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Sleep problems start early in ASD and are associated with abnormal hippocampal development

Sleep problems are common in infants who later develop autism spectrum disorders (ASD) and are associated with an abnormal growth trajectory of the hippocampus, a new study reports.

Katherine MacDuffie and colleagues analyzed MRI brain scans performed on 432 infants at 6, 12, and 24 months of age. In addition, they collected data on the children's sleep patterns. Of the infants, 127 were classified as low-risk because they did not have an older sibling with ASD, while the remainder were classified as high-risk. Seventy-one high-risk infants eventually received an ASD diagnosis.

The researchers found that sleep onset problems were more common in 6- to 12-month-old infants who later developed ASD than in other children. Additionally, infant sleep onset problems were related to hippocampal volume trajectories from 6 to 24 months for high-risk infants who developed ASD. Changes in hippocampal size have been associated with poor sleep in adults and older children, but MacDuffie says, "This is the first study we are aware of to find an association in infants as young as six months of age."

Study coauthor Annette Estes says, "It could be that altered sleep is part-and-parcel of autism for some children. One clue is that behavioral interventions to improve sleep don't work for all children with autism, even when their parents are doing everything just right. This suggests that there may be a biological component to sleep problems for some children with autism."

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The researchers conclude, "These findings provide initial evidence that sleep onset problems in the first year of life precede ASD diagnosis and are associated with altered neurodevelopmental trajectories in infants at high familial risk who go on to develop ASD. If replicated, these findings could provide new insights into a potential role of sleep difficulties in the development of ASD."

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"Sleep onset problems and subcortical development in infants later diagnosed with autism spectrum disorder," Katherine MacDuffie, Mark Shen, Stephen Dager, Martin Styner, Sun Hyung Kim, Sarah Paterson, Juhi Pandey, Tanya St. John, Jed Elison, Jason Wolff, Meghan Swanson, Kelly Botteron, Lonnie Zwaigenbaum, Joseph Piven, and Annette Estes, *American Journal of Psychiatry*, May 7, 2020 (online). Address: Katherine MacDuffie, UW Autism Center, CHDD, Box 357920, University of Washington, Seattle, WA 98195, uwautism@uw.edu.

—and—

"Sleep difficulties linked to altered brain development in infants later diagnosed with autism," news release, University of Washington, May 7, 2020.

Relationship between ASD, eating disorders explored

Research indicates that around 20% to 30% of adults with eating disorders, as well as 3% to 10% of children with eating disorders, also have autism spectrum disorders (ASD). In a new large-scale study, Francesca Solmi and colleagues report that ASD traits appear to precede eating disorders, indicating that ASD is a risk factor for disordered eating.

Using the Avon Longitudinal Study of Parents and Children, the researchers evaluated data on more than 5,000 children. Parents participating in the study completed the Social and Communication Disorders Checklist (SCDC) when the children were 7, 11, 14, and 16 years of age, allowing the researchers to determine the children's levels of social traits associated with ASD. In addition, data collected from the children

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CSF vasopressin levels may help to predict autism in infants

Researchers at Stanford report that low cerebrospinal fluid (CSF) levels of the hormone vasopressin—which affects social behaviors such as pair-bonding and fathering in male mammals—may be a biomarker for autism spectrum disorders (ASD).

Previous research by Karen Parker, John Constantino, and colleagues (Including Ozge Oztan, first author of the new study) revealed that CSF levels of vasopressin were significantly lower in children with ASD than in controls, and that individuals with the lowest CSF vasopressin levels had the most severe symptoms of autism. The researchers also found that administering vasopressin to children with autism improved their social ability.

In the new study, the researchers used samples of cerebrospinal fluid taken from newborn to three-month-old infants with fevers and stored for future research. Among these samples, the researchers identified 11 from infants who later developed ASD and matched them to 22 samples from controls. (Two samples in the ASD group were not large enough to test, leaving a total of 9.)

The researchers say that CSF vasopressin levels "were significantly lower among ASD cases than controls, and individually predicted case status, with highest precision when cases with comorbid attention-deficit/hyperactivity disorder [ADHD] were removed from the analysis." Individual vasopressin levels correctly predicted which children would develop ASD in seven of the nine autism cases, and the two samples that did not correctly predict autism came from children also diagnosed with ADHD. Levels of a related hormone, oxytocin, did not differ between infants with ASD and controls.

The researchers say, "These preliminary findings suggest that a biomarker of autism may be present before behavioral symptoms emerge. If replicated, this approach could be useful for assessing autism risk and facilitating early intervention in high-risk individuals." They caution, however, that their study involved a small number of samples and needs to be replicated in a larger group. They also plan to study children with other disorders to see if their finding is specific to autism. In addition, they want to study whether using a

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Reducing levels of tau prevents symptoms of autism from developing in mouse models of ASD

Reducing levels of a protein called *tau* prevents seizures and symptoms of autism from occurring in two separate mouse models of autism, according to a recent study. While tau has never been linked to autism, it is known to play a role in Alzheimer's disease and other neurodevelopmental conditions.

In earlier research, Chao Tai and colleagues found that reducing tau in a mouse model of Dravet syndrome—a severe form of epilepsy—could prevent seizures and cognitive deficits. "We wondered whether tau reduction could also prevent the signs of autism that are often seen in people with Dravet syndrome," Tai says.

To explore this question, the researchers used a mouse model of Dravet syndrome with one or both copies of the gene that encodes tau deleted. They found that reducing tau did stop core autism symptoms from developing, with even a 50 percent reduction leading to significant benefits. The researchers conducted the same experiment with a second mouse model of autism involving a different genetic mutation and achieved the same results.

In both mouse models, tau reduction also prevented enlargement of the brain, a common condition in autism. In addition, it prevented another autism-related phenomenon, over-activation of the PI3K-Akt-mTOR signaling pathway (which regulates many cell functions). The researchers found that tau reduction works by enhancing the activity of an enzyme called PTEN, which can prevent overactivation of this signaling pathway.

They conclude, "Our findings suggest an enabling role of tau in the pathogenesis of autism and identify tau reduction as a potential therapeutic strategy for some of the disorders that cause this condition." Currently, they are developing and testing drugs that could lower tau levels or increase the activity of PTEN. However, they caution that reducing tau levels may not be an effective treatment for all forms of autism, and that treatment may only work during the early stages of development.

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"Tau reduction prevents key features of autism in mouse models," C. Tai, C. W. Chang, G. Q. Yu, I. Lopez, X. Yu, X. Wang, W. Guo, and L. Mucke, *Neuron*, February 18, 2020 (epub prior to print publication). Address: lennart.mucke@gladstone.ucsf.edu.

—and—

"Could targeting an Alzheimer's associated protein prevent autism?" news release, Gladstone Institutes, March 2, 2020.

Pilot study: TMS may benefit individuals with ASD, depression

Transcranial magnetic stimulation (TMS) may be an effective treatment for depression in individuals with autism spectrum disorders (ASD) and may also have some positive effects on ASD symptoms, a new study reports.

McLeod Frampton Gwynette, who headed the study, says, "You'll see very high rates of major depressive disorder in adults with autism, up to 26 to 50%. When they have depression, it tends to be more severe than in typically developing individuals. They're also more likely to have suicidal ideation and more likely to attempt suicide. In addition, their depression is more likely to be refractory to treatment."

Gwynette and colleagues wanted to see if TMS, which has proven beneficial for many individuals with depression, would be effective for individuals with both depression and ASD. TMS involves placing a magnet on the scalp to generate electromagnetic pulses that activate neurons in the brain region near the magnet.

The researchers enrolled 13 adults with both ASD and depression in their study, in which participants underwent 25 daily TMS treatments. The treatments targeted the left dorsolateral prefrontal cortex, a brain region associated with depression.

The researchers report that after treatment, 70% of participants had a decrease in symptoms of depression, with 40% experiencing a remission. While participants themselves did not detect a change in their ASD symptoms, people who knew the participants reported decreases in repetitive behaviors, hyperactivity, and irritability.

Gwynette and his colleagues caution that this was a small, unblinded pilot study, and that larger, randomized, placebo-controlled trials are needed. However, study coauthor Mark George says, "These are promising results. I'm particularly intrigued by the improvements not just in depressive symptoms but also in other symptoms in the autism spectrum. That was unexpected."

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"Treatment of adults with autism and major depressive disorder using transcranial magnetic stimulation: an open label pilot study," McLeod Frampton Gwynette, Danielle W. Lowe, Erin A. Henneberry, Gregory L. Sahlem, Melanie Gail Wiley, Hussam Alsarraf, Sarah Brice Russo, Jane E. Joseph, Philipp M. Summers, Laura Lohnes, and Mark S. George, *Autism Research*, Vol. 13, No. 3, January 15, 2020 (online). Address: McLeod Frampton Gwynette, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, 5th Floor, South Tower, Room 509, Charleston, SC 29425, gwynette@musc.edu.

—and—

"Pilot study suggests promise of new approach to treat adults with autism and depression," news release, Medical University of South Carolina, April 7, 2020.

Vasopressin levels may help predict ASD in infants

(cont. from page 1)

blood biomarker is possible, since obtaining CSF samples is a difficult and highly invasive procedure.

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"Neonatal CSF vasopressin concentration predicts later medical record diagnoses of autism spectrum disorder," Ozge Oztan, Joseph P. Garner, John N. Constantino, and Karen J. Parker, *Proceedings of the National Academy of Sciences*, April 27, 2020 (online). Address: Karen J. Parker, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305, kjparker@stanford.edu.

—and—

"Potential autism biomarker found in babies," news release, Stanford University Medical Center, April 27, 2020.

EDITORIAL: Stephen M. Edelson, Ph.D.

Needed: a standard battery of assessments

Currently, there is no shortage of assessments for children or adults with autism. In fact, dozens of such assessments are in use today.

However, I believe there is a clear need for a *standardized* battery of assessments—and I believe that establishing such a battery will benefit researchers, therapists, clinicians, and, most importantly, individuals with autism spectrum disorders.

The current status of assessments

There are several well-established diagnostic tools in wide use today. Popular ones include the Autism Diagnostic Observation Scales (ADOS), the Autism Diagnostic Interview–Revised (ADI-R), and the Childhood Autism Rating Scales (CARS).

Over the years, other types of assessments have been developed. These include, but are not limited to, assessments of anxiety, communication, sensory dysregulation, repetitive and challenging behaviors, sleep, and social interaction.

Such assessments are often used by researchers to determine the incidence of symptoms, behaviors, and conditions (SBC), monitor changes over time, and evaluate individuals before and after treatment. Clinicians and therapists frequently rely on these assessments to determine appropriate treatments as well as to monitor their clients' progress.

Many SBC assessments were originally developed for individuals with developmental disabilities, while others were designed specifically for autism. SBC assessments developed to evaluate the non-autistic population include the Conners Comprehensive Behavior Rating Scale for evaluating ADHD symptoms and the Multidimensional Anxiety Scale for Children. Popular assessments specifically designed for autism include the Autism Behavior Inventory, the Anxiety Scale for Children with Autism Spectrum Disorder, and the Autism Social Skills Profile.

A number of assessments have also been adapted to take into account the unique challenges associated with autism. Adaptations often involve replacing self-reports (for instance, asking if an individual feels anxious) with observation of symptoms and behaviors typically associated with a condition (for instance, observing whether the individual exhibits behaviors indicating anxiety).

Arguments for a standard assessment battery

Researchers and clinicians do not always rely on the same set of assessments when evaluating study participants or patients. In fact, their selection of assessments varies considerably, and may depend on cost as well as the amount of time required and the ease of administering them. However, *one cannot assume that all assessments are equally sensitive when measuring the same SBC.*

I believe that it is time for us to actively make comparisons between assessments. This will allow us to weed out assessments that may be less useful, and to rely only on the most accurate as well as the most *valid* and *reliable* tests.

(Note: An assessment is considered *valid* if it can be shown to measure what it is intended to measure. It is considered *reliable* when different users obtain similar scores when reporting on the same individual, or when ratings collected at different times for the same individual are consistent.)

Narrowing down the current number of assessments to a standardized battery will admittedly be a challenging job. However, the results will benefit all professionals working with individuals with ASD.

With respect to research, for instance, it is preferable to compare findings using the same assessment measures, especially when researchers are attempting to replicate previous findings. As researchers as well as critics often comment, the autism field is replete with mixed findings. Although the heterogeneity of the spectrum is one reason for such discrepancies, the use of different assessment measures is another significant factor.

Optimally, the results from a standard battery of assessments would help therapists decide what treatment approaches to use, and even suggest specific interventions within an approach. Examples might include identifying a behavioral strategy such as differential reinforcement of other behaviors (DRO) to treat an individual's aggression, and a sensory integration approach, such as deep pressure, to help the individual fall asleep.

A standard battery of tests would also help clinicians plan treatments more effectively. Currently, some physicians simply offer a basic physical exam while others rely on extensive laboratory testing. Dr. Robert Hendren, a psychiatrist at the University of California, San Francisco, surveyed a group of experienced clinicians in order to learn about medical assessments used to determine potential biomedical interventions. (Note: This study did not examine the *general* medical assessment of ASD.) Dr. Hendren found little commonality among them. This finding was surprising since most of these physicians were known to communicate regularly through emails and at meetings.

Of course, when developing a standard battery of assessments, factors other than accuracy will need to be considered. As mentioned earlier, the cost as well as the ease and amount of time to administer the tests should also be taken into account. It is possible that the most accurate assessment measures are simply not practical for all research, clinical, and therapeutic settings.

In fact, a one-size-fits-all assessment for SBCs may not be possible. For example, some assessments may be more accurate for those with severe forms of autism, whereas others may be more accurate for those with little or no communication difficulties. Care will need to be taken to ensure that the selected battery of tests is not too limited to meet the needs of all individuals on the spectrum.

A standard battery of assessments will also need to include those SBCs that are prevalent in the autism population but are not considered as core autism features by popular diagnostic tests. These include gastrointestinal function, sensory sensitivities, nutritional status, communication difficulties, sleep problems, social interaction, and social antecedents and consequences of challenging behaviors.

Clearly, developing a standard battery of tests will take significant time and effort. However, given the number of assessments available today, it is definitely a "doable" undertaking. Such an initiative can be successful if it is supported by the medical, scientific, and autism communities.

A standard battery of assessments is the first step needed to develop an evidence-based standard of care for those on the autism spectrum. Now is the time for those of us in the autism field to take this step.

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.

Research Updates

Toddlers' vocalizations may point to ASD

Analyzing just six minutes of toddlers' vocalizations may help clinicians identify children at elevated risk for autism spectrum disorders (ASD), according to a new study by Elena Tenenbaum and colleagues.

The study involved toddlers between 16 and 31 months of age. Of the children, 22 had confirmed diagnoses of ASD, 8 had confirmed developmental or language delays (DLD) but not autism, and 22 were neurotypical controls.

The researchers sat the toddlers on a caregiver's lap and showed them six minutes of videos on a tablet. The videos, designed to elicit behaviors associated with ASD, included a mirror display in which toddlers could see their own faces; cascading bubbles; a mechanical bunny interacting with other animal puppets; children arguing over a toy; and other clips of social and nonsocial stimuli. At three intervals, the clinician also called the child's name to see how the child responded.

A coder blind to the children's diagnoses coded the children's vocalizations as nonsyllabic (consonant-only or vowel-only sounds that were not part of words), canonical (nonword consonant-vowel combinations), or syllabic (canonical vocalizations plus syllabic vocalizations from words containing at least one vowel). The coder also assessed whether a child spoke any words at all.

The researchers report that:

—Children with ASD or DLD were less likely to produce words than the neurotypical participants.

—The ratio of syllabic vocalizations to all vocalizations was higher in neurotypical children than in those in the ASD or DLD groups.

—The rates of nonsyllabic vocalizations were higher in the ASD group than in either the TD or DLD groups.

The researchers say, "Those producing more nonsyllabic vocalizations were 24 times more likely to be diagnosed with ASD." They conclude, "These results lend support to previous findings that early vocalizations might be useful in identifying risk for ASD in toddlers and demonstrate the feasibility of using a scalable tablet-based app for assessing vocalizations in the context of a routine pediatric visit."

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"A six-minute measure of vocalizations in toddlers with autism spectrum disorder," Elena J. Tenenbaum, Kimberly L.H. Carpenter, Maura Sabatos-DeVito, Jordan Hashemi, Saritha Vermeer, Guillermo Sapiro, and Geraldine Dawson, *Autism Research*, March 25, 2020 (free online). Address: Elena Tenenbaum, Duke Center for Autism and Brain Development, Duke University School of Medicine, Hock Plaza, 2424 Erwin Road, Suite 501, Durham, NC 27705, elena.tenenbaum@duke.edu.

Study indicates aluminum levels abnormal in ASD

A new postmortem study of brain tissue adds support to previous research suggesting that individuals with autism spectrum disorders (ASD) have excessive levels of aluminum in their brains.

Christopher Exley and Elizabeth Clarkson measured the aluminum content of 191 tissue samples taken from 20 brains of donors without known neurodegenerative diseases. The researchers say that the aluminum content of these tissues was "invariably low."

The researchers then compared this data to information collected on aluminum levels in the brains of individuals with ASD, multiple sclerosis, familial Alzheimer's disease, or sporadic Alzheimer's disease, measured using identical procedures. They say, "Detailed statistic analyses showed that aluminum was significantly increased in each of these disease groups compared to control tissues."

The findings relating to autism are consistent with a 2018 study of brain tissue from donors with ASD (see ARRI 32/1, 2018), in which Exley and colleagues reported detecting "some of the highest values for aluminum in human brain tissue yet recorded."

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"Aluminium in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism," Christopher Exley and Elizabeth Clarkson, *Scientific Reports*, Vol. 10, No. 1, May 8, 2020. Address: Christopher Exley, The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, ST5 5BG, UK, c.exley@keele.ac.uk.

Hospital programs tailored to patients with intellectual disability may save money

Hospitals may benefit financially by offering programs tailored to patients with intellectual disabilities, according to a new study.

Jordan Wirtz and colleagues note, "Approximately 1.2 million adults in the United States have an intellectual disability, representing 0.5% of the population 15 years or older. Although they make up a small portion of the U.S. population, those with intellectual disabilities have complex needs that stem from having limitations in intellectual functioning and adaptive behaviors." In addition, they note, these individuals often have unidentified health problems.

However, the researchers say, "The majority of healthcare providers… receive little information, either during their clinical training or on the job, about how to ensure that the needs of patients with intellectual disabilities are met."

Currently, some hospitals do offer programs that help meet the needs of patients with intellectual disabilities. These programs include specialized staff education, the use of patient coordinators, community outreach, and/or the use of care plans tailored to individuals with intellectual disabilities.

To determine whether such programs are cost-effective, Wirtz and colleagues analyzed data for patients with a primary or secondary diagnosis of intellectual disability and/or autism from five different hospitals. Two of the hospitals offered programs tailored to patients with intellectual disabilities and three did not.

The researchers found that "individuals treated at hospitals with programs tailored to patients with intellectual disabilities had significantly lower total costs than patients treated in hospitals without tailored programs," although they had similar readmission rates and lengths of stay. They add that while care at hospitals with tailored programs was more expensive in some analyses, these programs "were associated with lower total cost and cost per day after controlling for patient demographic characteristics and clinical factors."

They conclude, "Given that hospitals with tailored programs had lower costs overall, without increasing the risk of readmission within 30 days, hospital programs tailored to patients with intellectual disabilities are a promising approach for improving the quality and value of care."

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"Patient outcomes associated with tailored hospital programs for intellectual disabilities," Jordan Wirtz, Sarah H. Ailey, Samuel Hohmann, and Tricia Johnson, American Journal of Managed Care, Vol. 26, No. 3, March 6, 2020 (free online). Address: Tricia Johnson, Rush University, 1700 W. Van Buren St., TOB Ste. 126B, Chicago, IL 60612, tricia_j_johnson@rush.edu.

ARRI Survey: Seniors with Autism Spectrum Disorder

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.

Research Updates

Study explores risk of ASD for children if parents have a sibling with ASD

Children who have an aunt or uncle with an autism spectrum disorder (ASD) have an elevated risk of ASD, according to a new study. The study also calls into question the concept of a "female protective effect"—that is, the idea that females have a lower rate of ASD than males because more risk factors are required for girls to develop ASD.

Dan Bai and colleagues analyzed data on nearly 850,000 Swedish children and their family members. Of the children, slightly more than 13,000 were diagnosed with autism. The researchers found that children of mothers with one or more siblings with ASD were approximately 3 times more likely than children in the general population to have ASD. Children of fathers with one or more siblings with ASD were twice as likely as children in the general population to have ASD. The difference between children of mothers with a sibling with ASD and children of fathers with a sibling with ASD was not statistically significant. Additionally, there was no significant difference in ASD risk for children whos uncles had ASD, compared to children whose aunts had ASD.

In addition, the researchers say, "Within the second generation, ASD relative risk estimates did not differ between make and female offspring, contrary to the expected elevation for males under a female protective effect."

The researchers say their findings do not support the concept of a female protective effect, because such an effect "would imply that unaffected female individuals with a family history of ASD may carry and silently transmit proportionally greater genetic liability than unaffected male family members, amplifying recurrence rates in their male offspring, in particular."

They add, "While these results mitigate concern for amplification of maternally transmitted ASD risk, they affirm the importance of heightened surveillance for ASD in second-generation offspring."

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"Inherited risk for autism through maternal and paternal lineage," Dan Bai, Natasha Marrus, Benjamin Hon Kei Yip, Abraham Reichenberg, John N. Constantino, and Sven Sandin, *Biological Psychiatry*, May 2020 (free online). Address: Sven Sandin, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 6, SE-17177 Stockholm, Sweden, sven.sandin@ki.se.

—and—

"Autism risk estimated at 3 to 5% for children whose parents have a sibling with autism," news release, NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development, May 18, 2020.

Severe iron deficiency anemia seen in child with ASD, restricted eating

A new case study adds to mounting evidence that selective eating in individuals with autism spectrum disorders (ASD) can have serious repercussions.

Yoshitoki Yanagimoto and colleagues report on a two-year-old boy with ASD who had severe iron deficiency anemia, stunted growth, pallor, and tachycardia stemming from his refusal to eat any solid foods. The boy drank only breast milk and certain brands of juice, and only if he could use his favorite tableware.

The authors were able to successfully administer an oral iron supplement and enteral nutrients, and they report that "his anemia, nutritional condition, and clinical symptoms improved by treatment within one month." Overall, the boy required iron supplementation for five months and enteral nutrients for two years.

The researchers say that treating the boy's nutritional deficiencies led to other significant benefits. "It is of note," they say, "that nutritional treatment improved not only his malnutrition and stunted growth but also his food selectivity and developmental delay, suggesting that malnutrition worsens developmental delay and food selectivity. We believe that malnutrition and anemia due to iron deficiency caused hypocirculation in the brain and digestive organs and promoted repetitive eating. As the iron deficiency anemia improved, physical growth and repetitive eating improved."

The researchers conclude, "We recommend that iron deficiency anemia and nutritional condition should be evaluated when an autistic child presents with restricted eating behavior and pallor."

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"Iron deficiency anemia, stunted growth, and developmental delay due to avoidant/restrictive food intake disorder by restricted eating in autism spectrum disorder," Yoshitoki Yanagimoto, Yuko Ishizaki, and Kazunari Kaneko, *BioPsychoSocial Medicine*, Vol. 14, No. 8, 2020 (free online). Address: Yoshitoki Yanagimoto, yanagimy@taki.kmu.ac.jp.

Infants' differences in "attachment security" may be early ASD indicator

Abnormalities in a behavior called *attachment security* may be an early clue that a child has an autism spectrum disorder (ASD), according to a new study.

Katherine Martin and colleagues studied 15-month-old infants at high risk for ASD because they had a sibling with the condition. Sixteen of the infants in the group later developed ASD, compared to 40 who did not. The study also included a control group of 39 low-risk infants, none of whom later developed ASD.

The researchers used a test called the Strange Situation Procedure to evaluate behaviors related to attachment. In this test, infants are briefly separated from a parent on two occasions.

Many babies cry or are otherwise distressed when a parent leaves and they are left with a stranger. However, secure babies are soothed when the parent returns, while babies classified as "insecure-resistant" are not. Study coauthor Daniel Messinger says that these babies "not only cry when the parent leaves, but they never really settle down when the parent returns, which indicates that the infants are not confident in their ability to be calmed." Also, secure babies tend to explore their surroundings while their parents are present, while insecure-resistant babies explore their environment less.

The researchers found that high-risk infants categorized as insecure-resistant were more than nine times more likely to receive an ASD diagnosis by the time they were three years of age than high-risk infants with secure attachments. Messinger says, "There are a lot of questions about when early indications of autism emerge, and this is a pretty strong risk signal at 15 months among infants who have an older sibling with ASD. And while we can't stop future ASD diagnoses, this suggests we should… consider attachment-related interventions for high-risk infants who show insecurity. We don't do that at all right now."

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"Attachment security differs by later autism spectrum disorder: a prospective study," Katherine B. Martin, John D. Haltigan, Naomi Ekas, Emily B. Prince, and Daniel S. Messinger, *Developmental Science*, February 20, 2020 (epub prior to print publication). Address: Daniel S. Messinger, Department of Psychology, University of Miami, P.O. Box 248185, Coral Gables, FL 33124, dmessinger@miami.edu.

—and—

"Researchers find an early behavioral marker for autism," news release, University of Miami, March 13, 2020.

Sensory hypersensitivity in individuals with ASD may stem from defects in inhibitory neurons

Many individuals with autism spectrum disorders (ASD) are hypersensitive to touch, sounds, and other sensory input, and a new study has identified one cause of this over-reactivity.

Qian Chen and colleagues studied mice lacking a gene called Shank3. Mutations of the Shank3 gene are linked to autism, and mice who are missing the Shank3 protein exhibit many behaviors—such as repetitive behaviors and avoidance of social interaction—that are associated with ASD.

The researchers wanted to determine whether mice lacking the Shank3 gene also are hypersensitive to touch. To do this, they developed a way to measure the mice's sensitivity to slight deflections of their whiskers. They then trained the mice, as well as a control group of normal mice, to exhibit behaviors that signaled when they felt their whiskers being touched.

The researchers found that the mice missing the Shank3 gene noticed very slight deflections that the other mice missed. Guoping Feng, one of the study's senior authors, says, "They are very sensitive to weak sensory input, which barely can be detected by wild-type [control] mice. That is a direct indication that they have sensory over-reactivity."

Next, the researchers studied activity in the brains of the mice using an imaging technique that measures calcium levels, which indicate neural activity, in specific cell types. They found that when the whiskers of the mice were touched, excitatory neurons in a brain area called the somatosensory cortex were overactive in the mice missing the Shank3 gene.

Because synaptic activity should drop when Shank3 is missing, the researchers suspected that the hypersensitivity of the mice in the test group stemmed from low levels of Shank3 in inhibitory neurons that would normally reduce the activity of excitatory neurons. When they genetically engineered mice so they could turn off Shank3 expression only in inhibitory neurons in the somatosensory cortex, they indeed found that excitatory neurons in the mice were overactive even though these neurons had normal levels of Shank3.

Feng comments, "If you only delete Shank3 in the inhibitory neurons in the somatosensory cortex, and the rest of the brain and the body is normal, you see a similar phenomenon where you have hyperactive excitatory neurons and increased sensory sensitivity in these mice."

He adds, "Our study is one of several that provide a direct and causative link between inhibitory defects and sensory abnormality, in this model [Shank3] at least. It provides further evidence to support inhibitory neuron defects as one of the key mechanisms in models of autism spectrum disorders." He says the study suggests that reestablishing normal levels of neuronal activity could help reduce hypersensitivity in individuals with ASD.

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"Dysfunction of cortical GABAergic neurons leads to sensory hyper-reactivity in a Shank3 mouse model of ASD," Qian Chen, Christopher A. Deister, Xian Gao, Baolin Guo, Taylor Lynn-Jones, Naiyan Chen, Michael F. Wells, Runpeng Liu, Michael J. Goard, Jordane Dimidschstein, Shijing Feng, Yiwu Shi, Weiping Liao, Zhonghua Lu, Gord Fishell, Christopher I. Moore, and Guoping Feng, *Nature Neuroscience*, March 2, 2020 (online). Address: Guoping Feng, McGovern Institute for Brain Research, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, fengg@mit.edu.

—and—

"New study may explain why people with autism are often highly sensitive to light and noise," news release, Massachusetts Institute of Technology, March 2, 2020.

Both parental and grandparental age may affect odds of ASD

A new study adds to evidence that children born to older parents have higher odds of having an autism spectrum disorder (ASD). In addition, the study suggests that grandparental age might be a factor.

Using Danish national health registries, Yu Gao and colleagues analyzed data from nearly 1.5 million children born from 1990 to 2013. Of the group, more than 27,000 had an ASD diagnosis. The researchers also examined data for fathers and mothers for whom information on grandparental age was available.

The researchers report, "When parental age was analyzed continuously, we estimated that a five-year increase in maternal or paternal age was associated with a 9% increase in odds for ASD in children." When they adjusted for the age of the spouse, this was attenuated to 3% for maternal age and 7% for paternal age. The highest odds were seen in women over 40 years of age and men over 50 years of age, where the odds of having a child with ASD were 50% higher than for parents between 25 and 29 years of age.

These findings," the researchers say, "corroborate previous studies suggesting that advanced parental age is independently associated with increased ASD risk in children."

In addition, study coauthor Zeyan Liew says, "We observed that children with young maternal grandparents and children with young and old paternal grandparents had higher [autism] risk compared with children of grandparents who were 25 to 29 years old at the time of the birth of the parents." The reason for the increased risk seen in younger grandparents is unknown, but the researchers speculate that grandparents who gave birth as teenagers may have come from poorer and less supportive environments that could affect pregnancy and child health.

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"Association of grandparental and parental age at childbirth with autism spectrum disorder in children," Yu Gao, Yongfu Yu, Jingyuan Xiao, Jiajun Luo, Yawei Zhang, Ying Tian, Jun Zhang, Jørn Olsen, Jiong Li, and Zeyan Liew, *JAMA Network*, April 15, 2020 (online). Address: Zeyan Liew, Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale School of Public Health, 1 Church St., New Haven, CT 06510, zeyan.liew@yale.edu.

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"Children born to older parents have a 50 percent higher chance of autism," Roz Plater, Healthline, April 20, 2020.

Eating disorders and ASD
(continued from page 1)

when they were 14 years of age enabled the researchers to identify those who exhibited eating disorders such as fasting, purging, dieting, or binge eating.

The researchers found that 11.2% of 14-year-old girls reported engaging in at least one disordered eating behavior within the past year, compared to 3.6% of boys. Adolescents with eating disorders exhibited higher levels of autistic traits by 7 years of age, indicating that the ASD traits predated the disordered eating (as eating disorders were very rare at age 7). Children with higher rates of autistic traits at 7 years of age were 24% more likely to exhibit weekly disordered eating behaviors at the age of 14, while the presence of eating disorders at 14 years of age did not increase the level of autistic traits by age 16.

The researchers say children with ASD may be at greater risk for eating disorders because of their social and communicative issues, higher rates of anxiety and depression, sensory issues, rigidity of thinking, inflexible behaviors, or tendencies toward repetitive behaviors.

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"Trajectories of autistic social traits in childhood and adolescence and disordered eating behaviours at age 14 years: a UK general population cohort study," Francesca Solmi, Francesca Bentivegna, Helen Bould, William Mandy, Radha Kothari, Dheeraj Rai, David Skuse, and Glyn Lewis, *Journal of Child Psychology and Psychiatry*, May 2020 (free online). Address: Francesca Solmi, Division of Psychiatry, University College London, Wing B, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF, UK, francesca.solmi@ucl.ac.uk.

—and—

"Children with autism face higher risk of eating disorders," news release, University College London, May 13, 2020.

Kids with ASD may have more appendicitis complications

Children with autism spectrum disorders (ASD) may be at higher risk for complications of appendicitis than their neurotypical peers, according to a new study. Appendicitis is the most common surgical emergency in children.

Using the Military Health Systems database, Patrick Reeves and colleagues analyzed data from nearly 49,000 children diagnosed with ASD. They compared each child to five children without ASD matched for sex, date of birth, and enrollment time frame.

The researchers found no difference in the rates of appendicitis between the ASD and non-ASD groups. In addition, there was no overall increased risk of a perforated appendix in children with ASD. However, among older adolescents, specifically those between 15 and 17 years of age, those with ASD had significantly increased odds of perforation. In addition, a significantly higher number of children with ASD experienced sepsis, a dangerous response to infection. The researchers note that when a child with ASD is diagnosed with appendicitis, the child has "three times the elevated risk of developing sepsis as compared to neurotypical peers."

The researchers say there may be a number of reasons for this disparity, including language impairments in patients with ASD and the insensitivity to pain that many of these individuals exhibit. The overall number of medical visits was not a factor, they say, noting that the ASD and non-ASD groups had comparable rates of well-child visits.

Reeves and colleagues say that practitioners may be able to better help patients with ASD by recognizing that pain may exhibit as sleep disturbances or behavioral problems such as irritability or aggression; using parents as "interpreters;" and "searching to find what makes the pain better." They also say tools such as the Pediatric Appendicitis Score may need to updated with a behavioral component to increase awareness of atypical presentations. In addition, they recommend the use of ultrasound and fast-appendix (non-sedated) magnetic resonance imaging for children with ASD.

The researchers conclude, "Providers should display heightened awareness for the risk of complicated appendicitis in children with ASD."

Editor's note: We have heard of cases in which individuals with ASD experienced a perforated appendix without showing any symptoms, highlighting the need for the imaging approaches that Dr. Reeves and his colleagues recommend.

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"Brief report: association of complicated appendicitis in children with autism spectrum disorders," Patrick T. Reeves, Apryl Susi, Elizabeth Hisle-Gorman, Gregory H. Gorman, and Cade Nylund, *Journal of Autism and Developmental Disorders*, April 15, 2020 (online). Address: Patrick T. Reeves, Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, patrick.t.reeves.mil@mail.mil.

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Mouse study: direct link detected between gut microbiome, brain function

While increasing evidence points to a link between the gut microbiome and neurological conditions such as autism, researchers have had difficulty finding evidence of a direct connection between gut microbes and the brain. Now, however, researchers report that they have detected two microbial molecules present in both the gut and the brain in mice.

Heather Hulme and colleagues used a technique called mass spectrometry imaging to map the two molecules produced by gut bacteria as they traveled to distinct parts of the brain. The molecules have a structure similar to carnitine, which is used to help burn fatty acids for energy, and they localize with and antagonize the function of carnitine in the brain.

The researchers say, "This is the first mechanistic description of a microbial molecule inhibiting the function of the mitochondria in cells of the central nervous system…. Given their potency at the physiological concentrations found in the [mouse] brain, our findings indicate that neurological conditions where mitochondrial dysfunction has been described and where disturbances in the gut microbiome are noted should be looked at with increased emphasis on potential for microbiome input."

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"Microbiome-derived carnitine mimics as previously unknown mediators of gut-brain axis communication," Heather Hulme, Lynsey M. Meikle, Nicole Strittmatter, Justin J. J. van der Hooft, John Swales, Ryan A. Bragg, Victor H. Villar, Michael J. Ormsby, Stephanie Barnes, Sheila L. Brown, Alex Dexter, Maya T. Kamat, Jasper C. Komen, Daniel Walker, Simon Milling, Emily K. Osterweil, Andrew S. MacDonald, Chris J. Schofield, Saverio Tardito, Josephine Bunch, Gillian Douce, Julia M. Edgar, RuAngelie Edrada-Ebel, Richard J. A. Goodwin, Richard Burchmore, and Daniel M. Wall, *Science Advances*, March 11, 2020 (free online). Address: Daniel (Dónal) Wall, donal.wall@glasgow.ac.uk.

—and—

"Scientists describe new molecules that form direct link between gut microbiome and brain function," news release, University of Glasgow, March 12, 2020.

Cell Danger Response Biology—New Perspective

A new paper, partially funded by ARI, describes cell danger response biology—the new science that connects environmental health with mitochondria and the rising tide of chronic illness. You can read the paper at:

https://www.autism.org/cell-danger-response/

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