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Gastrointestinal and internalizing behaviors may be "bidirectional" in children, teens with ASD

Individuals with autism spectrum disorders (ASD) frequently suffer from gastrointestinal (GI) problems, and many also experience internalizing symptoms such as stress, anxiety, depression, and social withdrawal. A new study suggests that there is a bidirectional relationship between GI problems and internalizing symptoms in children and teens with autism—in other words, the two problems are simultaneously impacting each other.

In the study, Kristen Dovgan and colleagues analyzed data collected from parental reports on 621 individuals with ASD, all of whom were under the age of 18 and suffered from gastrointestinal issues. The researchers say, "The best-fitting model was a bidirectional model wherein internalizing symptoms, including withdrawn and anxious behavior, were correlated with GI problems, including constipation, diarrhea, nausea, and stomach pain."

Study coauthor Bradley Ferguson says his team's findings emphasize the importance of the gut-brain axis in autism.

Study coauthor Bradley Ferguson says the findings emphasize the importance of the gut-brain axis in autism. He comments, "Research has shown gastrointestinal issues are associated with an increased stress response as well as aggression and irritability in some children with autism. This likely happens because some kids with autism are unable to verbally communicate their gastrointestinal discomfort as well as how they feel in general, which can be extremely frustrating."

He adds, "Stress signals from the brain can alter the release of neurotransmitters like serotonin and norepinephrine in the gut, which control gastrointestinal motility, or the movement of stool through the intestines. Stress also impacts the balance of bacteria living in the gut, called the microbiota, which can alter gastrointestinal functioning. The gut then sends signals back to the brain, and that can, in turn, lead to feelings of anxiety, depression and social withdrawal. The cycle then repeats, so novel treatments addressing signals from both the brain and the gut may provide the most benefit for some kids with gastrointestinal disorders and autism."

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"Bidirectional relationship between internalizing symptoms and gastrointestinal problems in youth with autism spectrum disorder," Kristen Dovgan, Kyra Gynegrowski, and Bradley J. Ferguson, *Journal of Autism and Developmental Disorders*, April 20, 2022 (online). Address: Kristen Dovgan, Marist College, Department of Psychology, Poughkeepsie, NY 12601, kristen.dovgan@marist.edu.

—and—

"Study finds a bidirectional link between gastrointestinal issues and internalized symptoms in kids with autism," News-Medical.net, April 26, 2022.

Amygdala overgrowth in infancy found in children who later develop ASD

The amygdala—a region of the brain that helps to interpret the social and emotional meaning of sensory input—grows abnormally rapidly in young infants who later develop autism, according to recent research.

Mark Shen and colleagues used magnetic resonance imaging (MRI) to study amygdala development in 408 infants. The group included 58 children who were at elevated risk for ASD (because they had an older sibling with ASD) and later developed autism; 212 at-risk infants who did not develop autism; 109 neurotypical controls; and 29 infants with fragile X syndrome (a hereditary condition that causes many symptoms similar to those of ASD). The researchers obtained more than 1,000

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Implanted device may reduce seizures in individuals with ASD

Individuals with autism spectrum disorders (ASD) frequently suffer from epilepsy, and nearly one-third of people with ASD and comorbid epilepsy have seizures that cannot be controlled by medication. A new study suggests that a treatment called responsive neurostimulation may be beneficial for many of these individuals.

Responsive neurostimulation involves a device called a neurostimulator that is placed under the scalp and within the skull.

Fields and her team found that 63 percent of the patients experienced seizure reductions of more than 50 percent, with 21 percent of them experiencing reductions of more than 90 percent.

The device is connected to electrodes that monitor brain activity and detect seizures. When a seizure occurs, the device delivers a small electrical current to shorten or stop it.

Madeline Fields and colleagues conducted a multicenter study on the efficacy of responsive neurostimulation for individuals with ASD and drug-resistant epilepsy. The researchers evaluated 19 patients, ranging from 11 to 29 years of age, who had received the devices at least one year earlier.

Fields and her team found that 63 percent of the patients experienced seizure reductions of more than 50 percent, with 21 percent of them experiencing reductions of more than 90 percent. The response rate was 70 percent for individuals in whom the device had been implanted for more than two years. In addition, the researchers say, "Improvements in behaviors as measured by the Clinical Global Impression Scale-Improvement scale were noted in 79 percent." No surgical complications were seen.

The researchers conclude, "Based on the authors' experience in this small cohort of patients, the RNS System seems to be a promising surgical option in people with ASD [and drug-resistant epilepsy]."

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"Responsive neurostimulation for people with drug-resistant epilepsy and autism spectrum disorder," Madeline C. Fields, Christina Marsh, Onome Eka, Emily A. Johnson, Lara V. Marcuse, Churl-Su Kwon, James J. Young, Maite LaVega-Talbott, Mohankumar Kurukumbi, Gretchen Von Allmen, John Zempel, Daniel Friedman, Nathalie Jette, Anuradha Singh, Ji Yeoun Yoo, Leah Blank, Fedor Panov, and Saadi Ghatan, *Journal of Clinical Neurophysiology*, April 22, 2022 (online). Address: Madeline C. Fields, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York 10029.

Gender diversity more common in kids with ASD than in neurotypical peers

Gender diversity is more common among children with autism spectrum disorders (ASD) than among their neurotypical peers, according to a new study.

Previous research has shown that the rate of gender diversity is elevated in children with ASD. However, Blythe Corbett and colleagues, who authored the new study, note that this research relied solely on parental answers to a single question from the Child Behavior Checklist.

In their study, Corbett and her team used the Gender Diversity Screening Questionnaire Self-Report and Parent-Report to assess gender diversity in 140 children with ASD and 104 neurotypical controls, all between 10 and 13 years of age. In addition, they used the same question from the Child Behavior Checklist that was used by previous researchers.

The researchers say, "Results showed that autistic children endorsed much higher rates of binary gender diversity (less identification with their designated sex and more with the other binary sex) and nonbinary gender diversity (identification as neither male nor female) than typically developing children. Similarly, parents of autistic children reported significantly more gender-body incongruence experienced by their child than parents of typically developing children. Specifically, parents of autistic females-assigned-at-birth reported significantly more gender-body incongruence than autistic males-assigned-at-birth." Parental reports and self-reports were largely consistent.

The researchers conclude, "Results extend previous reports showing increased rates of gender diversity in autistic children, now based on both self-report and parent-report, and highlight the need to better understand and support the unique and complex needs of autistic children who experience gender diversity."

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"Greater gender diversity among autistic children by self-report and parent-report," Blythe A. Corbett, Rachael A. Muscatello, Mark E. Klemencic, Millicent West, Ahra Kim, and John F. Strang, *Autism*, April 1, 2022.Address: Blythe Corbett, Vanderbilt University Medical Center, 1500 21st Avenue S, Nashville, TN 37212, blythe.corbett@vumc.org.

Could autism stem from epigenetic changes before birth?

A new study suggests that cases of idiopathic autism—that is, autism with no known cause—may stem from epigenetic abnormalities detectable early in fetal development. Epigenetic changes are changes that alter the effects of DNA by turning genes "on" or "off" without changing the DNA sequence.

Chia-Wen Lin and colleagues hypothesized that a common cause could underlie the various types of immune dysregulation seen in autism, including inflammation of the brain and gut. To explore this theory, the researchers studied BTBR mice, which are used as a mouse model of autism. They focused on the hematopoietic cells from which immune cells are derived, as well as on the yolk sac and the aorta-gonad-mesonephros (AGM), which are involved in the process of creating hematopoietic cells.

The researchers found that dysregulation of epigenetic machinery mediated by an enzyme called HDAC1 altered the development of "progenitor" cells that later develop into the yolk sac and AGM and impacted the development of immune cells called microglia. "Subsequently," they say, "these changes result in the dysregulation of the immune system, leading to gut dysbiosis and hyperactive microglia in the brain." In addition, the researchers found that administering inhibitors of HDAC1 suppressed inflammation and microglial activation.

The researchers also found that dysregulated immunity in the mice led to specific profiles of gut dysbiosis. This, they say, could aid in the categorization of autism caused by immune dysregulation.

They conclude, "[I]t is clear that the abnormalities in the brain and peripheral organs (such as the intestines) seen in autism are caused by epigenetic abnormalities in the hematopoietic stem cell lineage, the ancestor of immune cells."

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"A common epigenetic mechanism across different cellular origins underlies systemic immune dysregulation in an idiopathic autism mouse model," Chia-Wen Lin, Dian E. Septyaningtrias, Hsu-Wen Chao, Mikiko Konda, Koji Atarashi, Kozue Takeshita, Kota Tamada, Jun Nomura, Yohei Sasagawa, Kaori Tanaka, Itoshi Nikaido, Kenya Honda, Thomas J. McHugh, and Toru Takumi, *Molecular Psychiatry*, May 2022 (online). Address: Toru Takumi, Department of Physiology and Cell Biology, Kobe University School of Medicine, Chuo, Kobe, 650-0017, Japan, takumit@med.kobe-u.ac.jp.

—and—

"Does autism begin in the womb?", news release, Kobe University, May 2, 2022.

Amygdala overgrowth in infancy found in children with ASD

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MRI scans of the children at 6, 12, and 24 months of age.

They report, "Infants who developed ASD had typically sized amygdala volumes at 6 months, but exhibited significantly faster amygdala growth between 6 and 24 months, such that by 12 months the ASD group had significantly larger amygdala volume… compared with all other groups." In addition, they say, "Amygdala growth rate between 6 and 12 months was significantly associated with greater social deficits at 24 months when the infants were diagnosed with ASD."

Senior study author Joseph Piven says, "Our research suggests an optimal time to start interventions and support children who are at highest likelihood of developing autism may be during the first year of life. The focus of a pre-symptomatic intervention might be to improve visual and other sensory processing in babies before social symptoms even appear."

Noting that very young infants who later develop ASD exhibit abnormal visual processing and other sensory anomalies, the researchers theorize that this could place increased stress on the amygdala, leading to overgrowth. Another possibility, they say, is that amygdala overgrowth is related to neuroinflammation occurring in infancy.

Senior study author Joseph Piven adds, "Our research suggests an optimal time to start interventions and support children who are at highest likelihood of developing autism may be during the first year of life. The focus of a pre-symptomatic intervention might be to improve visual and other sensory processing in babies before social symptoms even appear."

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"Subcortical brain development in autism and fragile X syndrome: evidence for dynamic, age- and disorder-specific trajectories in infancy," Mark D. Shen, Meghan R. Swanson, Jason J. Wolff, Jed T. Elison., Jessica B. Girault, Sun Hyung Kim, Rachel G. Smith, Michael M. Graves, Leigh Anne H. Weisenfeld, Lisa Flake, Leigh MacIntyre, Julia L. Gross, Catherine A. Burrows, Vladimir S. Fonov, D. Louis Collins, Alan C. Evans, Guido Gerig, Robert C. McKinstry, Juhi Pandey, Tanya St. John, Lonnie Zwaigenbaum, Annette M. Estes, Stephen R. Dager, Robert T. Schultz, Martin A. Styner, Kelly N. Botteron, Heather C. Hazlett, and Joseph Piven, *American Journal of Psychiatry*, March 2022 (online). Address: Mark Shen, mark_shen@med.unc.edu.

—and—

"Scientists identify overgrowth of key brain structure in babies who later develop autism," news release, University of North Carolina Health Care, March 25, 2022.

EDITORIAL: Stephen M. Edelson, Ph.D.

Defining degrees of autism: the controversy and a suggested solution

Over the years, a number of broad terms have been used to describe individuals with autism spectrum disorders (ASD). In general, these terms have focused on levels of functioning, intelligence, severity, and verbalization.

While these terms are widely used in the research literature as well as in the autism community, many people have raised concerns about their simplistic nature and their reliance on ill-defined criteria. In this editorial, I suggest a simpler and more accurate system for classifying individuals with ASD.

A brief history of ASD terminology

Initially, autism was referred to as *infantile autism* or *Kanner's syndrome*. Later, terms such as *classical autism* and *autistic-like* were used. The former term described individuals who exhibited most of the symptoms and behaviors described in Kanner's 1943 seminal paper[1], while the latter described individuals who exhibited fewer of them[2].

Soon after Lorna Wing introduced the autism community to a little-known article published in 1944 by Hans Asperger[3], she helped to popularize the term *autism spectrum disorder*, or ASD. Much later, in 1994, the term *Asperger syndrome* was officially recognized in the Diagnostic and Statistical Manual (DSM), version 4[4]; however, this diagnosis was removed 10 years later in the DSM, version 5[5]. It has been nearly a decade since this change was made, and the term *Asperger syndrome* is still used today among researchers, clinicians, and the general population[6-8].

Recently, a consensus report, sponsored by the *Lancet* journal, introduced the category *profound autism*[9]. Soon after the introduction of this term, many in the autism community raised serious concerns about the assumptions and applicability of this new "administrative term" to describe a subpopulation of individuals on the spectrum. The term refers to those with autism who suffer from "intellectual and language impairment," require 24-hour support, and are unable to take care of many, if not most, of their basic needs. These individuals may also have additional challenges such as "self-injury, aggression, and epilepsy."

Although at first glance the term *profound autism* may seem logical, there are many individuals with ASD whose condition is quite pronounced even though they have little or no impairment in intelligence and language. For example, these individuals may suffer from extreme anxiety, depression, and/or hyper-reactivity to sensory stimuli, making it difficult or impossible for them to live independently. Thus, a more accurate terminology is needed to describe individuals with ASD and identify the services they need.

Why not focus on level of independence?

One simple and straightforward way to classify individuals with ASD is with respect to their level of independence. In other words, how capable are they of taking care of their basic needs—for instance, preparing food, obtaining water, dressing in proper clothing, having a structured sleep schedule, and finding and maintaining adequate shelter?

Here are some examples of classifying individuals based on their level of independence:

- Individuals who are independent can live on their own and need minimal financial support. However, they may have mild or even severe challenges such as sensory sensitivities, sleep disturbances, anxiety, or depression. Consequently, they may seek help occasionally from family members and professionals.
- Individuals who live semi-independently may need some supervision and/or significant financial support and may face challenging issues occasionally or on a near-daily basis. However, they will not be solely reliant on care and support from others.
- Individuals who are dependent will need a great deal of support and care from others on a constant or near-constant basis.

The term *levels of independence* avoids the shortcomings of other popular terms that focus on functioning, intelligence, severity, and verbalization. These terms frequently fail to accurately address the true needs of individuals with ASD. For example, an individual who has limited verbal skills and occasionally engages in self-harming behavior such as hand-biting may still be able to live with minimal or no support from family members and government services. In contrast, another individual may have good communication skills but suffer from high anxiety, depression, and self-harming behavior. This person may need a great deal of support—especially in light of the high suicide rate among individuals with autism[10]—and may need to live in a dependent setting.

The current version of the DSM, version 5[5], does include severity levels in relation to needed support. These include Level I, "Requiring support;" Level II, "Requiring substantial support;" and Level III, "Requiring very substantial support." These levels are based primarily on individuals' social-communicative abilities in addition to their restricted, repetitive behaviors. However, as noted above, many individuals may still need a great deal of support even though they have reasonable social-communication skills and little or no repetitive, restrictive behaviors.

Also, it is important to note that one's level of independence is context-related. For example, an individual may be able to live completely independently but be unable to afford purchasing a house or even paying rent because of the cost of living in his or her community.

Some people have argued that individuals with ASD should not be classified and state that "labels are for cans and not for people." However, as pointed out by Lord et al. (2022)[9], categorization can be helpful in determining appropriate services. For example, professional training programs, such as those for special education teachers or residential caregivers, typically focus on helping a specific subset of the autism spectrum: individuals with challenging behaviors, little or no speech, and difficulties with adaptive living skills.

Categorization is also essential for planning purposes. Knowing an individual's level of independence will assist policymakers, school officials, and family members in estimating the financial costs for optimal care now and in the future.

Moreover, while many other terms rely on criteria that can be difficult to quantify, it is possible to objectively determine a person's level of independence. Factors such as challenging behaviors, daily adaptive skills, and physical and mental health issues can be quantified with respect to frequency, duration, and severity. This information can then be analyzed in relation to the amount of care and financial support required by an individual. Consequently, we can accurately project the level of independence for each person.

Thus, I suggest that we entertain the possibility of using the term *levels of independence* to classify individuals with ASD. This term makes intuitive sense, is easily understandable, provides a general sense of the needed guidance and care for each individual, and is accepted by most stakeholders in the community.

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References are available online. To view the references, visit www.ARRIReferences.org.

Research Updates

Psychiatric diagnoses are common in young women with ASD

Young women with autism spectrum disorders (ASD) are hospitalized for psychiatric conditions at a much higher rate than women without autism, according to a new study. The findings of the study were reported by Miriam Martini at the annual meeting of the International Society for Autism Research (INSAR) in May.

Using multiple databases, Martini and colleagues analyzed data collected on approximately 1.3 million people born in Sweden between 1985 and 1997. The researchers found that by the age of 25, more than 60 percent of women with ASD and approximately 45 percent of men with ASD had been diagnosed with a psychiatric condition, compared to 14 percent of non-autistic women and 9 percent of non-autistic men. In addition, more than 22 percent of women with ASD had been hospitalized for a psychiatric condition by the age of 25, a number five times greater than that for women without ASD and nearly double that for men with ASD. After the researchers controlled for multiple variables, their analyses still showed that both men and women with ASD received psychiatric diagnoses at a significantly elevated rate.

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"Sex differences in mental health in young autistic adults: a population-based cohort study," M. Martini, R. Kuja-Halkola, A. Butwicka, E. Du Rietz, B. D'Onofrio, F. Happe, A. Kanina, H. Larsson, S. Lundström, J. Martin, M. Rosenqvist, P. Lichtenstein, and M. Taylor, INSAR annual conference, May 2022. Address: Miriam Martini, Karolinska Institutet, Stockholm, Sweden.

—and—

"Psychiatric conditions hospitalize almost one in four autistic women by age 25," Niko McCarty, Spectrum News, May 17, 2022.

Meta-analysis casts doubt on efficacy of oxytocin

The hormone oxytocin enhances social recognition and social memory, and some studies have indicated that children with autism spectrum disorders (ASD) have lower blood levels of oxytocin than neurotypical children. However, treatment with intranasal oxytocin does not appear to be an effective treatment for adults with ASD, according to a meta-analysis by researchers in Iran.

Zahra Kiani and colleagues identified ten randomized controlled trials investigating the use of intranasal oxytocin for ASD. They report, "No study corroborated the efficacy of oxytocin for the treatment of anxiety and repetitive behavior. One out of four studies reported clinical improvement in severity, and one out of six studies indicated improvement in social function." Overall, the researchers say, their analysis showed no efficacy in the treatment of anxiety, repetitive behavior, or social function, and no effect on autism severity.

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"Oxytocin effect in adult patients with autism: an updated systematic review and meta-analysis of randomized controlled trials," Zahra Kiani, Tahereh Farkhondeh, Hamed Aramjoo, Michael Aschner, Hossein Beydokhti, Aliakbar Esmaeili, Morteza Arab-Zozani, and Saeed Samarghandian, *CNS & Neurological Disorders—Drug Targets*, 2022 (online). Address: Saeed Samarghandian, Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran.

Clock gene may play a role in causing ASD

Disruption of a circadian clock gene may play a role in autism spectrum disorders (ASD), according to a study by researchers in Greece and the United States.

Clock genes are genes that produce the circadian rhythms that control the timing of biological functions including waking and sleeping. "It has long been recognized that the function of the body clock is frequently disrupted in autism patients and these patients often exhibit various sleep problems," study coauthor Ruifeng Cao says. "But it is not known whether clock gene disruption can directly cause autism."

Studying mice with a deletion of the clock gene *Bmal1*, the researchers found that "global *Bmal1* deletion led to significant social impairments, excessive stereotyped and repetitive behaviors, as well as motor learning disabilities... all of which resemble core behavioral deficits in ASD." In addition, they say, mice with the deletion exhibited abnormal cell density and immature structure of dendritic spines in Purkinje cells, which are cells in the cerebellum that have been implicated in ASD. The mice also exhibited enhanced excitatory and inhibitory synaptic transmission and reduced firing rates in Purkinje cells, as well as other cellular and molecular changes in the cerebellum. Moreover, the researchers report, deleting the *Bmal1* gene solely in cerebellar Purkinje cells was sufficient to cause autistic-like behavioral and cellular changes.

The researchers conclude, "Our findings provide experimental evidence supporting a putative role for dysregulation of circadian clock gene expression in the pathogenesis of ASD."

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"Autistic-like behavior and cerebellar dysfunction in *Bmal1* mutant mice ameliorated by mTORC1 inhibition," Dong Liu, Carmen Nanclares, Konstanze Simbriger, Kun Fang, Ethan Lorsung, Nam Le, Inês Silva Amorim, Kleanthi Chalkiadaki, Salil Saurav Pathak, Jin Li, Jonathan C. Gewirtz, Victor X. Jin, Paulo Kofuji, Alfonso Araque, Harry T. Orr, Christos G. Gkogkas, and Ruifeng Cao, *Molecular Psychiatry*, March 2022 (online). Address: Christos G. Gkogkas, Biomedical Research Institute, Foundation for Research and Technology-Hellas, University Campus, 45110, Ioannina, Greece, cgkogkas@bri.forth.gr.

—and—

"Clock gene mutation found to contribute to the development of autism," news release, University of Minnesota Medical School, March 24, 2022.

Infections occurring during childhood may raise risk for autism, intellectual disability

There may be an association between childhood infections and subsequent diagnoses of autism spectrum disorder (ASD) or intellectual disability (ID), according to a recent large-scale study.

Håkan Karlsson and colleagues analyzed data collected on 556,732 Swedish children born between 1987 and 2010, identifying all children with documented treatment for childhood infections. Their initial analysis showed a significant association between childhood infections and later ASD or ID, with the strongest association being for ID. When the researchers further analyzed their data by controlling for a wide range of variables, excluding children with congenital causes of ASD/ID, and comparing the children with siblings to factor in both heritable and non-heritable factors, the association was smaller but remained significant.

The researchers conclude, "Based on our analysis of the timing of infections and the diagnoses of ASD and ID in this study, including careful consideration of potential confounding by shared familial factors, we suggest that infections during early childhood contribute to risk of a later diagnosis of ID, including ID co-occurring with ASD."

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"Childhood infections and autism spectrum disorders and/or intellectual disability: a register-based cohort study," Håkan Karlsson, Hugo Sjöqvist, Martin Brynge, Renee Gardner, and Christina Dalman, *Journal of Neurodevelopmental Disorders*, February 2022 (free online). Address: Håkan Karlsson Department of Neuroscience, Karolinska Institutet, 171 77, Stockholm, Sweden, hakan.karlsson.2@ki.se.

Research Updates

Hypertension screening rarer for kids with ASD

According to current U.S. medical guidelines, children three years of age or older should be screened for hypertension. However, a new study indicates that children with autism spectrum disorders (ASD) are less likely than other children to receive this screening.

Using two large national databases, James Nugent and colleagues analyzed data on preventive care visits from 2002 to 2018 involving patients between 3 and 21 years of age. These included visits to medical offices and hospital outpatient departments.

The researchers found that more than 75 percent of children without ASD were screened for hypertension, compared to less than 56 percent of children with ASD. In addition, they found that rates of hypertension screening increased over time for children without ASD, but not for those with ASD. In contrast, children with attention-deficit/hyperactivity disorder, asthma, depression, diabetes, cerebral palsy, epilepsy, and obesity were screened for hypertension at the same rate as children without these disorders.

The researchers say their findings are in line with other research showing gaps in preventive care for children with ASD. Noting that sensory issues may sometimes make screening patients with ASD difficult, they suggest that home blood pressure monitoring may be a feasible alternative to in-office measurement in such cases.

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"Screening for hypertension in children with and without autism spectrum disorder," James T. Nugent, Christine Bakhoum, Lama Ghazi, and Jason H. Greenberg, *JAMA Network Open*, April 2022 (free online). Address: James T. Nugent, Clinical and Translational Research Accelerator, Department of Medicine, Yale University School of Medicine, 60 Temple St., Ste. 6C, New Haven, CT 06510, james.nugent@yale.edu.

—and—

"Hypertension screening performed less often in children with autism," Conor Iapoce, HCP Live, April 7, 2022.

Rates of undiagnosed ASD may be high in individuals who commit suicide

A significant percentage of individuals who commit suicide may have undiagnosed autism spectrum disorders (ASD) or high levels of autistic traits, according to a study from Britain.

Sarah Cassidy and colleagues reviewed the coroners' inquest records of 372 people who committed suicide. The researchers found that nearly 11% of those who committed suicide exhibited evidence of elevated autistic traits, indicating likely undiagnosed autism. This rate is 11 times higher than the rate of autism in the United Kingdom. Moreover, the researchers say, "Given that coroners' records do not systematically gather evidence of autism and autistic traits, this is likely an underestimate of the true rate." Interviewing a subset of 29 families of victims, the researchers identified indications of autism in more than 40% of the victims (although none of these individuals met the threshold for autism).

Previous research by the same group has shown that up to 66 percent of adults with ASD have thought about taking their own life, and 35 percent have attempted suicide. In addition, while approximately one percent of people in the U.K. have ASD, up to 15 percent of people hospitalized after attempting suicide have an ASD diagnosis.

Noting that individuals with ASD die an average of 20 years earlier than people without ASD, and that suicide is one of the leading causes of premature death in this population, coauthor Simon Baron-Cohen comments, "Suicide rates are unacceptably high in autistic people and suicide prevention has to be the number one goal to reduce the worrying increased mortality in autistic people."

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"Autism and autistic traits in those who died by suicide in England," Sarah Cassidy, , Sheena Au-Yeung, Ashley Robertson, Heather Cogger-Ward, Gareth Richards, Carrie Allison, Louise Bradley, Rebecca Kenny, Rory O'Connor, David Mosse, Jacqui Rodgers, and Simon Baron-Cohen, *British Journal of Psychiatry*, February 15, 2022 (free online). Address: Sarah Cassidy, School of Psychology, University of Nottingham, U.K., sarah.cassidy@nottingham.ac.uk.

—and—

"Study reveals high rate of possible undiagnosed autism in people who died by suicide," news release, University of Nottingham, February 15, 2022.

ARI Survey: Seniors with Autism Spectrum Disorder

https://www.autism.org/adult_survey

If you or a person you care for is on the autism spectrum and is 50 years of age or older, we would appreciate it if you could complete this online form.

We hope the results from this survey will provide insight into the needs and challenges faced by seniors with autism and their support providers.

Central sensitivity syndromes may be very common in those with ASD

Conditions called "central sensitivity syndromes" (CSS) may be very common in individuals with autism spectrum disorders (ASD), according to a new study.

Central sensitivity syndromes include such conditions as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia syndrome (FMS), migraine, irritable bowel syndrome (IBS), restless legs syndrome (RLS), and temporomandibular joint disorder (TMJD). These conditions are believed to involve a process called central sensitization, in which the central nervous system becomes chronically upregulated, lowering the threshold for pain and causing increased sensitivity to other sensations such as touch or sound.

To determine how common CSS is in individuals with ASD, Sarah Grant and colleagues analyzed data collected from 973 autistic adults (410 men and 563 women) in the Netherlands. The researchers report, "Twenty-one percent of participants reported one or more CSS diagnoses, and 60 percent scored at or above the clinical cut-off for a CSS." Women were significantly more likely to report having a CSS diagnosis than men and experienced a greater number of CSS symptoms. Further analysis showed that sensory sensitivity, anxiety, age, and gender were significant predictors of CSS symptoms in individuals with ASD, "with sensory sensitivity and anxiety fully mediating the relationship between autistic traits and CSS symptoms."

The researchers conclude, "CSS diagnoses and symptoms appear to be very common in the autistic population. Increased awareness of an association between autism and central sensitization should inform clinicians and guide diagnostic practice, particularly for women where CSS are common and autism under-recognized." However, they note that more research is needed to confirm their results because, among other limitations, their study did not include a control group and ethnic minorities were under-represented.

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"Autism and chronic ill health: an observational study of symptoms and diagnoses of central sensitivity syndromes in autistic adults," Sarah Grant, Sam Norton, Ricarda F. Weiland, Anke M. Scheeren, Sander Begeer, and Rosa A. Hoekstra, *Molecular Autism*, February 2022 (free online). Address: Sarah Grant, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK, sarah.grant@kcl.ac.uk.

Screening tool may be highly effective in spotting ASD in infants, toddlers

An early screening tool developed by researchers in Australia appears to be highly effective at detecting autism spectrum disorders (ASD) in infants and toddlers, according to a recent study.

Josephine Barbaro and colleagues studied the accuracy of the tool, called the Social Attention and Communication Surveillance-Revised (SACS-R), in identifying cases of ASD in a group of more than 13,500 children in Australia. The test was administered at least once at the children's 12-, 18-, and/or 24-month checkups. In addition, the researchers analyzed the effectiveness of combining this tool with the SACS-Preschool (SACS-PR) tool, designed to identify ASD in toddlers. The SACS-PR was administered at children's 42-month checkup.

Barbaro and colleagues found that 83 percent of infants and toddlers between 12 and 24 months of age who were flagged by the SACS-R later received an autism diagnosis. When clinicians combined the SACS-R and SACS-PR, 96 percent of children with ASD were identified by the time they were three-and-a-half years of age.

The researchers report that 83 percent of infants and toddlers between 12 and 24 months of age who were flagged by the test later received an autism diagnosis. When clinicians combined the SACS-R and SACS-PR, 96 percent of children with ASD were identified by the time they were three-and-a-half years of age.

Barbaro notes that accurate screening of infants and toddlers can allow parents to seek early treatment. "Parents are often told to 'wait and see' when raising concerns about their child's development," she says. "This means the average age of diagnosis is around four to five, and opportunities for early supports have been missed."

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"Diagnostic accuracy of the Social Attention and Communication Surveillance-Revised with preschool tool for early autism detection in very young children," Josephine Barbaro, Nancy Sadka, Melissa Gilbert, Erin Beattie, Xia Li, Lael Ridgway, Lauren P. Lawson, and Cheryl Dissanayake, *JAMA Network Open*, March 2022 (free online). Address: Josephine Barbaro, Olga Tennison Autism Research Centre, School of Psychology and Public Health, La Trobe University, Bundoora, Australia 3086, j.barbaro@latrobe.edu.au.

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"Highly accurate tool for the detection of autism as early as 12 months of age," news release, La Trobe University, March 11, 2022.

Iron deficiency may be common in children with autism

A new study from Italy suggests that many children with autism spectrum disorders (ASD) suffer from iron deficiency and/or deficiencies of vitamin B12 or folic acid.

Andrea De Giacomo and colleagues enrolled 167 children in their study, including 93 children with ASD and 74 children with other neurodevelopmental disorders. Their analysis showed that the ASD group had significantly lower levels of ferritin. (Ferritin is a blood protein that contains iron; the lower the ferritin level, the less iron there is in the blood.) More than half of the children with ASD exhibited hypoferritinemia, or very low ferritin levels.

The researchers note that iron deficiency in ASD could contribute to autism due to iron's roles in early development, cell metabolism and survival, and brain function. Alternately, they say, low iron levels could be a result of the food selectivity and sensory issues common in ASD.

While their study focused primarily on iron, the researchers also say, "Our ASD group had significantly higher mean corpuscular volume (MCV) values compared with the [control] group." An elevated MCV value indicates the presence of red blood cells that are abnormally large, an anomaly that may point to a deficiency of vitamin B12 or folic acid.

The researchers conclude, "Our results may support the hypothesis of altered iron status in ASD, justifying more frequent examinations of blood iron parameters in these children." However, they note that their study has limitations, including a small sample size and the lack of a neurotypical control group.

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"Peripheral iron levels in autism spectrum disorders vs. other neurodevelopmental disorders: preliminary data," Andrea De Giacomo, Silvia Medicamento, Chiara Pedaci, Donatella Giambersio, Orazio Valerio Giannico, Maria Giuseppina Petruzzelli, Marta Simone, Massimo Corsalini, Lucia Marzulli, and Emilia Matera, *International Journal of Environmental Research and Public Health*, March 28, 2022 (free online). Address: Andrea De Giacomo, School of Medicine, University of Bari "Aldo Moro," 70124 Bari, Italy, andrea.degiacomo@uiba.it.

Study shows benefits of learning ASD diagnosis early in life

People who learn early in life that they have an autism spectrum disorder (ASD) may have a greater sense of well-being than those who learn that they have the condition later in life, according to a new study.

Tomisin Oredipe and colleagues surveyed 78 autistic university students, asking them to describe how and when they learned they were autistic, how they felt when they received their diagnoses, and how they currently felt about their lives and about being autistic. The researchers found that students who learned they were autistic at a young age had a better quality of life and a greater sense of well-being in adulthood compared to those who were diagnosed at an older age.

Study coauthor Bella Kofner says, "This is the first study, to our knowledge, to demonstrate that learning at a young age that one is autistic may have positive impacts on emotional health among autistic university students. Hopefully, this finding may begin to address concerns parents have about when to talk to their child about autism. 'When' the conversation begins is particularly important. Our findings suggest that learning at a younger age that one is autistic can help autistic people develop self-understanding and access support, providing the foundations for well-being in adulthood."

The researchers note, however, that those who learned they were autistic at an older age also felt empowered by this knowledge. Study coauthor Steven Kapp says, "Learning about autism at an older age is associated with more positive emotions about a diagnosis—especially relief."

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"Does learning you are autistic at a younger age lead to better adult outcomes? A participatory exploration of the perspectives of autistic university students," Tomisin Oredipe, Bella Kofner, Ariana Riccio, Eilidh Cage, Jonathan Vincent, Steven K. Kapp, Patrick Dwyer, and Kristen Gillespie-Lynch, *Autism*, April 2022 (online). Address: Kristen Gillespie-Lynch, College of Staten Island, The City University of New York, 2800 Victory Boulevard 4s-103, Staten Island, NY 10314, Kristen.Gillespie@csi.cuny.edu.

—and—

"Study suggests early self-awareness of autism leads to better quality of life," news release, University of Portsmouth, April 26, 2022.

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Abnormalities of astrocytes again implicated in autism

A new study adds to evidence that abnormalities in star-shaped cells called astrocytes, which provide support for neurons in the brain and central nervous system, may play a role in autism spectrum disorders (ASD).

In the study, Megan Allen and colleagues grew astrocytes from stem cells derived from individuals with ASD and transplanted them into the brains of newborn mice. The researchers found that following the transplants, the mice developed repetitive behaviors—a hallmark of autism spectrum disorders (ASD)—and exhibited memory deficits. However, the mice did not develop the social deficits associated with the disease.

Study coauthor Dilek Colak says, "Our study suggests that astrocyte abnormalities might contribute to the onset and progression of autism spectrum disorders. Astrocyte abnormalities may be responsible for repetitive behavior or memory deficits, but not other symptoms like difficulties with social interactions."

The researchers also found that the transplanted human astrocytes in the brains of the mice exhibited excessive calcium signaling. To determine if this increased calcium signaling was causing the mice's behavioral symptoms, the team infected astrocytes grown from the stem cells of individuals with ASD with a virus carrying a fragment of RNA designed to reduce calcium signaling to normal levels. When the researchers transplanted these astrocytes into the mice, the animals did not develop memory problems.

Allen comments, "Future therapies for autism might exploit this finding by using genetic tools to limit extreme calcium fluctuations inside astrocytes."

The new study adds to evidence that astrocytes play a role in autism. In a previous study, (see ARRI 2017, No. 4), Fabiele Baldino Russo and colleagues took dental pulp cells from the baby teeth of three children with non-syndromic autism spectrum disorders (ASD)—that is, ASD not due to any known cause—and reprogrammed the cells to become either neurons or astrocytes. The researchers then grew the cells into organoids, or "mini-brains." Examining these organoids microscopically, the researchers found that the neurons had structural defects and that some of the astrocytes had high levels of a pro-inflammatory protein called interleukin 6 (IL-6), which is toxic to neurons.

When Russo and colleagues combined astrocytes from the dental pulp of children with ASD with neurons from neurotypical controls and cultured them, they found that the neurons from the controls behaved like the neurons from the children with ASD. "But more importantly," according to study coauthor Alysson Muotri, "the opposite was true. When we co-cultured ASD neurons with normal astrocytes, we could rescue the cellular defects. The neurons reverted to normal functioning and behavior."

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"Astrocytes derived from ASD individuals alter behavior and destabilize neuronal activity through aberrant Ca2+ signaling," Megan Allen, Ben S. Huang, Michael J. Notaras, Aiman Lodhi, Estibaliz Barrio-Alonso, Pablo J. Lituma, Paul Wolujewicz, Jonathan Witztum, Francesco Longo, Maoshan Chen, David W. Greening, Eric Klann, M. Elizabeth Ross, Conor Liston, and Dilek Colak, *Molecular Psychiatry*, April 1, 2022 (free online). Address: Dilek Colak, dic2009@med.cornell.edu.

—and—

"Some autism spectrum disorder symptoms linked to astrocytes," news release, Weill Cornell Medicine, April 21, 2022.

—and—

"Modeling the interplay between neurons and astrocytes in autism using human induced pluripotent stem cells," Fabiele Baldino Russo, Beatriz Camille Freitas, Graciela Conceição Pignatari, Isabella Rodrigues Fernandes, Jonathan Sebat, Alysson Renato Muotri, and Patricia Cristina Baleeiro Beltrão-Braga, Biological Psychiatry, October 3, 2017 (online). Address: Patricia Cristina Baleeiro Beltrão-Braga, Av. Prof. Dr. Orlando Marques de Paiva 87, Cidade Universitária, 05508-270. São Paulo, SP. Brazil. patriciacbbraga@usp.br.

—and—

"Inflamed support cells appear to contribute to some kinds of autism," Scott LaFee, UC San Diego Health, October 18, 2017.

New to autism? If so, the Autism Research Institute has valuable information on seeking appropriate medical care. For a list of important questions to ask a potential medical provider, see:

https://www.autism.org/finding-a-clinician

Quotable.....

"Anxiety and depression are very common in neurodivergent women, especially those who remain undiagnosed. Women with autism are three to four times more likely to attempt suicide than neurotypical women. Comorbidities are very common in autistic women as well and can dramatically enhance the risk…. Knowing you have autism (along with other comorbid neurodivergences) and that you're prone to anxiety, depression and burnout can help suffering women get access to the treatment and support they may need.

"But better diagnostic criteria are just the beginning. We also need more programs, like group therapy and support groups for women who are diagnosed with autism in adulthood. Training teachers, doctors and psychologists on what to look for in girls and women and how to accommodate us should also become the new standard.

"Understanding autism in girls is also a matter of safety, as these girls are three times more likely to be sexually abused. We tend to be more trusting and naïve, because we are often very direct and straightforward and expect other people to be the same. Recognizing ill intentions and ulterior motives in others can be difficult for us. This can make us more vulnerable and susceptible to abuse.

"Every person deserves the opportunity to succeed and rise to their greatness, including women with autism. As more girls and women recognize they are neurodivergent, having accurate testing and the accommodations means we have a better chance to do our best."

Zhara Astra, in
"We need better diagnostic tests for autism in women,"
Scientific American*, April 7, 2022*

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Amy Moore Gaffney, M.A., CCC-SLP
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