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

Study indicates that early diagnosis can significantly benefit children with ASD

Children diagnosed with autism spectrum disorders (ASD) very early in childhood are likely to do significantly better than those diagnosed later, according to a new study from Israel.

In their research, Nitzan Gabbay-Dizdar and colleagues measured changes in core symptoms over a one- to two-year period in 131 children diagnosed with ASD. The children in the study had received an ASD diagnosis when they were between 1.2 and 5 years of age.

The researchers used the Autism Diagnostic Observation Schedule (ADOS) Calibrated Severity Scores (CSS) to measure changes in the children. They report that approximately 65 percent of children diagnosed before 2.5 years of age exhibited improvements in their scores, compared to only 23 percent of children diagnosed after this age. Girls and boys appeared to benefit similarly from early diagnosis.

To ensure that their results were not due to differences in ASD severity at the time of diagnosis, the researchers analyzed a subset of 36 children from each group who were matched for sex and severity scores at diagnosis. The results of this analysis were similar to the results seen for the group as a whole.

The researchers comment, "We suggest that greater brain plasticity and behavioral flexibility enable younger children to benefit more from autism spectrum disorder interventions even in community settings with heterogeneous services. This motivates further prioritization of early autism spectrum disorder screening as recommended by American Academy of Pediatrics guidelines."

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"Early diagnosis of autism in the community is associated with marked improvement in social symptoms within 1-2 years," Nitzan Gabbay-Dizdar, Michal Ilan, Gal Meiri, Michal Faroy, Analya Michaelovski, Hagit Flusser, Idan Menashe, Judah Koller, Ditza A. Zachor, and Ilan Dinstein, *Autism*, August 2022 (free online). Address: Ilan Dinstein, Psychology Department, Ben-Gurion University of the Negev, Beer-Sheva, 84105, Israel, dinshi@bgu.ac.il.

Anxiety in children with ASD linked to insistence on sameness

A new study suggests that children with autism spectrum disorders (ASD) who have a very strong preference for sameness in their daily routines may be more vulnerable to developing anxiety than children with ASD whose insistence on sameness is less pronounced.

Anxiety is common in children with ASD, with as much as 60 percent of this population suffering from anxiety by middle childhood. Insistence on sameness—in other words, a strong resistance to changes in daily routine—is also a hallmark of ASD.

In their new research, Danielle Baribeau and colleagues examined whether an elevated level of insistence on sameness increases the likelihood of a child with ASD developing anxiety. The researchers analyzed data collected on 421 children with ASD enrolled in a long-term study in Canada. Parents were asked to fill out checklists describing their children's levels of anxiety and insistence on sameness when the children were an average of 3, 4, 7, 9, and 11 years of age.

The researchers report that children with either elevated or increasing insistence on sameness between the ages of 6 and 9 had an increased risk for anxiety one to two years later. However, the link appeared to lessen as the children aged, with no association seen between insistence on sameness and anxiety at the age of 11.

Baribeau comments, "Perhaps by supporting these more vulnerable children and their families early in life to gradually build flexibility, face and tolerate uncertainty, and ensure supportive environments and gradual transitions, we might be able to help prevent or reduce the severity of anxiety experienced by autistic youth." In particular, she says, interventions aimed at helping 6- to 8-year-olds tolerate uncertainty and cope with changes may be beneficial.

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"Developmental cascades between insistence on sameness behaviour and anxiety symptoms in autism spectrum disorder," Danielle A. Baribeau, Simone N. Vigod, Eleanor Pullenayegum, Connor M. Kerns, Tracy Vaillancourt, Eric Duku, Isabel M. Smith, Joanne Volden, Lonnie Zwaigenbaum, Teresa Bennett, Mayada Elsabbagh, Anat Zaidman-Zait, Annie E. Richard, and Peter Szatmari, *European Child & Adolescent Psychiatry*, July 24, 2022 (online). Address: Danielle Baribeau, danielle.baribeau@mail.utoronto.ca.

—and—

"Yen for routine seeds anxiety in autistic children," Charles Q. Choi, Spectrum News, August 16, 2022.

Many children with autism do not receive early intervention

While early diagnosis and treatment of autism are associated with better outcomes (see related article on this page), a new study indicates that many children—even those in communities with many autism resources—are not receiving early help.

Josephine Shenouda and colleagues analyzed data collected between 2006 and 2016 on 4,050 8-year-olds with autism spectrum disorders (ASD). The researchers found that only 1,887 of them, or 47 percent, had received early intervention services. Children living in affluent areas were 80 percent more likely to receive early intervention services than children in disadvantaged areas, and black and Hispanic children were less likely than other children to receive these services.

Shenouda comments, "New Jersey is known as an epicenter of autism, but it also has many resources for autism detection and treatment. If only half of the children with autism in our study area are getting early interventions, chances are the disparities are even more pronounced in other communities and regions with fewer services."

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"Disparities in early intervention program participation by children with autism spectrum disorder in a US metropolitan area, 2006 to 2016," Josephine Shenouda, Emily Barrett, Amy L. Davidow, Kate Sidwell, Willliam Halperin, Vincent M. B. Silenzio, and Walter Zahorodny, *JAMA Pediatrics*, July 18, 2022 (online). Address: Josephine Shenouda, Department of Biostatistics and Epidemiology, School of Public Health, Rutgers, Piscataway, New Jersey 08854.

—and—

"Only half of children with autism receive early intervention services," news release, Rutgers University, July 27, 2022.

Two studies indicate that autoantibodies in maternal blood may provide diagnostic clues in ASD

Certain patterns of proteins in the blood of pregnant women may help to predict one type of autism spectrum disorder (ASD) in children, according to two new studies.

Both studies focused on maternal autoantibody-related autism spectrum disorder, or MAR ASD. In this type of autism, specific maternal immune proteins known as autoantibodies cross the placenta and react to certain proteins found in the fetal brain. This may affect brain development, leading to behaviors linked to ASD.

In the first study, conducted in California, Alexandra Ramirez-Celis and colleagues tested maternal blood samples collected during pregnancy from 540 mothers of children with ASD, 184 mothers of children with intellectual disability (ID) but without ASD, and 420 controls. The researchers found that autoantibody binding to nine specific combinations of proteins (known as MAR ASD patterns) successfully predicted autism in previously diagnosed children.

The researchers detected reactivity to at least one of the nine MAR ASD patterns in 10 percent of the ASD group, compared with 4 percent of the ID group and 1 percent of controls. Four patterns were seen only in mothers whose children were later diagnosed with ASD, making those particular autoantibody patterns highly predictive.

The researchers also found that a mother with reactivity to any one of the nine MAR ASD patterns had an approximately eightfold higher chance of having an autistic child. The pattern most strongly linked to ASD, called CRMP1+CRMP2, increased the odds of an ASD diagnosis by 16 times and was not detected in the non-ASD groups.

The researchers conclude, "Prenatal screening for these MAR patterns may lead to earlier identification of ASD and facilitate access to the appropriate early intervention services based on each child's needs."

In the second study, Kathleen Angkustsiri and colleagues analyzed blood samples from mothers of children with ASD in Pennsylvania and Arkansas to see if the findings from the California research could be duplicated. In this study, 68 mothers of children with ASD provided blood samples and completed behavioral questionnaires about their children. The researchers also used two diagnostic measures, the Autism Diagnostic Observation Schedule (ADOS) and the Social Communication Questionnaire (SCQ). to assess the children.

The researchers found that MAR ASD was present in 21 percent of the samples from Pennsylvania and 26 percent of the samples from Arkansas. Overall, 23.5 percent of the blood samples were found to be MAR positive.

Angkustsiri says, "Our study showed... MAR ASD frequencies in two other states similar to what we observed in Northern California. This suggests that the prevalence of MAR ASD is consistent across different demographics and geographic settings."

Angkustsiri and colleagues also found that children of mothers positive for MAR antibodies had higher autism severity scores than children of mothers without these antibodies. However, they did not find significant differences in these children's IQ, adaptive functioning, or behavior.

The researchers say additional study is needed to understand why mothers develop MAR antibodies and how long these antibodies persist.

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"Maternal autoantibody profiles as biomarkers for ASD and ASD with co-occurring intellectual disability," Alexandra Ramirez-Celis, Lisa A. Croen, Cathleen K. Yoshida, Stacey E. Alexeeff, Joseph Schauer, Robert H. Yolken, Paul Ashwood, and Judy Van de Water, *Molecular Psychiatry,* May 26, 2022 (free online). Address: Judy Van de Water, javandewater@ucdavis.edu.

—and—

"Pilot study of maternal autoantibody–related autism," Kathleen Angkustsiri, Jill J. Fussell, Amanda Bennett, Joseph Schauer, Alexandra Ramirez-Celis, Robin L. Hansen, and Judy Van de Water, *Journal of Developmental & Behavioral Pediatrics*, May 13, 2022 (online). Address: Kathleen Angkustsiri, Developmental Behavioral Pediatrics, Department of Pediatrics, University of California Davis Health, 2825 50th St, Sacramento, CA 95817, kangkustsiri@ucdavis.edu.

—and—

"Mother's blood may carry the secret to one type of autism," news release, UC Davis, June 23, 2022.

Abnormal proliferation seen in neural precursor cells in ASD

Abnormalities in neural precursor cells (NPCs) may play a key role in autism spectrum disorders (ASD), according to a new study.

NPCs are cells that produce three types of brain cells: neurons, oligodendrocytes, and astrocytes. NPCs form prenatally around weeks 8 to 24 of gestation.

Robert Connacher and colleagues examined NPCs cultured from adult stem cells taken from five individuals with ASD. Three of the individuals had idiopathic autism, or autism due to unknown causes, while the other two had autism due to a genetic abnormality (a 16p11.2 deletion). Three of the individuals—one of those with idiopathic autism, and both of those with the gene deletion—exhibited macrocephaly, or an enlarged head size.

The researchers found that NPCs cultured from the individuals with macrocephaly produced too many brain cells, while those cultured from the individuals who did not have macrocephaly produced too few brain cells. Study coauthor Emanuel DiCicco-Bloom comments, "The NPCs we studied from all samples showed abnormal proliferation, either 'too little' or 'too much,' which suggests that poor control of proliferation of brain cells is an important basis for ASD causation." He adds, "In the future, once we have reproduced these studies and extended them, we also may be able to use this knowledge as a biomarker, which could signal when to introduce therapy, or to identify signaling pathways to target with drugs."

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"Autism NPCs from both idiopathic and CNV 16p11.2 deletion patients exhibit dysregulation of proliferation and mitogenic responses," Robert Connacher, Madeline Williams, Smrithi Prem, Percy L. Yeung, Paul Matteson, Monal Mehta, Anna Markov, Cynthia Peng, Xiaofeng Zhou, Courtney R. McDermott, Zhiping P. Pang, Judy Flax, Linda Brzustowicz, Che-Wei Lu, James H. Millonig, and Emanuel DiCicco-Bloom, *Stem Cell Reports*, June 14, 2022 (free online). Address: Emanuel DiCicco-Bloom, Department of Neuroscience and Cell Biology, Rutgers Robert Wood Johnson Medical School, Piscataway, NJ 08854, diciccem@rwjms.rutgers.edu.

—and—

"Stem cells either overproduce or underproduce brain cells in autism patients," news release, Rutgers University, June 8, 2022.

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/

Parent Training Study

Dr. Lauren Moskowitz is seeking participants in a research study on the effectiveness of an online parent training program for parents of children with autism spectrum disorder (ASD) and co-occurring intellectual disability. The purpose of the program is to teach children to help overcome or cope with their fears or phobias. She is currently seeking parents to volunteer to participate in this program. English fluency is required. For more information on this study or to request a screening packet, please contact Dr. Moskowitz at St. John's University via email at moskowil@stjohns.edu.

EDITORIAL: Stephen M. Edelson, Ph.D.

A historical perspective on autism advocacy and research

Autism advocacy and research have a rich history, and they are beginning to attract much interest beyond the autism community. In this article, I will share some interesting historical information about the autism field, as well as insights into several major developments over the past six decades.

Autism in books and film

In 1964, autism was a little-understood disorder widely believed by psychiatrists to be caused by "refrigerator parents." That year, Dr. Bernard Rimland published his seminal book, *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*, which is credited with revolutionizing the field of autism research and jump-starting biological research into the disorder [1].

Four years later, ARI—formerly the Institute for Child Behavior Research—produced the first documentary on autism, *The Invisible Wall*. The groundbreaking film can be viewed at www.TheInvisibleWall.com. In this documentary, Dr. Rimland, then 40 years of age, shared his views on genetics and the environment as underlying contributors to autism. Dr. Ruth Sullivan, who is often credited as the first parent advocate in the field, is also featured in the film.

Today, autism is the topic of many popular books and documentaries. Two of the most widely read books are *In a Different Key*, published in 2016 by John Donvan and Caren Zucker [2], and *NeuroTribes*, published in 2015 by Steve Silberman [3]. *In a Different Key* was nominated for a Pulitzer Prize in 2017 for general nonfiction, and *NeuroTribes* has received much media attention. Prior to publication, all three authors visited the Autism Research Institute (ARI) in San Diego to learn about Dr. Rimland and ARI and to visit with Mark, Dr. Rimland's autistic son.

Donvan and Zucker have also produced a historical documentary on autism, and ARI contributed rare video footage for the film. You can find the film trailer by searching "autism" and "In a different key" on YouTube.

Prevalence rates

Until a few decades ago, autism was considered to be a relatively rare disorder. In 1966, Dr. Victor Lotter screened the entire population of 8- to 10-year-old children in the County of Middlesex, located in the southeastern region of the United Kingdom (UK). [4]. He identified 35 children on the spectrum, and, based on the population in the area, he estimated the prevalence rate to be 4.5 out of 10,000 children, or nearly 1 in 2,000. In 1978, Dr. Lotter screened more than 1,300 children at institutions for people with intellectual disability in six African countries and found only nine children who qualified for a diagnosis and 30 others with features of autism [5].

Since the 1960s and 1970s, the number of children diagnosed with autism has climbed rapidly. Based on data collected in 2018, the Centers for Disease Control and Prevention (CDC) now estimates the prevalence rate of autism to be 1 in 44 [6].

Diagnosis

In 1943, Dr. Leo Kanner, often considered the father of child psychiatry, described in great detail 11 children who shared very similar symptoms and behaviors [7]. This article is considered by many to be the first official recognition of autism in a science-based journal. Donald T., the first case described in Kanner's paper, is now in his late 80s.

In 1961, the British Working Party, directed by Dr. Mildred Creek and consisting of 13 members from various clinics and hospitals in the UK, established nine criteria for diagnosing autism [8]. In short, these included: impairment of emotional relationships with people, unawareness of one's own identity, preoccupation with particular objects, resistance to change, impairment in perception, illogical anxiety, speech loss or a failure to develop any speech, and a "distortion in motility patterns."

Three years later, Dr. Rimland published a diagnostic checklist in the appendix of his 1964 book [1]. Titled "Diagnostic Check List for Behavior-Disturbed Children," it was developed primarily to diagnose classical autism or Kanner's syndrome. Four years after that, in 1968, the American Psychiatry Association's Diagnostic and Statistical Manual (DSM), version II, used the term "autistic" as part of the diagnostic criteria for childhood schizophrenia for the first time [9]. Twelve years later, in 1980, autism had its own category in the DSM-III and was referred to as "infantile autism" [10].

The DSM's definition of autism spectrum disorders continues to change with each new edition. For example, controversy arose when the category of "Asperger syndrome" was removed in the latest edition, potentially affecting services for many on the spectrum.

Genetics

In 1964, Dr. Rimland argued in support of a genetic basis of autism (chapter 7) [1]. Thirteen years later, in 1977, Folstein and Rutter counted the number of same-sex children in 21 sets of twins in which one or both had autism [11]. They reported 36 percent co-occurrence in monozygotic or identical twins (i.e., 100 percent overlap in genes), and 0 percent in dyzygotic or fraternal twins (50 percent overlap in genes). These results supported Rimland's 1964 conclusion.

Today, there is overwhelming evidence that genetics plays an instrumental role in autism, with at least 20 percent of cases attributed to an underlying genetic cause. This is often referred to as syndromic autism [12]. There is also mounting evidence of a genetic susceptibility to certain toxins in the environment, which may explain the other 80 percent. These toxins include pesticides, particulate matter (found in car and truck exhaust), plastics, and heavy metals [13].

Neurostructural findings

In his 1964 book, Dr. Rimland proposed that a specific neural structure, the reticular formation (RF), was impaired in autism (see chapter 6) [1]. The RF, located in the center of the brainstem, is instrumental in regulating arousal level and is related to alertness, consciousness, and sleep. Over the years, researchers have not found significant impairment in the brainstem; however, electrophysiological research has reported some dysregulation [14].

Two decades later, in 1985, Drs. Margaret Bauman and Thomas Kemper published the first brain autopsy study on a 29-year-old autistic individual [15]. Several neural structures were shown to be impaired, including the amygdala, hippocampus, mamillary body, and neocerebellar cortex. This study received international attention, including a featured story in the *Boston Globe*.

Today, as Dr. David Amaral and his colleagues at the MIND Institute note, "Postmortem and structural magnetic resonance imaging studies have highlighted the frontal lobes, amygdala, and cerebellum as pathological in autism" [16]. However, the researchers conclude that "there is no clear and consistent pathology that has emerged for autism," adding that "recent studies emphasize that the time course of brain devel-

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Research Updates

Electroretinograms may aid in identifying ASD, ADHD

A new study suggests that a diagnostic test called an electroretinogram (ERG) may aid in diagnosing autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), and differentiating between the two conditions.

Paul Constable and colleagues performed ERG tests—which measure the electrical activity of the retina in response to a light stimulus—on 226 individuals, all of them children or young adults. Participants included 55 individuals with ASD, 15 individuals with ADHD, and 156 controls. The researchers found that individuals with ADHD showed elevated overall ERG energy, while those with ASD showed reduced ERG energy.

Constable notes that ASD and ADHD often share similar traits, which can make it difficult to differentiate between them. He says, "Retinal signals have specific nerves that generate them, so if we can identify these differences and localize them to specific pathways that use different chemical signals that are also used in the brain, then we can show distinct differences for children with ADHD and ASD and potentially other neurodevelopmental conditions."

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"Discrete wavelet transform analysis of the electroretinogram in autism spectrum disorder and attention deficit hyperactivity disorder," Paul A. Constable, Fernando Marmolejo-Ramos, Mercedes Gauthier, Irene O. Lee, David H. Skuse, and Dorothy A. Thompson, *Frontiers in Neuroscience*, June 2022 (free online). Address: Paul Constable, College of Nursing and Health Sciences, Caring Futures Institute, Flinders University, Adelaide, SA, Australia, Paul.Constable@flinders.edu.au.

—and—

"When it comes to ADHD and ASD, the eyes could reveal all," news release, University of South Australia, June 16, 2022.

IBD in mothers associated with autism in offspring

Inflammatory bowel disease (IBD) in parents (and mothers in particular) may be associated with autism spectrum disorders (ASD) in children, according to new research. IBD is an umbrella term for conditions including ulcerative colitis and Crohn's disease.

Aws Sadik and colleagues conducted four separate studies to investigate possible associations between parental IBD and autism in children. First, the researchers analyzed data on 2.3 million children and their parents, obtaining the information from medical and administrative databases in Sweden. They found that IBD in mothers was associated with a 32 percent increased chance of autism in their children compared with controls, while IBD in fathers was associated with a 9 percent increased chance.

The researchers then conducted three separate studies to analyze the effects of genetics on this association. Their findings indicated that the association may be due not to genetic correlations between IBD and autism, but to factors in the *in utero* environment—for instance, maternal inflammation or impaired nutrient absorption.

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"Parental inflammatory bowel disease and autism in children," Aws Sadik, Christina Dardani, Panagiota Pagoni, Alexandra Havdahl, Evie Stergiakouli, The iPSYCH Autism Spectrum Disorder Working Group, Golam M. Khandaker, Sarah A. Sullivan, Stan Zammit, Hannah J. Jones, George Davey Smith, Christina Dalman, Håkan Karlsson, Renee M. Gardner, and Dheeraj Rai, *Nature Medicine*, June 2022 (free online). Address: Christina Dardani, christina.dardani@bristol.ac.uk.

—and—

"Autism linked to inflammatory bowel disease in parents," Emily Harris, Spectrum News, June 28, 2022.

Rates of ASD higher in people with synesthesia, first-degree relatives

There is an increased incidence of autism spectrum disorders (ASD) in people with synesthesia and their relatives, according to a new study by British researchers.

Synesthesia is a condition in which sensory stimuli in one modality trigger additional sensations in the same modality or sensations in a different modality. For example, a person seeing the written letter "a" may experience a visual sensation of the color red, or a person hearing the word "hello" may experience the taste of bacon.

Max Nugent and Jamie Ward evaluated 282 adults with synesthesia and 281 controls. The researchers report that rates of ASD were higher in individuals with synesthesia and their first-degree relatives than in the controls. While there is some suggestive evidence for a link between synesthesia and schizophrenia, the researchers detected no increase in schizophrenia in people with synesthesia. They also detected no link between synesthesia and type 1 diabetes, which was selected to control for the effects of medical conditions in general.

The researchers found that compared to controls, people with synesthesia were more likely to have relatives with synesthesia. In addition, they say, "People with three or more types of synesthesia were more likely (compared to synesthetes with fewer types) to have synesthetic relatives and to report autism in themselves." Finally, they say, "People with two or more types of synesthesia (compared to synesthetes with only one type) were more likely to report familial autism."

They conclude, "The results suggest a shared genetic predisposition between synesthesia and autism, and more extreme synesthetes may tend to hail from more neurodiverse families."

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"Familial aggregation of synaesthesia with autism (but not schizophrenia)," Max Nugent and Jamie Ward, *Cognitive Neuropsychiatry*, July 7, 2022 (free online). Address: Jamie Ward, School of Psychology University of Sussex, Falmer, Brighton, BN1 9QH, UK, jamiew@sussex.ac.uk.

Breastfeeding may lower odds of ASD in children

Breastfeeding may offer some protection against autism spectrum disorders (ASD), according to a new meta-analysis by researchers from Iran.

Ensiyeh Jenabi and colleagues identified seven epidemiological studies that investigated the risk of ASD in breastfed and non-breastfed children. In all, the study population included 3,270 individuals.

The researchers say their meta-analysis showed that children who were not breastfed had 1.81 times the risk of developing ASD compared to children who were breastfed. They note that their findings are consistent with two other meta-analyses suggesting a positive effect of breastfeeding.

The researchers conclude, "Our findings suggest that the possible association between ASD and not breastfeeding should be added to the list of reasons to provide breastfeeding support."

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"Not breastfeeding and risk of autism spectrum disorders among children: a meta-analysis," Ensiyeh Jenabi, Saeid Bashirian, Amir Mohammad Salehi, and Salman Khazaei, *Clinical and Experimental Pediatrics*, July 19, 2022 (free online). Address: Salman Khazaei, Autism Spectrum Disorders Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, salman.khazaei61@umsha.ac.ir.

Moving?
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Research Updates

Sleep problems in ASD affect other areas of life

Sleep problems are very common in individuals with autism spectrum disorders (ASD), and a new meta-analysis indicates that these problems have a significant impact on other aspects of life.

Gloria Han and colleagues analyzed 49 published studies and 51 samples providing data on a total of more than 15,000 individuals with ASD. The researchers report that "sleep problems were significantly associated with more clinical symptomatology and worse daytime functioning," with the strongest association seen for mood and anxiety symptoms.

They conclude, "Findings highlight the far-reaching consequences of sleep problems on daytime functioning for autistic individuals and support the continued prioritization of sleep as a target for intervention through integrated care models to improve wellbeing."

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"Associations between sleep problems and domains relevant to daytime functioning and clinical symptomatology in autism: a meta-analysis," Gloria T. Han, Dominic A. Trevisan, Emily A. Abel, Elise M. Cummings, Carter Carlos, Armen Bagdasarov, Shashwat Kala, Termara Parker, Craig Canapari, and James C. McPartland, *Autism Research*, May 30, 2022 (online). Address: James McPartland, School of Medicine, Child Study Center, Yale University, 40 Temple Street, Suite 6A2, New Haven, CT 06510, james.mcpartland@yale.edu.

Anticonvulsant drugs linked to increased odds of ASD, ID in kids

Prenatal exposure to the anticonvulsant drugs topiramate or valproate may increase the odds of a child having autism spectrum disorder (ASD) or intellectual disability (ID), according to a new study. The study also found that prenatal exposure to certain combinations of anticonvulsant drugs may increase children's odds of having neurodevelopmental disorders.

Marte-Helene Bjørk and colleagues analyzed data on 4,494,926 children. The researchers found that for ASD and ID, the adjusted hazard ratios were 2.8 and 3.5, respectively, after topiramate exposure and 2.4 and 2.5, respectively, after valproate exposure. Risks increased with higher doses of antiseizure medications.

In addition, an increased risk for neurodevelopmental disorders was seen in children of women with epilepsy who took combined levetiracetam and carbamazepine or combined lamotrigine and topiramate. However, the researchers say, "no consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital." They also detected no increased risks for children of mothers who took a combination of levetiracetam and lamotrigine.

They conclude, "The most important findings were robust and dose-dependent associations between prenatal topiramate and valproate exposure and neurodevelopmental disorders. These associations persisted after accounting for potential confounding factors."

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Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability," Marte-Helene Bjørk, Helga Zoega, Maarit K. Leinonen, Jacqueline M. Cohen, Julie Werenberg Dreier, Kari Furu, Nils Erik Gilhus, Mika Gissler, Óskar Hálfdánarson, Jannicke Igland, Yuelian Sun, Torbjörn Tomson, Silje Alvestad, and Jakob Christensen, *JAMA Neurology*, May 31, 2022 (online). Address: Marte-Helene Bjørk, Helse Bergen, Haukeland University Hospital, Department of Neurology, Postbox 1400, N-5020 Bergen, Norway, marte.bjork@uib.no.

—and—

"Prenatal exposure to certain antiseizure meds linked to autism," news release, Medical Xpress, May 21, 2022.

Antipsychotic drugs linked to significant weight gain

A meta-analysis conducted by researchers in Canada and Denmark indicates that antipsychotic drugs, frequently prescribed for individuals with autism spectrum disorders (ASD), often cause weight problems.

Emily Smith and colleagues reviewed 18 randomized trials involving a total of 1,376 individuals with intellectual and/or developmental disabilities (IDD). The researchers found that "antipsychotic use is associated with significant weight gain among patients with IDD."

They say, "Concerningly, most reported studies were in children and adolescents, which sets up an already vulnerable population for adverse medical sequalae at an early age." In addition, they note that long-term studies on the effects of antipsychotics in adults with IDD are lacking.

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"The metabolic adverse effects of antipsychotic use in individuals with intellectual and/or developmental disability: A systematic review and meta-analysis," Emily Smith, Nicolette Stogios, Emily Au, Kateryna Maksyutynska, Riddhita De, Andrew Ji, Mikkel Erlang Sørensen, Laura St John, Hsiang-Yuan Lin, Pushpal Desarkar, Yona Lunsky, Gary Remington, Margaret Hahn, and Sri Mahavir Agarwal, *Acta Psychiatrica Scandinavica*, July 2022 (epub prior to print publication). Address: Sri Mahavir Agarwal, Department of Psychiatry, Centre for Addiction and Mental Health, University of Toronto, 1051 Queen St. W, Toronto, ON M6J 1H3, Canada, mahavir.agarwal@camh.ca.

Impaired sleep in ASD may affect early development

Sleep problems in children with autism spectrum disorder (ASD) may be associated with slowed development during early childhood, according to a new study.

Jonah Levin and colleagues examined data collected on 8,540 young children with ASD whose parents filled out quarterly assessments for three years. Parents assessed their children's development using five subscales (expressive language, combinatorial receptive language, sociability, sensory awareness, and health).

The researchers say 57 percent of caregivers reported that their children had no sleep problems, while 43 percent reported mild, moderate, or severe sleep problems. Comparing 643 children with moderate or severe sleep problems to those with no sleep problems, the researchers found that "[c]hildren with no sleep problems developed faster compared to matched children with sleep problems in all subscales."

The greatest difference in developmental trajectories between the two groups was seen on the health subscale. When the researchers controlled for health scores as well as several other factors, the effect of sleep problems decreased for four of the subscales; however, the effect on combinatorial receptive language actually increased. The researchers say this suggests that sleep problems may impair the acquisition of combinatorial language (which involves combining sounds into meaningful words or sentences) regardless of overall health.

(see related story on this page)

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"Longitudinal developmental trajectories in young autistic children presenting with sleep problems, compared to those presenting without sleep problems, gathered via parent-report using a mobile application," Jonah Levin, Edward Khokhlovich, and Andrey Vyshedskiy, *Research in Autism Spectrum Disorders*, September 2022 (online). Address: Andrey Vyshedskiy, Boston University, Boston, MA 02215, vysha@bu.edu.

Did you know? The Autism Research Institute recently received its fifth annual four-star rating—the highest possible rating—from Charity Navigator.

Levels of tryptophan metabolites in ASD, ADHD, DD studied

Alterations in the tryptophan pathway may play a role in autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), according to a new study.

Tryptophan, which is an essential amino acid, is a building block of multiple neurotransmitters. "Some of these," Ramkripa Raghavan and colleagues note, "are well known such as serotonin, 5-hydroxytryptophan (5-HTP), and melatonin and have been implicated in a number of conditions including depression, mood disorders, ASD, and ADHD." However, they say, "very few studies to date have assessed other less known tryptophan metabolites, especially in the context of neurodevelopmental conditions."

To explore this issue, Raghavan and colleagues analyzed the associations between cord-blood levels of tryptophan as well as several metabolites—5-methoxytryptophol (5-MTX), 5-hydroxytryptophan (5-HTP), serotonin, and N-acetyltryptophan—and diagnoses of ASD, ADHD, and other developmental disabilities in childhood. Their study included 996 cord blood samples collected at birth from 326 neurotypical children, 87 children with ASD, 269 children with ADHD, and 314 children with other developmental disabilities (DD). Participants were enrolled in the study at birth and followed up from October 1, 1998 to June 30, 2018.

The researchers report that higher levels of cord blood 5-MTX were significantly associated with lower odds of a diagnosis of ASD or ADHD after adjusting for potential confounders. "Our study supports the hypothesis that 5-MTX may possess neuroprotective abilities with higher levels in cord blood associated with a lower risk of both ASD and ADHD," they say. "This further suggests a shared etiology between ASD and ADHD."

The researchers also found that higher levels of tryptophan, 5-HTP, and N-acetyltryptophan were associated with higher odds of ADHD, but not higher odds of ASD or DD. Cord serotonin was not associated with ASD, ADHD, or DD.

Raghavan and colleagues caution that their findings are preliminary, and that additional research is needed to explore temporal relationships between 5-MTX levels and the development of ASD or ADHD symptoms. They add, "Future studies can also explore the combination of metabolites [in] ASD and ADHD, since some research suggests this may lead to good discrimination between individuals with vs. without ADHD."

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"Association between cord blood metabolites in tryptophan pathway and childhood risk of autism spectrum disorder and attention-deficit hyperactivity disorder," Ramkripa Raghavan, Neha S. Anand, Guoying Wang, Xiumei Hong, Colleen Pearson, Barry Zuckerman, Hehuang Xie, and Xiaobin Wang, *Translational Psychiatry*, July 9, 2022 (free online). Address: Xiaobin Wang, Center on Early Life Origins of Disease, Department of Population, Family and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205, xwang82@jhu.edu.

Association seen between orthorexia nervosa, autistic traits

University students with elevated levels of autistic traits are more likely to have elevated levels of orthorexia nervosa (ON) symptoms, according to a study from Italy.

ON is a condition characterized by an abnormal fixation on and obsession with healthy eating. Individuals with ON tend to follow very restrictive diets, progressively excluding more and more foods and focusing so much attention on their diets that they restrict their social lives and sometimes even damage their own health. While not recognized by the current *Diagnostic and Statistical Manual of Mental Disorders*, ON is considered to fall on the spectrum of eating disorders.

In the new study, Liliana Dell'Osso and colleagues asked 2,140 university students to fill out two self-reports: the AdAS Spectrum, which measures autistic traits, and the ORTO-R, which measures ON traits. The researchers found that participants with elevated levels of autistic traits reported significantly higher levels of ON symptoms compared to subjects with low autistic traits. ON scores were higher among women and among vegetarians and vegans than among men and omnivores. While ORTO-R scores rose with an increase in AdAS Spectrum scores for both genders, the rise was more pronounced among females.

Prior research has found a higher rate of a different eating disorder, anorexia nervosa, among individuals with autism spectrum disorders (ASD), particularly among females. Dell'Osso and colleagues say their new findings suggest that "the overlap between autism and eating disorder spectra among females may extend also to ON."

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"Investigating orthorexia nervosa with the ORTO-R in a sample of university students with or without subthreshold autism spectrum: focus on dietary habits and gender differences," Liliana Dell'Osso, Ivan Mirko Cremone, Ilaria Chiarantini, Alessandro Arone, Danila Casagrande, Gabriele Massimetti, Claudio Carmassi, and Barbara Carpita, *Frontiers in Psychiatry*, July 14, 2022 (free online). Address: Barbara Carpita, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, barbara.carpita1986@gmail.com.

Electronic toys may reduce speech use during play

While both neurotypical children and children with autism spectrum disorders (ASD) are highly attracted to electronic toys, a new study suggests that these toys—even when educational in nature—can reduce the quality and quantity of children's speech during play.

In the study, Courtney Venker and Jennifer Johnson instructed 28 parent-child pairs (14 in the ASD group and 14 in the neurotypical group) to play with electronic toys in one session and with traditional toys in another. Afterward, they analyzed the children's speech production in each play session.

The researchers report, "Children with ASD and age-matched children with typical development talked significantly less and produced significantly fewer unique words when playing with electronic toys than with traditional toys. Observations of the electronic play sessions indicated that the talking, singing, music, and animal sounds produced by the toys often left little room for children to contribute." They add that the sights and sounds produced by the electronic toys "dominated the interaction, interrupting children's utterances and decreasing the space available for parent-child communication."

The researchers conclude, "Although electronic toys are often advertised as educational, the current findings add to growing evidence that electronic toys decrease the quality of play interactions between children and their parents." They add that while this may have little effect on typically developing children, "children with ASD are likely to be vulnerable even to seemingly subtle disruptions in parent-child interactions." They note, however, that electronic toys can be highly motivating, and thus could be beneficial when offered on a limited basis and for a useful purpose. In addition, they caution that their sample was limited and their findings need to be verified by larger studies with more diverse participants.

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"Electronic toys decrease the quantity and lexical diversity of spoken language produced by children with autism spectrum disorder and age-matched children with typical development," Courtney E. Venker and Jennifer R. Johnson, *Frontiers in Psychology*, July 2022 (free online). Address: Courtney Venker, Lingo Lab, Department of Communicative Science and Disorders, Michigan State University, East Lansing, MI 48824, cvenker@msu.edu.

New approach may improve learning, generalization in ASD

A new study from researchers in Israel suggests that a technique based on "memory flashes" may speed learning for individuals with autism spectrum disorders (ASD) and enhance generalization of learned skills to new settings.

Study coauthor Nitzan Censor says, "In my laboratory we focus on the study of learning in humans, and already today we know that a large part of learning does not happen in formal training settings but afterwards, in processes of assimilation and reinforcement of memory that occur 'offline;' for example, when our brain is asleep. However, standard teaching methods still advocate an approach where longer practice equals better learning: If you want to play the piano, you should practice playing the piano for many hours every day until the playing becomes second nature to you. We have identified an alternative learning mechanism that uses 'memory flashes'—a brief exposure to a task that has already been learned—in order to assimilate and generalize skill developed."

In the laboratory's new study, led by Shira Klorfeld-Auslender, the researchers asked participants to perform a visual task (for example, identifying the direction of lines that appeared briefly on a computer screen). Of the participants, 13 had ASD and 10 were neurotypical controls.

Rather than performing the task for long stretches of time each day, both groups learned the task on the first day and then participated in three sessions, conducted two days apart, in which only five brief trials were conducted per session. "Remarkably," the researchers say, "individuals with ASD improved their visual discrimination ability in the task substantially, demonstrating successful learning." The magnitude of improvement was similar for participants with ASD and neurotypical controls.

Additionally, the researchers say, participants with ASD were able to generalize their learning to other situations with a high degree of success. "This generalization test following reactivation learning was important," the researchers say, "since when a similar cohort of age- and gender-matched ASD subjects was tested with the same task but under extensive-learning conditions, generalization failed."

The researchers also tested a separate group of individuals with ASD to see if the "memory flashes" were an important part of learning. They found that participants who underwent the original training but not the memory reactivations did not exhibit significant learning or generalization.

The researchers note that standard multiple-repetition learning is time-consuming and often results in overly specific learning, limiting generalization. In contrast, Censor says, their findings "could pave the way for more meaningful approaches to learning for people with autism, in a wide variety of tasks."

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"A distinct route for efficient learning and generalization in autism," Shira Klorfeld-Auslender, Yaniv Paz, Ilana Shinder, Jonathan Rosenblatt, Ilan Dinstein, and Nitzan Censor, *Current Biology*, Vol. 32, July 25, 2022, pp. 3203-3209. Address: Nitzan Censor, School of Psychological Sciences, Tel Aviv University, Tel Aviv 69978, Israel, censornitzan@tauex.tau.ac.il.

—and—

"A new learning method could help people with autism improve visual perception capabilities," news release, Tel Aviv University, August 1, 2022.

A historical perspective on autism advocacy and research

(continued from page 3)

opment rather than the final product is most disturbed in autism."

Treatment

Pioneering researchers in Southern California were instrumental in transitioning the field of autism from a psychogenic (parent-blaming) perspective to a biological perspective. Initially, the Neuropsychiatric Institute, or NPI, at UCLA took a lead role in investigating interventions that included biological and behavioral treatments. Dr. Edward Ritvo and his colleagues experimented with various drugs, while Dr. O. Ivar Lovaas treated challenging behaviors using behavior modification techniques.

Within a short period of time, there were significant disagreements among these researchers regarding the efficacy and adverse side effects of their treatments. Soon after, Lovaas moved his research laboratory to the psychology department, located on the other side of UCLA's campus.

Today, there continues to be controversy over both drug and behavioral treatments for autism. One of the most important changes in this area is that individuals with autism are gaining a long-overdue voice in this conversation, serving on policy-making boards and participating in the design of research studies.

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The Autism Research Institute plans to celebrate its fifty-fifth anniversary this year by opening a museum dedicated to the history of autism in the fall of 2022. The museum will include exhibits, artifacts, little-known but important facts about autism, and original artworks.

References are available at www.ARRIReferences.org.

Mouse study offers more clues about the possible role of gut microbes in ASD

A study from researchers in Italy and Switzerland adds to evidence that gut microbes play a role in autism spectrum disorders (ASD).

In the experiment, Ennio Avolio and colleagues studied three groups of mice. Six of the mice received fecal microbiota transplants from children with ASD, while another six mice were exposed to the anticonvulsant valproic acid (VPA) during gestation. (VPA is known to produce autistic-like symptoms in mice; thus, mice exposed to this drug in utero are considered a mouse model for autism.) A third group of mice were treated with fecal transplants from children without ASD and served as controls.

The researchers say that both VPA-exposed mice and mice that received fecal transplants from children with ASD exhibited autistic-like behaviors when tested. In addition, both groups exhibited alterations of gut bacteria compared to the control mice. In particular, both groups had higher populations of Tenericutes and lower levels of Candidatus S. and Actinobacteria. Both groups of mice also exhibited atrophy of the intestinal villi (the finger-like projections that line the small intestine) and infiltration of inflammatory cells in the small intestine, and the mice that received fecal transplants from children with ASD exhibited increases in several pro-inflammatory factors in the brain and small intestine. Finally, the two treated groups exhibited altered methylation—the mechanism in which genes are turned "on" or "off"— in the brain, and the mice who received the fecal transplants from children with ASD also exhibited reduced methylation activity in the bowel.

"Overall," the researchers say, "findings of the present study corroborate a key role of gut microbiota in ASD." This suggests, they say, that the gut microbiome could be a target for treatment. "However," they say, "further investigations are required before any possible manipulation of gut bacteria with appropriate diets or probiotics can be conducted in ASD individuals."

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"Modifications of behavior and inflammation in mice following transplant with fecal microbiota from children with autism," Ennio Avolio, Ilaria Olivito, Eleonora Rosina, Lorenzo Romano, Tommaso Angelone, Anna De Bartolo, Manuel Scimeca, Dina Bellizzi, Patrizia D'Aquila, Giuseppe Passarino, Raffaella Alò, Rosa Maria Facciolo, Claudia Bagni, Antonino De Lorenzo, and Marcello Canonaco, *Neuroscience*, August 21, 2022, pp. 174-189. Address: Marcello Canonaco, Laboratory of Comparative Neuroanatomy, Department of Biology, Ecology and Earth Science (DiBEST), University of Calabria, Cosenza, Italy, marcello.canonaco@unical.it.

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