and colleagues say that they have identified two distinct groups of children with ASD and comorbid chronic constipation and colonic inflammation. One group, dubbed fast responders, experiences a stable remission of GI symptoms in response to brief immunosuppression followed by continuing anti-inflammatory therapy. Another group, dubbed slow responders, has recurrent right-sided constipation that necessitates regular colon cleanouts.

To see if they could identify molecular biomarkers for each group, the researchers took ascending colon tissue biopsies from 35 children with ASD, including 20 slow responders and 15 fast responders. They report, "Significant differences were found between the two clusters with the fast responder-predominant cluster showing an upregulation of [RNA] transcripts involved in the activation of immune and inflammatory response and the slow responder-predominant cluster showing significant over-representation of pathways impacting colonic motility (e.g. genes involved in tryptophan and serotonin degradation and mitochondrial dysfunction)." They identified one specific long non-coding RNA that could predict cluster assignment with very high specificity, sensitivity, and accuracy.

The researchers say their findings, if replicated, may help doctors determine which patients with ASD will respond to standard anti-inflammatory therapy and which might benefit from an alternative strategy.

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"A molecular biomarker for prediction of clinical outcome in children with ASD, constipation, and intestinal inflammation," Stephen J. Walker, Carl D. Langefeld, Kip Zimmerman, Marshall Z. Schwartz, and Arthur Krigsman, *Scientific Reports*, Vol. 9, No. 1, 2019, 1-13. Address: Stephen Walker, Wake Forest University Health Sciences, Winston Salem, NC 27157, swalker@wakehealth.edu.

Melatonin improves sleep, behavior in kids with ASD

Prolonged-release melatonin appears to improve sleep and reduce externalizing behaviors such as hyperactivity and aggression in children with autism spectrum disorders (ASD), according to a new study. In addition, the researchers report, giving melatonin to children with ASD improves the quality of life for their parents.

One hundred and twenty-five children from 24 sites participated in the study by Athanasios Maras, Carmen Schroder, and colleagues. In the first part of the study, half of the children took pediatric prolonged-release melatonin (2 mg for 3 weeks, followed by either 2 or 5 mg for 10 weeks). The other half of the children received a placebo. Afterward, children in both groups participated in a nine-month open-label trial in which they took melatonin (2 or 5 mg per day for 18 weeks, and then 2, 5, or 10 mg for the remainder of the trial).

The researchers report that in the first part of the study, children taking melatonin slept better and exhibited significant improvements on the Child Externalizing Behavior Scale of the Strength and Difficulties Questionnaire (SDQ). The improvements in sleep quality continued during the open-label part of the study, with children falling asleep more quickly and sleeping longer. The only side effects seen were fatigue and mood swings in a small percentage of participants. The children's parents reported greater satisfaction with their children's sleep, improvements in their own sleep, and improvements in their quality of life.

Schroder comments that the team's findings show that "pediatric prolonged-release melatonin is efficient not only short term but maintains its effect long-term in children and adolescents with ASD and has positive effects on their caregivers."

The researchers found that the effective dose of melatonin varied widely. About one third of the children needed only a 2 mg dose, about half needed 5 mg, and the remainder needed 10 mg.

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"Melatonin benefits kids with autism, ups parents' quality of life," Liam Davenport, Medscape.com, April 15, 2019. Maras and colleagues presented their findings at the European Psychiatric Association Congress in April 2019.

Wearable AI-driven device helps children with ASD master social skills

A wearable artificial-intelligence-driven device can improve the social skills of children with autism spectrum disorders (ASD), according to a new study.

Catalin Voss and colleagues investigated the effectiveness of Superpower Glass, a Google Glass-based device that uses a computer vision system wirelessly connected to a smart phone app. The system tracks faces and classifies the emotions people are experiencing, providing emoticons and audio cues to help children develop social skills. It also includes two games, "guess the emotion" (in which children try to determine which emotion a person is exhibiting) and "capture the smile" (in which children try to elicit an emotion from another person—for instance, by telling a joke to make the person smile).

Enrolling 71 young children with ASD in their study, the researchers randomly assigned 40 children to receive the glasses and 31 to act as controls. Both groups of children continued to receive applied behavioral analysis (ABA) therapy. The researchers asked participants and their caregivers or therapists to use the glasses for 20 minutes four times a week for six weeks, although participants averaged only half the recommended days of use.

The researchers say that compared to controls, the children using the glasses showed significant improvements on the Vineland Adaptive Behaviors Scale socialization subscale. They also showed improvements on several other measures of social skills, but these did not reach significance.

The researchers say, "Overall, these results support the hypothesis that the Superpower Glass intervention can improve social skills of children with ASD between the ages of 6 and 12 years as an augmentation to standard of care therapy."

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"Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder: a randomized clinical trial," Catalin Voss, Jessey Schwartz, Jena Daniels, Aaron Kline, Nick Haber, Peter Washington, Qandeel Tariq, Thomas N. Robinson, Manisha Desai, Jennifer M. Phillips, Carl Feinstein, Terry Winograd, and Dennis P. Wall, *JAMA Pediatrics*, March 25, 2019 (free online). Address: Dennis P. Wall, Department of Pediatrics, Division of Systems Medicine, Stanford University, 1265 Welch Road, Medical School Office Bldg. x14, Stanford, CA 94305, dpwall@stanford.edu.

—and—

"Digital intervention ups socialization in children with autism," Medical Xpress, March 26, 2019.

Research Updates

Prospective study: Early vitamin D deficiency not linked to later ASD

New research casts doubt on the idea that low vitamin D levels in early childhood are a risk factor for autism spectrum disorders (ASD).

In a prospective study designed to determine if lower vitamin D levels precede an ASD diagnosis, Yamna Ali and colleagues analyzed data on more than 3,800 preschool children. The data included the children's blood concentrations of 25 hydroxyvitamin D and parental reports about vitamin D supplementation.

Over the course of the follow-up, which averaged two and a half years, 41 of the children received a diagnosis of ASD. Controlling for a wide variety of factors including age, sex, family history of ASD, maternal ethnicity, and neighborhood household income, the researchers found no association between vitamin D status and a later ASD diagnosis. In addition, they found no association between vitamin D supplementation and an ASD diagnosis.

The researchers conclude, "Vitamin D in early childhood may not be associated with incident physician diagnoses of autism spectrum disorder."

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"Prospective cohort study of vitamin D and autism spectrum disorder diagnoses in early childhood," Yamna Ali, Laura N. Anderson, Sharon Smile, Yang Chen, Cornelia M Borkhoff, Christine Koroshegyi, Gerald Lebovic, Patricia C Parkin, Catherine S Birken, Peter Szatmari, and Jonathon L Maguire, *Autism*, March 8, 2018 (online). Address: Jonathan Maguire, Applied Health Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, 250 Yonge Street, Toronto, ON M5G 1B1, Canada, jonathon.maguire@utoronto.ca.

Dogs help relieve stress in adults with ASD

Animal assisted therapy (AAT) can help reduce stress-related problems in adults with high-functioning autism spectrum disorders (ASD), a new study reports.

Carolien Wijker and colleagues enrolled 53 adults with ASD, all with normal to high intelligence, in their study. All of the participants had high scores on a scale measuring stress. Half of the participants participated in AAT, while the other half were placed on a waiting list.

The intervention consisted of 10 weekly 60-minute one-on-one sessions conducted by therapists who specialized in working with individuals with ASD. A trained therapy dog participated in each session.

The researchers assessed each individual in the therapy group at baseline, after 10 weeks of therapy, and at a follow-up 10 weeks after therapy ended. Control group members were assessed at the same times. The researchers compared therapy participants to controls using questionnaires (filled out by participants as well as by spouses, other family members, or friends) measuring perceived stress, symptoms of stress, impairments in social responsiveness, and self-esteem.

The researchers report that compared to the waiting list condition, "animal assisted therapy with a dog reduced perceived stress and agoraphobia symptoms in adults with ASD." Furthermore, they say, "the results implied that AAT reduced impairments in social responsiveness as rated by participants' spouses, close family members, or friends." In addition, they note, "There was an indication that depressive symptoms reduced due to the therapy." They also comment that "participant adherence to the therapy program was noteworthy," with all participants taking part in at least nine of the ten sessions, and that the positive effects were still seen at follow-up. No significant effects were detected for self-esteem.

The researchers note that the significant effect on agoraphobia was surprising. They say, "A possible explanation for the effect on agoraphobia may be that during the last three sessions of the intervention, participants, accompanied by the therapist and the dog, worked on social fears and controlling environmental stimuli by leaving the mental health facility and practicing in the outside world."

The researchers conclude, "The remarkable adherence to the therapy program by study participants and the program's clinically relevant effects indicate that AAT with dogs can be used to reduce perceived stress and symptoms of agoraphobia, and to improve social awareness and communication in adults with ASD with normal to high intelligence."

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"Effects of dog assisted therapy for adults with autism spectrum disorder: an exploratory randomized controlled trial," Carolien Wijker, Ruslan Leontjevas, Annelies Spek, and Marie-Jose Enders-Slegers, *Journal of Autism and Developmental Disorders*, March 21, 2019 (free online). Address: Carolien Wijker, GGZ Oost Brabant, P.O. Box 3, 5427 ZG Boekel, The Netherlands, carolien.wijker@ou.nl.

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Visual filtering problems resolve in adolescence

While young children with autism spectrum disorders (ASD) appear to have difficulty filtering out visual distractions when reading or doing schoolwork, a new study suggests that this is no longer a problem by the time these children reach their early teens.

In previous research, Shawn Christ and colleagues detected impairments in blocking out visual distractions in young children with ASD but not in older teens or adults. In the current study, the team was able to identify with even greater accuracy the age range in which difficulties in visual filtering are apparent.

The new study by Christ, Kelly Boland, and colleagues included 80 individuals, 36 of whom had ASD. All participants were between 11 and 20 years of age. Participants were asked to respond as quickly as possible to a visual target on a computer screen while ignoring visual distractions close to the target's location.

This time, the researchers report, they saw no evidence of group differences in visual filtering performance. They conclude, "Taken together with previous research, these results suggest that during early adolescence the previously observed impairment may resolve or compensatory strategies develop, allowing individuals with ASD to perform as well as their neurotypical peers."

Christ comments, "Here is a cognitive difficulty that is more apparent during one age than another. Now we can say there is a time period when these children may benefit from an intervention that focuses on accommodating or helping them overcome this difficulty. This could have a significant impact on their academic and social success. They may not need that same intervention later on in life."

The researchers say a number of strategies—for example, using a reading window on a page to block out most of the words, or creating "quiet rooms"—could help young children with ASD overcome their impairments in visual filtering.

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"Brief report: flanker visual filtering ability in older adolescents with autism spectrum disorder," Kelly M. Boland, Janine P. Stichter, David Q. Beversdorf, and Shawn E. Christ, *Journal of Autism and Developmental Disorders*, Vol. 49, No. 1, January 2019, 422-28. Address: Shawn E. Crist, Department of Psychological Sciences, University of Missouri, Columbia, MO 65211, christse@missouri.edu.

—and—

"A defining moment: Age-related differences appear in children with autism," news release, University of Missouri, March 12, 2019.

Animal study: cerebellum influences social behavior

New research indicates that the cerebellum, known to play a role in motor coordination, also helps to control the brain's reward and social circuitry. Abnormalities of the cerebellum are strongly linked to autism.

Ilaria Carta and colleagues studied mice using a technique that involves modifying neurons so they can be activated or deactivated using pulses of light. When the researchers activated neurons in the cerebellum that connect to the ventral tegmental area (VTA)—an area involved in reward processing and encoding—they found that this led to increased activation in the VTA.

The researchers then investigated whether input from the cerebellum to the VTA influenced behavior related to rewards. Placing mice in an open chamber, they used pulses of light to activate cerebellar neurons linked to the VTA whenever the mice entered a specific part of the chamber. They found that mice showed a strong preference for remaining in this area, spending more than 70% of their time there. In addition, the researchers discovered that the mice were willing to work, or to spend time in normally disliked conditions (for instance, light vs. dark areas), to activate the cerebellar-VTA pathway.

The researchers say, "Our data delineate a major, previously unappreciated role for the cerebellum in controlling the reward circuitry and social behavior."

Next, the researchers studied the effect of input from the cerebellum to the VTA on social preferences. At baseline, mice preferred to remain in a "social" chamber rather than an empty chamber or one containing only non-social objects. When the researchers inactivated the cerebellar projections into the VTA, however, the mice no longer showed this preference. Long-term inactivation of this pathway completely erased the normal social preference of the mice.

The researchers conclude, "Our data delineate a major, previously unappreciated role for the cerebellum in controlling the reward circuitry and social behavior."

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"Cerebellar modulation of the reward circuitry and social behavior," Ilaria Carta, Christopher H. Chen, Amanda L. Schott, Schnaude Dorizan, and Kamran Khodakhah, *Science*, Vol. 363, No. 6424, January 18, 2019 (online). Address: Kamran Khodakhah, Albert Einstein College of Medicine, Rose F. Kennedy Center, 1410 Pelham Parkway South, Room 903, Bronx, NY 10461, k.khodakhah@einstein.yu.edu.

—and—

"New findings reveal surprising role of the cerebellum in reward and social behaviors," news release, National Institute of Mental Health, January 17, 2019.

General anesthesia during C-sections may increase ASD risk

A study by researchers in Israel suggests that the increased risk of autism spectrum disorders (ASD) seen in children delivered by Cesarean section is due not to the procedure itself, but rather to exposure to general anesthesia.

Maayan Huberman Samuel and colleagues examined the birth records of 347 children with ASD, 117 children with other developmental delays, and 2,226 matched neurotypical controls. The researchers found a significant link between C-sections and increased risk for ASD, but only for children whose mothers received general anesthesia. Study coauthor Idan Menashe comments, "C-sections performed with other types of anesthesia such as epidural or spinal sedation are relatively safe." (C-section delivery with or without general anesthesia did not increase the risk of developmental delay.)

The researchers also compared planned C-sections to unplanned procedures performed due to birth complications, and detected no significant difference in ASD risk between the two.

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"Exposure to general anesthesia may contribute to the association between Cesarean delivery and autism spectrum disorders," Maayan Huberman Samuel, Gal Meiri, Ilan Dinstein, Hagit Flusser,Analiya Michaelovski, Asher Bashiri, and Idan Menashe, *Journal of Autism and Developmental Disorders*, May 3, 2019 (online). Address: Idan Menashe, Public Health Department, Ben-Gurion University of the Negev, Beer Sheva, Israel, idanmen@bgu.ac.il.

—and—

"Israel study links autism to general anesthesia in C-sections," *Times of Israel*, May 3, 2019.

Atypical vocalizations may emerge early in children with ASD

A new report suggests that children who later develop autism spectrum disorders (ASD) may exhibit differences in vocalizing with caregivers beginning as early as four months of age.

Gordon Ramsay and colleagues studied the vocal communications between 78 infants and their caregivers from birth until the children reached two years of age. Of the children, 33 had no family history of autism. The remainder were younger siblings of children with ASD, putting them at increased risk for developing ASD themselves. The researchers recorded vocal interactions between children and caregivers one day each month over the course of the study, using a device called Language Environment Analysis (LENA) that the babies wore in a pocket in their clothes.

By the age of three, 10 of the high-risk children received an ASD diagnosis. The researchers report that babies in the high-risk group who developed autism began showing fewer vocalizations than controls as early as four months of age. Even high-risk children who did not receive an ASD diagnosis diverged from the control group by 18 months.

The researchers are currently investigating a larger group of more than 200 infants, and plan to examine other measures of vocalization such as babbling and crying.

—

"Signs of autism may be heard early in infancy," Jessica Wright, Spectrum News, May 4, 2019. Ramsay and colleagues presented their findings at the May 2019 International Society for Autism Research (INSAR) meeting in Montreal, Canada.

Participants needed for ASD microbiome study

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

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

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

Gene linked to autism also shown to affect the gut

(continued from page 1)

—

"Gastrointestinal dysfunction in patients and mice expressing the autism-associated R451C mutation in neuroligin-3," Suzanne Hosie, Melina Ellis, Mathusi Swaminathan, Fatima Ramalhosa, Gracia O. Seger, Gayathri K.Balasuriya, Christopher Gillberg, Maria Råstam. Leonid Churilov, Sonja J. McKeown, Nalzi Yalcinkaya, Petri Urvil, Tor Savidge, Carolyn A. Bell, Oonagh Bodin, Jen Wood, Ashley E. Franks, Joel C. Bornstein, and Elisa L. Hill-Yardin, *Autism Research*, May 22, 2019 (free online). Address: Elisa L. Hill-Yardin, School of Health and Biomedical Sciences, RMIT University, 225-245 Clements Drive, Bundoora, Victoria 3083 Australia, elisa.hill@rmit.edu.au.

—and—

"Research confirms gut-brain connection in autism," news release, RMIT University, May 30, 2019.

ASD fecal transplants lead to symptoms of autism in mice

Colonization with gut microbes from individuals with autism spectrum disorders (ASD) causes mice to develop symptoms of autism, a new study reports.

Gil Sharon and colleagues transplanted human stool from individuals with and without ASD into the guts of "germ-free" mice with no gut bacteria, and then studied offspring from each group. The researchers used a tracking system to monitor the behavior of the mice. In addition, they recorded how often the mice buried marbles in their cages—a sign of repetitive behavior—and used ultrasonic microphones to listen to the animals' communications.

The researchers found that the offspring colonized with microbes from individuals with ASD exhibited deficits in social behavior, abnormalities in vocal interactions, and repetitive behaviors. For example, the mice did not produce as many ultrasonic squeaks as control mice, and did not wrestle, push, and sniff other mice as frequently. In addition, they buried far more marbles than the control mice.

The brains of offspring colonized with microbes from individuals with ASD exhibited alterations in gene splicing, and the researchers detected an altered pattern of metabolites in the colons of the mice. In particular, levels of 5-aminovaleric acid (5AV) and taurine were lower. In a follow-up experiment, the researchers gave these two metabolites to another group of mice bred to exhibit autistic-like behavior, and found that the social skills of the mice improved and their repetitive behaviors lessened.

The researchers note that more studies are needed to determine if their findings will translate into human treatments. However, they are hopeful that in the future, microbiota-based interventions such as probiotics, fecal microbiota transplantation, or supplementation with metabolites may prove to be effective therapies for ASD.

—

"Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice," Gil Sharon, Nikki Jamie Cruz, Dae-Wook Kang, Michael J. Gandal, Bo Wang, Young-Mo Kim, Erika M. Zink, Cameron P. Casey, Bryn C. Taylor, Christianne J. Lane, Lisa M. Bramer, Nancy G. Isern, David W. Hoyt, Cecilia Noecker, Michael J. Sweredoski, Annie Moradian, Elhanan Borenstein, Janet K. Jansson, Rob Knight, Thomas O. Metz, Carlos Lois, Daniel H. Geschwind, Rosa Krajmalnik-Brown, and Sarkis K. Mazmanian, *Cell*, May 30, 2019 (free online). Address: Gil Sharon, gsharon@caltech.edu.

Free Autism Continuing Education and Webinars

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

August 28, 2019
10:00 a.m. to 11:00 a.m. PST
RESEARCH ON MICROBIOTA TRANSFER THERAPY IN PATIENTS WITH ASD
Dr. Rosa Krajmalnik-Brown
Associate Professor, Swette Center for Environmental Biotechnology,
Arizona State University

October 2, 2019
10:00 a.m. to 11:00 a.m. PST
BEHAVIORAL SUPPORT TRAINING FOR PARENTS
Dr. Suzannah Joy Iadarola
Pediatric Psychologist and BCBA
Neurodevelopmental and Behavioral Pediatrics Division,
University of Rochester Medical Center

October 23, 2019
10 a.m. to 11 a.m. PST
FRAGILE X AND ASD
Randi Hagerman, M.D.
Medical Director, UC Davis Mind Institute

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** We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.*

Prenatal vitamin use may lower ASD risk in siblings

Mothers of children with autism spectrum disorders (ASD) may reduce their odds of having a second child with ASD by taking prenatal vitamins, a new study suggests.

Rebecca Schmidt and colleagues analyzed data from children and mothers enrolled in the MARBLES (Markers of Autism Risk in Babies: Learning Early Signs) study. Their final sample included 241 younger siblings of children with ASD.

The researchers report that the prevalence of ASD was 14.1% for younger siblings whose mothers took prenatal vitamins in the first month of pregnancy, compared to 32.7% for younger siblings whose mothers did not take prenatal vitamins during that time. In addition, in younger siblings who developed autism, early prenatal vitamin use was linked to less severe autism symptoms and better cognitive and memory skills.

The researchers say, "Additional research is needed to confirm these results; to investigate dose thresholds, contributing nutrients, and biologic mechanisms of prenatal vitamins; and to inform public health recommendations for ASD prevention in affected families."

—

"Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings," Rebecca J. Schmidt, Ana-Maria Iosif, Elizabeth Guerrero Angel, and Sally Ozonoff, *JAMA Psychiatry*, February 27, 2019 (epub prior to print publication). Address: Rebecca Schmidt, MIND Institute, University of California, Davis, 2825 50th Street, Sacramento, CA 95817.

Quotable...

"Immune processes have a vital role in CNS homeostasis, resilience and brain reserve..... Autoimmunity, chronic inflammation, infection and psychosocial stress can tip the scales towards disruption of higher-order networks. However, not only classical neuroinflammatory diseases, such as multiple sclerosis and autoimmune encephalitis, are caused by immune dysregulation that affects CNS function. Recent insight indicates that similar processes are involved in psychiatric diseases such as schizophrenia, autism spectrum disorder, bipolar disorder and depression.... These discoveries challenge our traditional classification of neurological and psychiatric diseases. New clinical paths are required to identify subgroups of neuropsychiatric disorders that are phenotypically distinct but pathogenically related and to pave the way for mechanism-based immune treatments."

"Immunoneuropsychiatry—novel perspectives on brain disorders," K. Pape et al., *Nature Reviews Neurology*, April 15, 2019

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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.

•

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•

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