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Brief administration of the hormone oxytocin may lead to long-term benefits for men

Men with autism spectrum disorders (ASD) who receive intranasal oxytocin may have fewer repetitive behaviors and find it easier to form close relationships, a new study from Belgium suggests.

Sylvie Bernaerts and colleagues measured saliva levels of oxytocin, a hormone that plays a role in bonding, in 40 men with ASD. The researchers found that levels of oxytocin were inversely related to self-reported attachment issues.

Bernaerts and her team then administered intranasal oxytocin to half of the men for four weeks, giving the other half of the men a placebo. They followed the study participants for one year, evaluating them on four different occasions.

The researchers report that there was no difference in social interaction between the active and placebo groups. However, the men in the experimental group reported significantly less repetitive behavior and fewer problems in forming close relationships.

Study coauthor Kaat Alaerts comments, "Participants who took oxytocin every day for four weeks experienced positive effects until up to a year later. That's a remarkable result." However, she notes that this was a pilot study, saying, "A lot of further research needs to be done before oxytocin can be used to treat people with autism."

The researchers note that only men participated in the study because autism is more common in men and because women's hormonal cycles could influence test results.

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"Behavioral effects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up," Sylvie Bernaerts, Bart Boets, Guy Bosmans, Jean Steyaert, and Kaat Alaerts, *Molecular Autism*, January 2020 (free online). Address: Kaat Alaerts, Department of Rehabilitation Sciences, Research Group for Neurorehabilitation, KU Leuven, Tervuursevest 101 box 1501, 3001 Leuven, Belgium, kaat.alaerts@kuleuven.be.

—and—

"'Love hormone' improves attachment issues in people with autism," news release, Tine Danschutter and Katrien Bollen, KU Leuven, January 2020.

Abnormalities in brain cells that produce myelin linked to ASD

A new study shows that people with autism spectrum disorders (ASD) have a cellular abnormality that impairs the production of myelin, the fatty insulation around nerve fibers in the brain.

BaDoi Phan and colleagues studied mice with a gene mutation that causes a condition known as Pitt-Hopkins syndrome when it occurs in humans. Pitt-Hopkins, which is a rare neurodevelopmental disorder, produces autistic-like symptoms.

The researchers found that in mice with the mutation, a genetic abnormality disrupts the function of oligodendrocytes, which are cells that control myelin production. They then looked at other mouse models of ASD caused by different mutations associated with autism, and found consistent evidence for abnormalities involving oligodendrocytes. Finally, they identified the same abnormalities in brain tissue from deceased people with ASD who did not suffer from Pitt-Hopkins syndrome but had more common forms of ASD.

Study coauthor Brady Maher says, "Myelination is essential to healthy brain development; it's a process that begins just before birth and continues throughout the lifespan. If impaired, it leads to abnormal brain development that likely results in communication and behavior challenges associated with ASD."

He adds, "It appears that in many people who suffer from ASD, their [oligodendrocytes] are not maturing sufficiently or functioning properly. This suggests they are not producing enough myelin insulation for their neurons, which could profoundly disrupt brain development and electrical communication in the brain."

The researchers say that while most researchers studying ASD are investigating problems involving neurons, "These findings

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Large-scale study: co-existing conditions are very common in ASD; girls receive diagnoses significantly later than boys

A large-scale study shows that girls with autism spectrum disorders (ASD) typically receive a diagnosis much later than boys, and that individuals with ASD have high rates of co-occurring disorders.

Carolyn McCormick and colleagues analyzed data from the first 1,000 participants in the Rhode Island Consortium for Autism Research and Treatment (RI-CART). The researchers found that girls with ASD are diagnosed on average nearly 1.5 years later than boys. The researchers speculate that this is because girls with ASD tend to have more advanced language skills compared to boys.

Study coauthor Eric Morrow comments, "The major treatment that has some efficacy in autism is early diagnosis and getting the children into intensive services, including behavioral therapy. So if we're identifying girls later, that may delay their treatment."

In addition, the researchers found that individuals with ASD frequently have comorbid conditions. Nearly half of the participants had another neurodevelopmental disorder such as attention-deficit/hyperactivity disorder (ADHD) or intellectual disability. In addition, 44.1 percent had a psychiatric disorder, 42.7 percent had a neurological condition such as epilepsy, migraines, or tics, and 92.5 percent reported at least one general medical condition.

The researchers conclude, "Psychiatric and medical comorbidities in ASD constitute a substantial burden and warrant adequate attention as part of overall treatment."

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"Autism heterogeneity in a densely sampled U.S. population," Carolyn E. B. McCormick, Brian C. Kavanaugh, Danielle Sipsock, Giulia Righi, Lindsay M. Oberman, Daniel Moreno De Luca, Ece D. Gamsiz Uzun, Carrie R. Best, Beth A. Jerskey, Joanne G. Quinn, Susan B. Jewel, Pei-Chi Wu, Recbecca L. McLean, Todd P. Levine, Hasmik Tokadjian, Kayla A. Perkins, Elaine B. Clarke, Brittany Dunn, Alan H. Gerber, Elena J. Tenenbaum, Thomas F. Anders, Stephen J. Sheinkopf, and Eric M. Morrow, *Autism Research*, January 20, 2020 (epub prior to print publication). Address: Eric Morrow, eric.morrow@brown.edu, or Stephen Sheinkopf, stephen.sheinkopf@brown.edu.

—and—

"Autism study finds later diagnoses for girls, high rates of co-occurring disorders," news release, Kerry Benson, Brown University, January 21, 2020.

Facial features of siblings of children with autism offer evidence of broad autism phenotype

The facial features of both male and female siblings of children with autism spectrum disorders (ASD) tend to be more masculine than the features of sex- and age-matched controls, according to a new study that offers support for the idea that there is a broad autism phenotype. In addition, the study is consistent with the "extreme male brain" hypothesis, which links ASD to elevated exposure to testosterone in the womb.

In earlier research, Diana Weiting Tan and colleagues found that both male and female children with ASD tend to have a masculinized facial structure. In the new study, they used 3D facial photogrammetry to analyze the facial features of 55 non-autistic siblings (30 boys and 25 girls) of children with ASD, comparing them to age-matched children without siblings with ASD.

The researchers found that the facial features of male siblings were significantly more masculine than the features of male controls. The facial features of female siblings were also more masculine than the features of female controls, but to a lesser degree.

The researchers say the patterns they detected are consistent with the findings of a recent study that examined levels of autistic traits measured using the child version of the Autism-spectrum Quotient (AQ-Child). On that scale, they say, there was no difference in scores between male children with ASD and their non-autistic male siblings, with both groups scoring higher than controls. The scores of non-autistic girl siblings fell between the scores for their female siblings with ASD and controls.

The researchers conclude, "The current study presents the first evidence for facial masculinity to express as a broad autism phenotype. This finding builds upon prior evidence linking prenatal testosterone exposure to postnatal facial masculinity and corroborates the 'extreme male brain theory' that ASD may be, in part, linked to elevated levels of testosterone *in utero*. More broadly, these data suggest that facial masculinity is a feature of ASD that is likely to be connected to genetic influences."

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"A broad autism phenotype expressed in facial morphology," Diana Weiting Tan, Murray T. Maybery, Syed Zulqarnain Gilani, Gail A. Alvares, Ajmal Mian, David Suter, and Andrew J. O. Whitehouse, *Translational Psychiatry*, January 2020 (free online). Address: Diana Weiting Tan, School of Psychological Science, University of Western Australia, Perth, Australia, diana.tan@uwa.edu.au.

Drug may reduce ASD symptoms in young children by altering GABA/glutamate ratio in brain

A prescription drug used to treat edema (fluid buildup in the body) appears to reduce some symptoms of autism spectrum disorder (ASD) in young children by altering the balance between the neurotransmitters GABA and glutamate, according to a new study by researchers in China and the United Kingdom.

Lingli Zhang and colleagues tested the effects of the drug bumetanide (0.5 mg twice a day) on 42 children with ASD, all between three and six years of age, comparing them to a control group of 41 children with ASD who received no treatment. Assessing the children at the end of the three-month trial using the Childhood Autism Rating Scale (CARS), the researchers report, "Compared with the control group, the bumetanide group showed significant reduction in symptom severity, as indicated by both total CARS score and number of items assigned a score greater than or equal to 3 [a score indicating moderate abnormality]." The researchers also found that the drug decreased the ratio of the GABA to glutamate in two key regions of the brain: the insular cortex (which plays a role in emotions, empathy, and self-awareness) and the visual cortex (which integrates and processes visual information).

While GABA is an inhibitory chemical in the adult brain, it is primarily excitatory in the brain during early development. There is some evidence that ASD may result from altered brain development involving an excitatory-inhibitory imbalance, and the researchers say their findings provide support for the hypothesis that "bumetanide can restore excitatory-inhibitory balance in the autistic brain, thereby promoting normal brain function and social emotional cognition."

The researchers report that the drug was well tolerated, with no participants withdrawing from the trial due to adverse effects. Mild side effects included frequent urination (15 children), small decreases in potassium levels (4 children), loss of appetite (4 children), fatigue (one child), and a mild elevation of uric acid in the blood (one child).

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"Symptom improvement in children with autism spectrum disorder following bumetanide administration is associated with decreased GABA/glutamate ratios," Lingli Zhang, Chu-Chung Huang, Yuan Dai, Qiang Luo, Yiting Ji, Kai Wang, Shining Deng, Juehua Yu, Mingyu Xu, Xiujuan Du, Yun Tang, Chun Shen, Jianfeng Feng, Barbara J Sahakian, Ching-Po Lin, and Fei Li, *Translational Psychiatry*, January 2020 (free online). Address: Qiang Luo (qluo@fudan.edu.cn), Ching-Po Lin (chingpolin@gmail.com), or Fei Li (feili@shsmu.edu.cn).

—and—

"Prescription drug improves symptoms of autism by targeting brain's chemical messengers," news release, University of Cambridge, January 27, 2020.

Free E-Newsletters

In collaboration with the Schafer Autism Report, the Autism Research Institute publishes an e-newsletter titled *Clinical Research in Autism*. This newsletter provides online links to up-to-date clinical research related to patient care, and is designed for pediatricians, nurses, and obstetricians (although other readers are welcome as well). You can subscribe here:

https://www.ClinicalResearchInAutism.com

The monthly ARI e-newsletter includes news, webinar updates, and autism-related information and articles. You can subscribe here:

https://www.autism.org/ari-monthly-e-newsletter/

Defects in myelin-producing cells linked to ASD

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offer an alternative to the neurocentric view of developmental disorders and suggest that myelination might be a new therapeutic target for the treatment of ASD."

The researchers are now testing compounds that may boost myelination in the brain. Maher says, "Because myelination is a lifelong process it provides a unique therapeutic opportunity that we can tap into throughout the lifespan. Along these lines, we are eager to see whether enhancing myelination in these mice can improve their ASD-associated behaviors. Promising [drug] candidates could then be considered for clinical studies."

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"A myelin-related transcriptomic profile is shared by Pitt–Hopkins syndrome models and human autism spectrum disorder," BaDoi N. Phan, Joseph F. Bohlen, Brittany A. Davis, Zengyou Ye, Huei-Ying Chen, Brent Mayfield, Srinidhi Rao Sripathy, Stephanie Cerceo Page, Morganne N. Campbell, Hannah L. Smith, Danisha Gallop, Hyojin Kim, Courtney L. Thaxton, Jeremy M. Simon, Emily E. Burke, Joo Heon Shin, Andrew J. Kennedy, J. David Sweatt, Benjamin D. Philpot, Andrew E. Jaffe, and Brady J. Maher, *Nature Neuroscience*, February 3, 2020 (free online). Address: Andrew Jaffe, andrew.jaffe@libd.org, or Brady Maher, brady.maher@libd.org.

—see also—

"New study links autism to specific cell, paves way for potential approach to treatment," news release, Lieber Institute for Brain Development, February 3, 2020.

GUEST EDITORIAL

Researchers have identified a relationship between Ehlers-Danlos Syndrome and autism

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Editor's note: Ehlers-Danlos Syndromes have recently received much attention among members of the autism community. This is due, in large part, to the research conducted by Dr. Emily Casanova. ARI funded a portion of her research. In addition, she has presented her findings at ARI's annual think tank.

The Ehlers-Danlos Syndromes (EDS) are a group of hereditary connective tissue disorders (HCTD), which are the result of heritable impairments in growth and repair of the connective tissues of the body. These include tissues such as ligaments, tendons, skin, bone, and even blood and fatty tissue. Connective tissue acts like the glue that holds the body together.

There are currently 13 recognized types of EDS, 12 of which are considered rare and typically present with mutations in collagen or collagen-related genes. Collagen proteins are major building blocks of connective tissue, providing both strength and flexibility.

The most common type of EDS is known as Hypermobile EDS (hEDS) and although prevalence estimates aren't available due to the recency of changes within its diagnostic criteria, it is believed by most clinicians, researchers, and patients to be a common condition, occurring in greater than 1 in 2,000 people. Unlike the other forms of EDS, there are currently no recognized gene mutations associated with hEDS—although that will hopefully change with current efforts to perform whole genome sequencing on a large number of people with the condition.

Recent research suggests that EDS may share strong links with autism. Case studies have previously been published identifying individuals who are both on the autism spectrum and have a diagnosis of EDS. In addition, a 2016 study performed in Sweden indicated that people with EDS are more likely to have a diagnosis of autism than individuals without the condition. Other research has also shown that autistic people have higher rates of joint hypermobility in general, a major feature of EDS.

More recently, our own laboratory has found that mothers with EDS or a diagnosis of the closely related Hypermobility Spectrum Disorders (HSD) (formerly known as Joint Hypermobility Syndrome) are just as likely to have autistic children as mothers who themselves are on the autism spectrum. This suggests that maternal EDS/HSD may be a significant risk factor for the development of autism in the child.

Reasons for this tentative relationship are still uncertain and may involve the roles that connective tissue proteins like collagen play in brain development. However, our laboratory has also found that EDS/HSD mothers with autistic children report more immune problems than EDS/HSD mothers whose children are not on the spectrum. This may indicate that the mother's immune system plays an important role in the child's neurodevelopment. In fact, we already know there are links between the maternal immune system and autism risk in the general population, so it stands to reason these effects may be exaggerated in a clinical population like EDS that has a lot of immune disorders.

People with EDS/HSD are also more likely to develop autoimmune disorders, conditions in which the body's own immune system attacks parts of the body, causing damage or dysfunction to those areas. These can include conditions like psoriasis, rheumatoid arthritis, and Hashimoto's hypothyroidism. The other immune disorders in EDS/HSD, such as Mast Cell Activation Syndrome (MCAS), seem to predispose towards autoimmunity, although this doesn't happen in every case. Autoimmunity has also been reported in families of those on the autism spectrum, although it's not entirely certain whether a mother's autoantibodies influence the development of autism during pregnancy. However, there have been animal models that suggest maternal autoantibodies can influence brain and ultimately behavioral development.

Besides the immune system, EDS and autism seem to share symptom overlap when it comes to autonomic disorders (aka "dysautonomias"). The branch of the nervous system that lies outside the brain and spinal cord is known as the peripheral nervous system. This system contains a subbranch known as the autonomic nervous system. This system helps control automated processes such as breathing, cardiac output, digestion, temperature, and perspiration. The autonomic nervous system is subsequently divided into the sympathetic ("fight or flight") and parasympathetic ("rest and digest") nervous systems.

In both autism and EDS, the fight-or-flight sympathetic nervous system appears to be overactive, while the rest-and-digest parasympathetic branch is underactive. This can lead to many symptoms such as abnormal heart rate, gastrointestinal problems like constipation, increased anxiety, and even lightheadedness and dizziness. Some providers have started treating some of these symptoms in their autistic patients with beta blockers like propranolol with some success (although it is contraindicated in people with asthma). My husband, Dr. Manuel Casanova, has also done work treating autonomic disorders in autistic children using low-frequency repetitive transcranial magnetic stimulation (rTMS), which seems to help calm some of the hyperexcitability of the brain in autism and also has positive calming effects on the fight-or-flight branch of the nervous system and stimulatory effects on the rest-and-digest branch, helping the two to better normalize. After treatment, behavioral improvements in areas like socialization, including desire to socialize, as well as ability to concentrate have been seen.

As with autism, people with EDS also frequently experience symptoms of autonomic dysregulation, which may be linked with lower average blood volume and poorer circulation when moving from a seated to standing position (also known as "orthostatic intolerance"). This can lead to a reduction in blood flow to the brain, resulting in symptoms such as brain fog, dizziness, and even fainting. These patients also have chronic sympathetic overactivation and hypoactivation of the parasympathetic nervous system. Similar to autism, this can lead to symptoms of anxiety, difficulty concentrating, gastrointestinal disorders, temperature sensitivity, shortness of breath (sometimes misdiagnosed as asthma), and sleep disturbances. The beta blocker propranolol is also sometimes used to treat people with EDS and autonomic dysregulation, especially individuals who experience problems with tachycardia (unusually fast heart rate), as the medicine helps to slow down the heart. We are hopeful that in the future these patients may also benefit from low-frequency rTMS, alleviating some of the more severe symptoms of dysautonomia.

My laboratory is currently working to address EDS/HSD overlap with autism. One of our ongoing studies is investigating EDS-related symptoms in mothers of children with autism vs. mothers of children with ADHD. Although the data is very preliminary and subject to change, our current results suggest that hypermobility-related disorders in mothers of autistic children may lead to significantly more pain and physical impairment than those seen in mothers within the ADHD group. Likewise, these pain-related disorders are strongly linked with maternal immune disorders.

Finally, in another of our studies, we are investigating a subset of those with EDS/HSD who are Fragile X premutation carriers. We are hoping that this may be the first identifiable genetic variation associated with the EDS/HSD clinical phenotype and may help us better understand what is occurring

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Research Updates

Families raising children with ASD face burdens

Families of children with autism spectrum disorders (ASD) experience significant physical, mental, and social burdens, according to a new study from Rutgers University.

Xue Ming and colleagues conducted interviews with 25 caregivers of 16 individuals with ASD ranging in age from 2 to 20 years. The researchers found that the majority of caregivers reported experiencing burdens related to raising a child with autism, and about half of them reported family discord associated with caring for their child. They add, "Nine of the 16 families reported being ridiculed, misjudged for child abuse, or [viewed as] inappropriately submissive by the general public, thus limiting their child from attending to social events or places such as churches, supermarkets, restaurants, or public transportation, suggesting the inclusiveness of families with ASD in the general public remains to be improved." The researchers also found that:

- Emotional burnout was more common in families of children with low-functioning ASD and comorbidities.
- Social isolation tended to occur in families who reported significant emotional burnout.
- Families with more than one caregiver experienced less emotional burnout and social isolation than families with only one caregiver.
- Families with higher incomes tended to spend more money on medical treatments that were not covered by insurance.
- The age of the child did not affect the level of emotional burnout, social isolation, or familial discord.
- Families with an aggressive and irritable child tended to experience more social isolation and emotional burnout.
- Comorbid medical and/or behavioral disorders were common in the individuals with ASD.

Families also reported positive aspects of raising a child with autism, including strengthening bonds with their partners, becoming more understanding of people in general, appreciating life more, and being inspired by their children.

The researchers say their findings may encourage professionals to provide more support and resources for families caring for a child with ASD, and may help to raise public acceptance of children with ASD.

(See related article on page 6.)

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"Family burdens of caring for a child with an autism spectrum disorder," Xue Ming, Binhao Wu, Max Yang, and Apoorva Polavarapu, *International Journal of Autism & Related Disabilities*, November 8, 2019 (free online). Address: Xue Ming, Department of Neurology, Rutgers New Jersey Medical School, New Jersey, mingxu@njms.rutgers.edu.

—and—

"Families of children with autism face physical, mental and social burdens," news release, Patti Verbanas, Rutgers University, January 2, 2020.

Scurvy a risk for children with ASD, restricted diets

A recent research review indicates that children with autism spectrum disorders (ASD) and restricted diets are at risk for scurvy, a disease caused by vitamin C deficiency. Symptoms of scurvy include gum disease, easy bleeding, weakness, and fatigue.

William Sharp and colleagues searched medical databases for case reports of children diagnosed with both ASD and scurvy. Cases of scurvy due to issues other than dietary restriction were excluded.

The researchers identified 20 case reports involving 24 children. They note, "The eventual diagnosis of scurvy followed a wide range of negative diagnostic testing; treatment with ascorbic acid [vitamin C] or a multivitamin resulted in rapid improvement."

The researchers say, "Symptoms of scurvy mimic other pediatric conditions (e.g., cancer). The range of diagnostic testing increased costs and healthcare risks (radiation, sedation) and delayed the diagnosis of scurvy. In children with ASD and severe food selectivity, a nutrition evaluation and laboratory testing are warranted before a more elaborate testing."

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"Scurvy as a sequela of avoidant-restrictive food intake disorder in autism: a systematic review," W. G. Sharp, R. C. Berry, L. Burrell, L. Scahill, and B. O. McElhanon, *Journal of Developmental and Behavioral Pediatrics*, February 10, 2020 (epub prior to print publication). Address: William G. Sharp, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, wgsharp@emory.edu.

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/

ASD sleep problems linked to shallow brain waves

Many children with autism spectrum disorders (ASD) have sleep disturbances, and a new study from Israel suggests that this problem is linked to shallower brain waves during sleep.

Ayelet Arazi and colleagues analyzed overnight electroencephalogram (EEG) recordings performed during sleep evaluations of 29 children with ASD and 23 neurotypical children. They report, "Children with ASD exhibited significantly weaker slow wave activity power, shallower slow wave activity slopes, and a decreased proportion of slow wave sleep in comparison to controls…. Furthermore, slow wave activity power of children with ASD was significantly, negatively correlated with the time of their sleep onset in the lab and at home, as reported by parents."

The brain waves of children with ASD were on average 25% shallower than those of neurotypical children. The difference between controls and children with ASD was largest during the first two hours of sleep, during which periods of deep sleep normally occur.

Senior author Ilan Dinstein comments, "It appears that children with autism, and especially those whose parents reported serious sleep issues, do not tire themselves out enough during the day, do not develop enough [biological] pressure to sleep, and do not sleep as deeply."

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"Reduced sleep pressure in young children with autism," Ayelet Arazi, Gal Meiri, Dor Danan, Analya Michaelovski, Hagit Flusser, Idan Menashe, Ariel Tarasiuk, and Ilan Dinstein, *Sleep*, December 18, 2019 (online). Address: Ayelet Arazi, Ben-Gurion University (room 123, building 97), 1 Ben-Gurion Blvd., Beer Sheva, 8410501, Israel, araziay@post.bgu.ac.il.

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

In identical twins with ASD, symptom severity varies

A new study sheds light on the influence of nature and nurture on autism spectrum disorders (ASD) by showing that when identical twins have ASD, one twin frequently has more severe symptoms than the other.

In the study, Lauren Castelbaum and colleagues analyzed data from three previous twin studies. In all, they looked at data from 366 identical twin pairs with and without ASD, looking at clinicians' assessments or parents' ratings on a standardized questionnaire, or both.

The researchers found that if one twin had ASD, there was a 96% chance that the other did as well. However, the severity of symptoms varied widely in twin pairs. In fact, Castelbaum and colleagues estimated that genetic factors accounted for only 9% of the cause of trait variation between the twins. In contrast, the scores for traits were very similar for identical twins without ASD.

The researchers say their study shows that "although ASD itself is highly heritable, variation in severity of symptomatology above the diagnostic threshold is substantially influenced, in contrast, by non-shared environmental factors which may identify novel targets of early ASD amelioration."

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"On the nature of monozygotic twin concordance and discordance for autistic trait severity: a quantitative analysis," Lauren Castelbaum, Chad M. Sylvester, Yi Zhang, Qiongru Yu, and John N. Constantino, *Behavior Genetics*, December 18, 2019 (online). Address: John N. Constantino, constantino@wustl.edu.

—and—

"Severity of autism symptoms varies greatly among identical twins," news release, Eunice Kennedy Shriver National Institute of Child Health and Human Development, December 27, 2019.

Many young children with ASD are not diagnosed

One quarter of young children with autism spectrum disorders (ASD) do not have an autism diagnosis, according to a new study.

Lisa Wiggins and colleagues reviewed the education and medical records of 266,000 U.S. children who were eight years old in 2014, identifying 4,498 children who had sufficient social and behavioral deficits to meet criteria for ASD and/or already had an ASD diagnosis. Of this group, the researchers say, "1,135 (25%) had ASD indicators without having an ASD diagnosis." They add, "Of those 1,135 children without a documented ASD diagnosis, 628 (55%) were not known to receive ASD services in public school." Children were more likely to be undiagnosed if they were non-white, did not have an intellectual disability, were older when developmental concerns first arose, were older at the time of their first developmental evaluation, were eligible for special education for reasons other than ASD, or needed fewer supports.

Study coauthor Walter Zahorodny says, "There may be various reasons for the disparity, from communication or cultural barriers between minority parents and physicians to anxiety about the complicated diagnostic process and fear of stigma. Also, many parents whose children are diagnosed later often attribute their first concerns to a behavioral or medical issue rather than a developmental problem."

The researchers say, "These results highlight the importance of reducing disparities in the diagnosis of children with ASD characteristics so that appropriate interventions can be promoted across communities."

(See related story on page 1)

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"Disparities in documented diagnoses of autism spectrum disorder based on demographic, individual, and service factors," Lisa D. Wiggins, Maureen Durkin, Amy Esler, Li-Ching Lee, Walter Zahorodny, Catherine Rice, Marshalyn Yeargin-Allsopp, Nicole F. Dowling, Jennifer Hall-Lande, Michael J. Morrier, Deborah Christensen, Josephine Shenouda, and Jon Baio, *Autism Research*, December 23, 2019 (online). Address: Lisa D. Wiggins, lwiggins@cdc.gov.

—and—

"One-fourth of children with autism are undiagnosed," news release, Patti Verbanas, Rutgers University, Jaunary 9, 2020.

Postpartum depression common in moms with ASD

Mothers with autism spectrum disorders (ASD) are more likely than other mothers to experience postpartum depression, according to a new study by Alexa Pohl and colleagues.

In the study, 355 mothers with ASD and 132 mothers without ASD completed an anonymous online survey. All of the mothers had at least one child with ASD, to ensure that differences in results could be attributed to a mother being autistic, rather than having an autistic child.

Pohl and her team found that 60% of mothers with ASD reported that they had experienced postnatal depression, compared to only 12% of women in the general population. In addition, the researchers say, "[Mothers with ASD] reported greater difficulties in areas such as multi-tasking, coping with domestic responsibilities, and creating social opportunities for their child. They were also more likely to report feeling misunderstood by professionals, and reported greater anxiety, higher rates of selective mutism, and not knowing which details were appropriate to share with professionals. They were also more likely to find motherhood an isolating experience, to worry about others judging their parenting, or to feel unable to turn to others for support in parenting."

Study coauthor Simon Baron-Cohen comments, "This worryingly high number of autistic mothers who experience postnatal depression means we are failing them and their infants at a critical point in their lives. We now need more research into why the rates are so much higher, whether they are seeking help and not getting it, or if they are not seeking help and for what reasons."

Despite the challenges faced by mothers with ASD, the women reported that they were able to act in the best interest of their child, putting their child's needs first and seeking opportunities to boost their child's self-confidence. In addition, Pohl notes, "an overwhelming majority of autistic mothers reported that parenting overall was a rewarding experience."

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"A comparative study of autistic and non-autistic women's experience of motherhood," A. L. Pohl, S. K. Crockford, M. Blakemore, C. Allison, and S. Baron-Cohen, *Molecular Autism*, January 2020 (free online). Address: S. K. Crockford, Autism Research Centre, Department of Psychiatry, Cambridge University, Douglas House, 18b Trumpington Road, Cambridge, CB2 8AH, UK, skc48@cam.ac.uk.

—and—

"Higher rates of postnatal depression among moms with autism," Traci Pederson, psychcentral.com, January 14, 2020.

Mutations in father's sperm may offer clues about odds of having a second child with ASD

Analyzing the sperm of fathers who already have a child with an autism spectrum disorder (ASD) may help families to better understand the odds of future children having the condition, a new study suggests.

Research indicates that as many as 30 percent of cases of ASD are caused by *de novo* mutations, which are mutations occurring spontaneously in a parent's sperm or eggs at conception. Martin Breuss and colleagues note that "de novo mutations arising on the paternal chromosome make the largest known contribution to autism risk, and correlate with paternal age at the time of conception."

In the new study, Breuss and his team analyzed the sperm of eight fathers who were parents of children with ASD, looking for *mosaicism*—that is, the presence of two or more genetically different sets of cells. Using a technique called deep whole genome sequencing, they detected variants in the children that were matched only in the fathers' sperm.

"While medical textbooks teach us that every cell in the body has an identical copy of DNA," Breuss says, "this is fundamentally not correct. Mutations occur every time a cell divides, so no two cells in the body are genetically identical." He adds, "If a mutation occurs early in development, then it will be shared by many cells within the body. But if a mutation happens just in sperm, then it can show up in a future child but not cause any disease in the father."

The researchers determined that mutations were present in up to 15 percent of the fathers' sperm cells. This information could not be determined through other means, such as blood samples.

Breuss and colleagues say it may be possible to develop a clinical test that will help fathers of children with ASD determine their odds of having another child with the condition. In addition, they say, the test may benefit men who have not yet had children but want to know their odds of having a child with ASD.

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"Autism risk in offspring can be assessed through quantification of male sperm mosaicism," Martin W. Breuss, Danny Antaki, Renee D. George, Morgan Kleiber, Kiely N. James, Laurel L. Ball, Oanh Hong, Ileena Mitra, Xiaoxu Yang, Sara A. Wirth, Jing Gu, Camila A. B. Garcia, Madhusudan Gujral, William M. Brandler, Damir Musaev, An Nguyen, Jennifer McEvoy-Venneri, Renatta Knox, Evan Sticca, Martha Cristina Cancino Botello, Javiera Uribe Fenner, Maria Cárcel Pérez, Maria Arranz, Andrea B. Moffitt, Zihua Wang, Amaia Hervás, Orrin Devinsky, Melissa Gymrek, Jonathan Sebat, and Joseph G. Gleeson, *Nature Medicine*, December 23, 2019 (online). Address: Joseph Gleeson, Department of Neurosciences, Howard Hughes Medical Institute, University of California, San Diego, La Jolla, CA, jogleeson@ucsd.edu.

—and—

"Measuring mutations in sperm may reveal risk for autism in future children," Medical Xpress, December 23, 2019.

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.

Challenging behaviors in ASD increase risk for parental PTSD

Parents of children with autism spectrum disorders (ASD) or rare diseases frequently exhibit symptoms of post-traumatic stress disorder (PTSD), according to a study from Australia. The study also reports that challenging child behaviors positively predict PTSD in both groups.

Michelle Stewart and colleagues enrolled 395 parents in their study. These included 226 parents of children with ASD, 139 parents of children with rare diseases, and 30 parents of typically developing children. The researchers used the Life Events Checklist for DSM-5 to screen parents for histories of traumatic events, asked the parents to use the Developmental Behavior Checklist to describe their children's emotional and behavioral problems, and administered the PTSD Checklist for DSM-5 to the parents to determine how many PTSD symptoms they had.

Stewart and colleagues report that using stringent criteria, they found that 18.6% of parents of children with ASD and 12.2% of parents of children with rare diseases reported symptoms consistent with a PTSD diagnosis. No parents of typically developing children reported symptoms consistent with PTSD.

Moreover, the researchers found that challenging behaviors in children with ASD—for example, kicking, hitting, and anxiety-related behaviors—accounted for more than 30% of the variance in PTSD symptoms in parents. "Further," they say, "69% of parents of children with ASD who reported challenging child behaviors within the clinical threshold range also exceeded the clinical cut-off score for consideration of a PTSD provisional diagnosis." For parents of children with rare diseases, anxiety-related behaviors were the only positive predictor of PTSD symptoms.

The researchers conclude, "Health professionals need to be aware that some parents of children with ASD and parents of children with a rare disease may be exposed to events related to their child's behaviors that lead to the experience of traumatic stress."

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"Challenging child behaviours positively predict symptoms of posttraumatic stress disorder in parents of children with autism spectrum disorder and rare diseases," Michelle Stewart, Alexandra Schnabel, David J. Hallford, Jane A. McGillivray, David Forbes, Madeline Foster, Kerrie Shandley, Madeleine Gardam, and David W. Austin, *Research in Autism Spectrum Disorders*, Vol. 69, 2020. Address: Alexandra Schnabel, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Melbourne, VIC, 3125, Australia.

The Kids First Initiative

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.

New study investigates why behavior often improves during fevers for children with ASD

Many parents report that the behavior of children with autism spectrum disorders (ASD) improves when the children have fevers, and a new study by researchers at Harvard and the Massachusetts Institute of Technology offers clues as to why this happens.

Earlier research by Gloria Choi and Jun Huh found that mice born to mothers that experienced a severe infection during pregnancy were much more likely than other mice to exhibit repetitive behaviors, abnormal communication, and deficits in sociability. The researchers discovered that this was due to exposure to maternal IL-17a, an immune molecule, which produced defects in a brain region called S1DZ in the developing embryos. S1DZ appears to be responsible for sensing where the body is in space.

The team found that during their fevers, the mice produced IL-17a, which bound to receptors in S1DZ. The immune molecules reduced neural activity in the brain region, making the mice more sociable. When the researchers inhibited IL-17a or knocked out the receptors for it, this increased sociability did not occur.

In the new study, Choi and Huh, along with lead authors Michael Douglas Reed and Yeong Shin Yim, studied mice that exhibited behavioral symptoms similar to autism due to previous exposure to inflammation during fetal development. The researchers injected the mice with a bacterial component to induce a fever, and found that the social interactions of the animals temporarily became normal.

The team found that during their fevers, the mice produced IL-17a, which bound to receptors in S1DZ. The immune molecules reduced neural activity in the brain region, making the mice more sociable. When the researchers inhibited IL-17a or knocked out the receptors for it, this increased sociability did not occur. In addition, simply raising the body temperature of the mice had no effect on behavior.

"This suggests that the immune system uses molecules like IL-17a to directly talk to the brain," Choi says, "and it can actually work almost like a neuromodulator to bring about these behavioral changes."

Dan Littman, a professor of immunology who was not involved in the study, commented, "What's remarkable about this paper is that it shows that this effect on behavior is not necessarily a result of fever but the result of cytokines [immunoregulatory proteins] being made. There's a growing body of evidence that the central nervous system, in mammals at least, has evolved to be dependent to some degree on cytokine signaling at various times during development or postnatally."

The researchers performed the same experiments on three different genetic mouse models of autism (mice lacking Shank3, Cntnap2, or Fmr1), but giving these mice fevers did not stimulate IL-17a production and did not alter their behavior. However, when the researchers injected the genetically modified mice with IL-17a, their behavior did improve. Reed and colleagues say this suggests that mice exposed to inflammation during gestation develop immune systems that are primed to more readily produce IL-17a during subsequent infections.

Huh comments, "It was amazing to discover that the same immune molecule, IL-17a, could have dramatically opposite effects depending on context: promoting autism-like behaviors when it acts on the developing fetal brain and ameliorating autism-like behaviors when it modulates neural activity in the adult mouse brain."

In separate research, Choi and Huh found that presence of certain bacteria in the gut can also prime IL-17a responses. The researchers are now investigating whether gut bacteria play a role in the fever-induced reversal of social impairments that they detected in their study.

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"IL-17a promotes sociability in mouse models of neurodevelopmental disorders," Michael Douglas Reed, Yeong Shin Yim, Ralf D. Wimmer, Hyunju Kim, Changhyeon Ryu, Gwyneth Margaret Welch, Matias Andina, Hunter Oren King, Ari Waisman, Michael M. Halassa, Jun R. Huh, and Gloria B. Choi, *Nature*, December 18, 2019 (online). Address: Jun Huh, jun_huh@hms.harvard.edu.

—and—

"Study may explain how infections reduce autism symptoms," news release, Anne Trafton, Massachusetts Institute of Technology, December 19, 2019.

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.

—April 15, 2020—
1 p.m. Eastern Time
Research Finds GI issues Coincide with Problem Behaviors in ASD
Bradley Ferguson, Ph.D.

—May 13, 2020—
1 p.m. Eastern Time
Catatonia and Autism Spectrum Disorders
Robert L. Hendren, D.O.

—June 10, 2020—
1 p.m. Eastern Time
Transition to Adulthood
Stephen Shore, Ed.D.

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

Editorial: Researchers have identified a relationship between Ehlers-Danlos Syndrome and autism

(cont. from page 3)

in these individuals at the biological level—knowledge which we may be able to apply to the rest of the EDS/HSD spectrum. In addition, because Fragile X spectrum disorders share clear links with autism, this may also help us to understand why these connective tissue disorders are so often associated with the neurodevelopmental condition.

EDS/HSD has been poorly studied to date, but there is a rapidly growing interest from the patient communities and a push for more research. We hope in the future, scientists and funding agencies will realize the importance of this overlap, as well as the implications it has for overall quality of life for those on the spectrum and their affected family members, and invest more time and money into studying the relationship between EDS/HSD and autism.

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The Autism Research Institute (ARI) is the oldest autism research organization in the world, founded by Dr. Bernard Rimland in 1967.

ARI'S WORK INCLUDES:

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

•

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

•

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

•

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