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

Preemptive intervention for at-risk infants may reduce ASD risk and symptoms, study suggests

Preemptive intervention for infants who exhibit signs of autism spectrum disorder (ASD) may reduce the intensity of their ASD traits and lower their odds of receiving an ASD diagnosis by three years of age, a new study suggests.

Andrew Whitehouse and colleagues tested the effects of an intervention called iBASIS-Video Interaction to Promote Positive Parenting (iBASIS-VIPP). In this approach, parents participate in ten biweekly sessions in which they watch videos of their interactions with their children and receive communication tips from therapists. They then practice their skills with their children for at least 15 minutes each day.

Whitehouse and colleagues initially enrolled 103 children between 9 and 14 months of age in a five-month trial of the program in 2019. In that study, the researchers found no difference between the 50 children in the intervention group and 53 controls on a measure of autism traits at 18 months of age.

In the new study, the researchers re-evaluated 89 of the children at two and three years of age, and evaluated them for ASD at three years of age. This time, they found that children in the intervention group had less severe behavioral symptoms of ASD when measured over the two years between baseline and three years of age. In addition, only three children in the intervention group received an ASD diagnosis, compared to nine children in the control group.

"To our knowledge," the researchers say, "this randomized clinical trial is the first to demonstrate that a preemptive intervention for infants showing early signs of ASD led to a small but enduring reduction in ASD symptom severity and reduced odds of ASD diagnosis in early childhood."

Study coauthor Jonathan Green comments, "Many therapies for autism have tried previously to replace developmental differences with more 'typical' behaviors. In contrast, iBASIS-VIPP works with each child's unique differences and creates a social environment around the child that helps them learn in a way that [is] best for them."

While their findings are encouraging, the researchers note that "[the] effects were small in extent, and their clinical significance is uncertain." In addition, they say, some children who did not get an ASD diagnosis at the age of three could still be diagnosed later. Thus, they say, it will be important to determine if the benefits of the intervention are lasting.

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"Effect of preemptive intervention on developmental outcomes among infants showing early signs of autism: a randomized clinical trial of outcomes to diagnosis," Andrew J. O. Whitehouse, Kandice J. Varcin, Sarah Pillar, Wesley Billingham, Gail A. Alvares, Josephine Barbaro, Catherine A. Bent, Daniel Blenkley, Maryam Boutrus, Abby Chee, Lacey Chetcuti, Alena Clark, Emma Davidson, Stefanie Dimov, Cheryl Dissanayake, Jane Doyle, Megan Grant, Cherie C. Green, Megan Harrap, Teresa Iacono, Lisa Matys, Murray Maybery, Daniel F. Pope, Michelle Renton, Catherine Rowbottam, Nancy Sadka, Leonie Segal, Vicky Slonims, Jodie Smith, Carol Taylor, Scott Wakeling, Ming Wai Wan, John Wray, Matthew N. Cooper, Jonathan Green, and Kristelle Hudry, *JAMA Pediatrics*, September 20, 2021 (free online). Address: Andrew Whitehouse, Telethon Kids Institute, University of Western Australia, Northern Entrance, Perth Children's Hospital, 15 Hospital Ave, Nedlands, Western Australia, Australia 6009, andrew.whitehouse@telethonkids.org.au.

—and—

"A landmark autism intervention study has shown dramatically reduced diagnosis rates," Jacinta Bowler, ScienceAlert, September 21, 2021.

—and—

"Uncertainty clouds test of 'preemptive' therapy to ease autism traits," Peter Hess, Spectrum News, September 24, 2021.

Role of the habenula in autism spectrum disorders explored

A new study suggests that a small brain region called the habenula may play a role in autism spectrum disorders (ASD).

The habenula is a pea-sized structure located near the thalamus. This structure, Jürgen Germann and colleagues say, "has been identified as the central structure modulating the reward value of social interactions, behavioral adaptation, sensory integration, and circadian rhythm." All of these, they note, are altered in ASD.

To examine the volume of the habenula in individuals with and without ASD, the researchers analyzed magnetic resonance imaging data on 220 individuals with ASD and 303 age-matched controls. Subjects were between 6 years and 30 years of age.

The researchers found that the habenula was significantly enlarged in individuals with ASD compared to controls, a finding seen across the entire age range. Thus, they say, "the habenula volume difference did not show any evidence of being the product of an altered developmental trajectory." In addition, there was no evidence of an association between habenula enlargement and sex or symptom severity on the Social Responsiveness Scale (SRS). "The fact that there is a strong effect of diagnosis independent of age, sex, or symptoms severity as assessed by the SRS score," they say, "might point to the habenula being implied in a broader range of behavioral symptoms, beyond the classic deficits of social behavior and social interaction."

The researchers also report that machine modeling based on habenula volume, age, and sex classified ASD with 85% accuracy and 64% accuracy in cross validation.

Germann and colleagues caution that their study has a number of limitations. For instance, it did not include very young children, and the number of female subjects was relatively small. However, they say, "the robust finding of increased habenula volume in ASD compared to typically developing control subjects provides the first evidence in human subjects of an involvement of the habenula in some aspect of the pathophysiology of ASD."

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"Involvement of the habenula in the pathophysiology of autism spectrum disorder," Jürgen Germann, Flavia Venetucci Gouveia, Helena Brentani, Saashi A. Bedford, Stephanie Tullo, M. Mallar Chakravarty, and Gabriel A. Devenyi, *Nature Scientific Reports*, October 27, 2021 (free online). Address: Jürgen Germann, University Health Network, 399 Bathurst Street, Toronto, ON, Canada. Address: Jürgen Germann, germannj@gmail.com.

Study hints at association between maternal exposure to flame retardant chemicals and ASD

A new animal study suggests that maternal exposure to a class of fire-retardant chemicals called polybrominated diphenyl ethers (PBDEs) may play a role in autism spectrum disorders (ASD).

Elena Kozlova and colleagues exposed mice orally to PBDEs during pregnancy and nursing, and later found that female offspring exhibited exaggerated marble-burying behavior—a behavior considered to be similar to the repetitive behaviors seen in ASD—as well as deficits in short-term social recognition and long-term social memory.

One finding, study coauthor Margarita Curras-Collazo says, was that "the female offspring of mother mice exposed to PBDEs showed olfactory deficits that dampened their ability to recognize other mice. In effect, these offspring do not distinguish new mice from familiar ones." The researchers note that children with ASD also exhibit abnormalities in olfactory processing, such as impairments in detecting and identifying odors or unusual reactions to them.

In addition, the researchers found alterations in the expression of oxytocin and vasopressin, two hormones that affect social information processing and social cognition, in specific areas of the brain. This suggests, they say, that PBDEs target distinct brain systems, resulting in neurodevelopmental abnormalities.

The researchers conclude, "Our work demonstrates that developmental PBDE exposure produces ASD-relevant neurochemical, olfactory processing, and behavioral phenotypes that may result from early neurodevelopmental reprogramming within central social and memory networks."

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"Persistent autism-relevant behavioral phenotype and social neuropeptide alterations in female mice offspring induced by maternal transfer of PBDE congeners in the commercial mixture DE-71," Elena V. Kozlova, Matthew C. Valdez, Maximillian E. Denys, Anthony E. Bishay, Julia M. Krum, Kayhon M. Rabbani, Valeria Carrillo, Gwendolyn M. Gonzalez, Gregory Lampel, Jasmin D. Tran, Brigitte M. Vazquez, Laura M. Anchondo, Syed A. Uddin, Nicole M. Huffman, Eduardo Monarrez, Duraan S. Olomi, Bhuvaneswari D. Chinthirla, Richard E. Hartman, Prasada Rao S. Kodavanti, Gladys Chompre, Allison L. Phillips, Heather M. Stapleton, Bernhard Henkelmann, Karl Werner Schramm, and Margarita C. Curras-Collazo, *Archives of Toxicology*, October 23, 2021 (free online). Address: Margarita C. Curras-Collazo, mcur@ucr.edu.

—and—

"Study shows flame retardants cause brain changes in mice offspring," news release, University of California Riverside, November 5, 2021.

Researchers report new findings about oxytocin and ASD

While a new meta-analysis of 31 studies suggests that children with autism spectrum disorders (ASD) have lower levels of oxytocin in their blood compared to neurotypical children, a separate study indicates that administering oxytocin to children with ASD does not confer any benefits.

Oxytocin is a hormone that enhances social recognition and social memory and reduces stress. Some research has suggested that administering oxytocin to individuals with ASD may reduce their symptoms.

In the meta-analysis, Simon John and Adrian Jaeggi examined studies measuring oxytocin in plasma/serum, saliva, or cerebrospinal fluid in autistic and neurotypical individuals. The researchers found that oxytocin levels were significantly lower in individuals with ASD than in controls, and that "this overall effect was driven entirely by differences among children but not adults."

"Our finding of lower oxytocin levels in autistic children points to an involvement of the oxytocin system in the development or manifestation of ASD," the researchers say. "….Furthermore, in at least 19 articles, oxytocin levels were correlated with ASD symptom severity, with the majority reaching significance." They add, "Together with studies relating oxytocin levels to socio-cognitive functions in neurotypical individuals as well as in siblings of autistic children, our finding is consistent with oxytocin levels mediating a continuous range of socio-cognitive function, at the extreme of which are autistic people."

The researchers say that their findings regarding adults suggest that oxytocin levels in individuals with ASD might normalize as they grow older. Consistent with this possibility, they note, symptoms of autism often improve in adulthood. This could explain, they say, why intranasal administration of oxytocin in autistic adults frequently has little or no effect on symptoms.

They conclude that while more studies are needed to investigate the connections between the oxytocin system and social deficits in ASD, and to determine whether social deficits cause low oxytocin levels or vice versa, "[T]hese results support further research into the use of oxytocin to treat social deficits in children."

A new large-scale study, however, questions the usefulness of administering oxytocin to children with ASD. Linmarie Sikich and colleagues conducted a 24-week, placebo-controlled trial to examine the effects of intranasal oxytocin therapy on children and adolescents with ASD. Subjects were between 3 and 17 years of age, and the researchers used the Aberrant Behavior Checklist and several other scales to measure outcomes.

Of the 290 children enrolled in the trial, 139 in the oxytocin and 138 in the control group completed it. The researchers say they detected "no significant between-group differences" on measures of social or cognitive functioning at the end of the trial.

Sikich comments, "This is really a major setback. We were really hoping to find a benefit and just couldn't see it anywhere."

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"Oxytocin levels tend to be lower in autistic children: a meta-analysis of 31 studies," Simon John and Adrian V. Jaeggi, *Autism*, July 2021 (free online). Address: Simon John, Institute of Evolutionary Medicine, University of Zurich, 8057 Zurich, Switzerland, simon.john@uzh.ch.

—and—

"Intranasal oxytocin in children and adolescents with autism spectrum disorder," Linmarie Sikich, Alexander Kolevzon, Bryan H. King, Christopher J. McDougle, Kevin B. Sanders, Soo-Jeong Kim, Marina Spanos, Tara Chandrasekhar, Pilar Trelles, Carol M. Rockhill, Michelle L. Palumbo, Allyson Witters Cundiff, Alicia Montgomery, Paige Siper, Mendy Minjarez, Lisa A. Nowinski, Sarah Marler, Lauren C. Shuffrey, Cheryl Alderman, Jordana Weissman, Brooke Zappone, Jennifer E. Mullett, Hope Crosson, Natalie Hong, Stephen K. Siecinski, Stephanie N. Giamberardino, Sheng Luo, Lilin She, Manjushri Bhapkar, Russell Dean, Abby Scheer, Jacqueline L. Johnson, Simon G. Gregory, and Jeremy Veenstra-VanderWeele, *New England Journal of Medicine*, October 14, 2021 (online). Address: Linmarie Sikich, linmarie.sikich@dm.duke.edu.

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"Study: 'Sociability hormone' didn't help kids with autism," Lindsey Tanner, Medical Xpress, October 14, 2021.

Microbiome differences may be due to restricted diets

While researchers are examining the possibility that differences in the gut microbiome may contribute to autism spectrum disorders (ASD), a new study suggests that these microbiome differences may actually arise from the restricted diets of children with ASD.

In the study, Chloe Yap and colleagues analyzed stool samples from 247 children, all between 2 and 17 years of age. Subjects included 99 children diagnosed with ASD, 51 paired undiagnosed siblings, and 97 unrelated, undiagnosed children.

The investigators analyzed the samples using a technique called metagenomic sequencing, which they note provides a more accurate representation of microbiome composition than the technique used in many of the earlier studies linking microbiome anomalies to autism.

"We also carefully accounted for diet in all our analyses, along with age and sex,"

continued on page 7

EDITORIAL: Stephen M. Edelson, Ph.D.

Setting priorities for autism research

Autism organizations, individuals with autism spectrum disorders (ASD), and parents have differing views on how best to proceed with autism research. However, nearly all of us can agree that the progress that has been made in understanding autism has been frustratingly slow.

True, many individuals on the autism spectrum are receiving much better treatment today than even a decade ago. However, numerous individuals with ASD are dissatisfied with the directions in which research is proceeding. Families are disappointed with the slow progress in developing interventions to help their children, especially those with severe challenging behaviors, those suffering from comorbid medical conditions, and those in their adult and senior years. Clinicians and therapists are frustrated by the limitations of current interventions. And due to the lack of well-validated treatment strategies, health insurance coverage and government-funded educational services are minimal rather than optimal.

Reviewing the progress so far

Only a handful of breakthroughs have stood the test of time since autism was first described by Leo Kanner in 1943. These include the realization that autism is a biological condition (Rimland, 1964); documentation of a genetic contribution (Folstein & Rutter, 1977); the discovery of solid evidence of neurological impairment (Kemper & Bauman, 1985); and the development of behavior therapy (Lovaas, 1987).

Although these were important steps forward, we still know far too little about autism and about how to help individuals on the spectrum. A few months before Dr. Rimland passed away, he shared with me his disappointment that the pressing questions about autism were still unanswered after nearly 50 years of his tireless efforts. Little has changed since we had that conversation.

While there are a number of reasons for this slow progress in autism research, I strongly believe that one of the biggest problems is our failure to prioritize specific research issues *common among all areas of study*. Fortunately, this is a problem we can solve.

Moving the needle forward

In my opinion, there are four steps we can take immediately to speed the progress of autism research:

1. Subtyping autism.

As I have stated many times, the highest priority for the autism research community should be to subtype autism. Accurate subgroupings will allow us to focus our efforts on individuals who are very similar to one another, rather than grouping together a wide spectrum of individuals who differ greatly with regard to their symptoms, their behaviors, and ultimately, their underlying biology.

Researchers have studied autism subtypes over the years, but often they have relied on a limited number of measured characteristics (for instance, brain size, immune factors, medical conditions, or sensory sensitivities) or have examined relatively small numbers of individuals. To speed up subtyping efforts, ARI recently began working on a research project, in collaboration with Droice Laboratories, to determine whether specific subtypes of autism can be accurately defined. Our sample includes more than 40,000 cases that have been documented over a 50-year period.

Once valid subtypes of autism are established, all fields of study can focus their efforts on specific subtypes in order to determine their causes and appropriate treatments.

2. Creating and using standardized assessments.

Only a handful of assessment measures have been shown to accurately evaluate individuals on the autism spectrum. Quite a few widely used assessment tools have been validated on neurotypical children and adults or intellectually challenged individuals rather than on individuals with ASD, and some have not been validated at all.

For example, two recent studies examined the impact of gluten-free, casein-free diets on gastrointestinal (GI) issues in individuals with ASD (Gonzalez-Domenech et al., 2020; Piwowarczyk et al., 2020). Both studies found the diets to be ineffective in reducing GI issues. However, the first research team used a non-validated questionnaire to assess GI issues, and the second team relied on the Rome III questionnaire, which has been criticized as insensitive to evaluating GI issues often associated with autism (Gorrindo et al., 2012; Margolis et al., 2019).

Using validated assessments created specifically for individuals with ASD would allow us to better evaluate treatments and make comparisons between them. This would speed the development of effective treatments, while preventing researchers from wasting time and resources exploring less productive avenues.

3. Examining factors related to challenging behaviors.

There is an urgent need to find solutions for debilitating problems experienced by the majority of individuals with ASD, such as anxiety, aggression, self-injurious behaviors, and sleep disturbances. Research has clearly documented a relationship between these issues and a number of underlying biological conditions, many of which are highly treatable. (Note: Jane Johnson, a former ARI Board member, and I recently completed a three-book series on multidisciplinary perspectives on anxiety, self-injurious behavior, and sleep disturbances.)

4. Integrating different perspectives.

We now know that autism is a holistic condition. It is associated with numerous interactive systems including the nervous, metabolic, immune, gastrointestinal, and sensory systems, in addition to social and executive cognitive processing. It is time for us to explore, through controlled experimentation, how these pieces interconnect.

For instance, oral sensitivities may lead to picky eating. This, in turn, may impact the microbiome and lead to chronic constipation. The internal sensations caused by constipation may be heightened by dysfunctional interoception. This can then lead to anxiety as well as aggression, self-injurious behavior, and sleep disturbances. Separately, researchers have investigated each element in this process; however, they have not integrated their findings into a whole. Viewing issues such as these holistically will give us greater power to address them.

The message for the autism community

It is becoming clear that progress in understanding autism will result not from one "big finding" that answers all questions, but from multiple research threads coming together. Thus, if we truly want to find answers to the questions surrounding autism, we need a well-coordinated effort by all stakeholders in the autism community, including those on the spectrum, parents, clinicians, therapists, and researchers.

Moreover, we need to place top priority on the strategies that will have the most benefits for individuals with ASD and their families not decades in the future, but *here and now*. ARI is actively supporting research based on these strategies, and we hope others in the autism community will join us.

References can be found at ARRIReferences.org.

Research Updates

Job losses, cuts in hours or pay during COVID increase depression in adults with ASD

A new study indicates that rates of depression rise significantly in individuals with autism spectrum disorders (ASD) if they experience a job loss or reduction in hours or pay.

"Though unemployment has been linked to mental health problems in the general population," Julie Lounds Taylor and colleagues say, "this relationship is seldom considered among adults with autism." The COVID-19 pandemic, the researchers say, provided a natural opportunity to study this issue.

The researchers used online surveys to collect data from individuals with ASD at two times: just before widespread social distancing took place, and again ten weeks later. At both points, the researchers also measured participants' depressive symptoms.

Of the 144 young adults who were employed at the first point, the researchers say, more than one-third reported employment changes during the first two months of the pandemic. In most cases, these involved losing a job or having their hours or pay reduced.

"Controlling for Time 1 depressive symptoms," they say, "young adults who experienced job loss/reduction had significantly higher depressive symptoms at Time 2 than those without an employment change."

The researchers say, "Our study is the first to find that employment changes—particularly job loss or reduction—had a significant negative effect on the mental health of young adults with ASD compared to stable employment. This association suggests important directions for future research and practice—both as the economy recovers from COVID-19 and likely beyond. Better supporting adults with ASD in the workplace may not only decrease the likelihood of job loss, but also combat the exceedingly high rates of depression in this group."

The researchers also note that currently, treatments for individuals with ASD who are diagnosed with depression focus almost exclusively on psychotropic medications or cognitive behavioral therapy, while the role of day-to-day issues such as unemployment is rarely taken into account. "Findings from this study," they say, "suggest that employment changes (and likely other daily experiences) may need to be considered when treating depression in this population."

As part of their study, the researchers asked participants about their perceptions concerning the impact of job changes. Interestingly, they say, "we observed that perceived negative impact and perceived positive impact were associated with higher depressive symptoms, relative to those who perceived that the employment change had no impact on their wellbeing." This suggests, they say, that any perceived impact of a job change—either positive or negative—may increase the risk of depression for individuals with ASD.

The researchers conclude that "targeting the employment situations of adults with ASD may represent a critical avenue for improving their psychological health." However, they note that their findings need to be replicated because their study group was fairly small and the study focused solely on short-term job changes.

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"Job loss predicts worsening depressive symptoms for young adults with autism: A COVID-19 natural experiment," Julie Lounds Taylor, Ryan E. Adams, Florencia Pezzimenti, Shuting Zheng, and Somer L. Bishop, *Autism Research*, October 2021 (free online). Address: Julie Lounds Taylor, Vanderbilt Kennedy Center, PMB 40-230 Appleton Pl., Nashville, TN 37203, julie.l.taylor@vanderbilt.edu.

ARI Resources for Coping with COVID-19

To aid individuals with autism and their families during the COVID-19 pandemic, ARI is offering these resources:

- Free presentations offering evidence-based strategies to manage at home during extended school closures.
- Social stories and short videos on hygiene and medical procedures.
- Physician resources for supporting patients diagnosed with autism.

To view these, visit this link:

https://www.autism.org/

In addition, we are inviting families to tell their stories about how they are coping during the COVID-19 pandemic. We invite you to share your snapshots and stories about life at home. We will share your stories on social media with #AutismCOVID19Stories.

Pregnancy spacing may affect odds of ASD

Mothers of children with autism spectrum disorders (ASD) may reduce their odds of having another child with ASD if they time a second pregnancy to occur 2.5 to 3 years after the birth of the child with ASD, according to a new study.

Gavin Pereira and colleagues studied data from more than 925,000 births in Denmark, Finland, and Sweden. More than 9,300 of the children in the birth cohort were later diagnosed with ASD.

The researchers found that the association between ASD and the intervals between pregnancy was U-shaped for all three countries. Pereira says, "Our research found that the siblings of children with autism were less likely to be diagnosed on the spectrum if there was a 30- to 39-month gap between both pregnancies…. Across the general population, this study also showed that children born to mothers who became pregnant again three months after giving birth had a 50 percent higher chance of being diagnosed with autism, and those born five years later had a 24 percent greater chance."

Pereira comments, "The results of this large-scale, multi-country research may help to inform family planning counseling, particularly for those families that are already at a higher risk because of a genetic history of neurological disease." He and his team speculate that "about 5% to 9% of autism cases might be avoided by optimizing birth spacing."

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"Optimal interpregnancy interval in autism spectrum disorder: A multi-national study of a modifiable risk factor," Gavin Pereira, Richard W. Francis, Mika Gissler, Stefan N. Hansen, Arad Kodesh, Helen Leonard, Stephen Z. Levine, Vera R. Mitter, Eric T. Parner, Annette K. Regan, Abraham Reichenberg, Sven Sandin, Auli Suominen, and Diana Schendel, *Autism Research*, August 23, 2021 (online). Address: Gavin Pereira, School of Public Health, Curtin University, Perth, WA 6102, Australia, gavin.f.pereira@curtin.edu.au.

—and—

"Sibling's likelihood of autism diagnosis impacted by age gap," news release, Curtin University, August 25, 2021.

— Employment Resources —

Free Resources for
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Job Coaches, and Employers

Visit https://www.autism.org/employment-resources-for-individuals-with-autism

Research Updates

Low maternal vitamin D may raise risk for autism

Maternal vitamin D deficiency during pregnancy may significantly increase the risk of autism spectrum disorders (ASD) in children, according to a large new study by researchers in Finland and the United States.

Andre Sourander and colleagues analyzed data collected on 1,558 children with ASD and an equal number of matched controls born in Finland between January 1987 and December 2004 and followed up until December 2015. Factoring in a wide range of variables, they found that maternal vitamin D deficiency during pregnancy was associated with a 44% increased risk of ASD.

Sourander comments, "The results are significant for public health as vitamin D deficiency is readily preventable."

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"Maternal vitamin D levels during pregnancy and offspring autism spectrum disorder," Andre Sourander, Subina Upadhyaya, Heljä-Marja Surcel, Susanna Hinkka-Yli-Salomäki, Keely Cheslack-Postava, Sanju Silwal, Minna Sucksdorff, Ian W. McKeague, and Alan S. Brown, *Biological Psychiatry*, Vol. 90, Issue 11, 790-797, December 1, 2021. Address: Andre Sourander, andsou@utu.fi.

Visual behavior when inspecting objects may help predict ASD in infants

Infants who exhibit unusual behaviors when visually inspecting objects may be at elevated risk for autism spectrum disorders (ASD), a new study suggests.

Meghan Miller and colleagues evaluated 89 infants at high risk for ASD because they had a sibling with an ASD diagnosis and 58 low-risk infants whose siblings did not have ASD. The researchers found that "infants who developed autism exhibited more frequent unusual visual inspection of objects—a particular type of repetitive behavior involving prolonged visual inspection, examination of the object from odd angles or from peripheral vision, or squinting or blinking repeatedly while examining the object—by 9 months of age compared to those who did not develop autism." In addition, they say, unusual visual inspection at 9 months predicted social behavior at 12 months, while the opposite (social behavior at 9 months predicting behavior during visual inspection at 12 months) was not true.

Miller comments, "The findings support major theories of autism which hypothesize that infants' over-focus on objects might be at the expense of their interest in people. Ultimately, this study suggests that unusual visual inspection of objects may precede development of the social symptoms characteristic of ASD."

The researchers conclude, "Close monitoring of unusual visual inspection of objects by 9 months of age may be an important aspect of early detection and may be valuable to integrate into early screening tools."

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"Repetitive behavior with objects in infants developing autism predicts diagnosis and later social behavior as early as 9 months," Meghan Miller, Shuai Sun, Ana-Maria Iosif, Gregory S. Young, Ashleigh Belding, Andrew Tubbs, and Sally Ozonoff, *Journal of Abnormal Psychology*, August 2021, 665-675. Address: Meghan Miller, UC Davis MIND Institute, 2825 50th Street, Sacramento, CA 95817, mrhmiller@ucdavis.edu.

—and—

"Unusual visual examination of objects may indicate later autism diagnosis in infants," Medical Xpress, September 24, 2021.

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

Contextual clues can trip up individuals with ASD

Adolescents with autism spectrum disorders (ASD) may have difficulty understanding other people's emotions because they do not use contextual clues, a new study suggests.

The study, by Steven Stagg and colleagues, compared 20 teenagers with ASD to 20 neurotypical teens. All participants were between 13 and 15 years of age.

In the first part of the experiment, the groups viewed photos of people displaying static emotions (fear, anger, happiness, sadness, disgust, and surprise). The teens with ASD and the neurotypical controls identified the emotions in the images equally well.

In the second part of the experiment, the groups watched six short videos. In the first part of each video, a main character displayed an emotion that matched the context of the scene. Later in each video, the character displayed a feigned emotion masking his or her true feelings.

For example, one video showed an individual buying a cup of coffee and then being bumped into by another individual, making him spill his coffee. The main character first appeared angry, but after receiving an apology, he displayed a forced smile.

The researchers found that while the teens did not differ in their ability to identify the emotions being displayed on the faces of the characters in the videos, those with ASD could not correctly identify how the characters actually felt. For example, they identified the feigned smile of the man in the coffee video as happiness.

Stagg comments, "Our findings suggest that children with autism may misjudge the feelings of others due to an overreliance on facial cues to the detriment of contextual cues, rather than an inability to recognize facial emotion. In fact, we found that children with autism are just as capable as their typically developing peers at recognizing static images of facial emotion. However, in everyday life, facial expressions are not presented in a vacuum. People commonly attempt to hide their feelings, and therefore accurate recognition of emotion involves processing both facial expressions and contextual cues."

In this study, he says, "the children with autism struggled when asked to describe how the actors were feeling. We believe this is because these children have difficulties integrating the narrative with the facial expressions, and instead their judgments are guided only by the visible emotion on display. In part, this may be due to the higher cognitive demand that more complex stimuli, such as context, place on processing capacity."

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"Emotion recognition and context in adolescents with autism spectrum disorder," Steven Stagg, Li-Huan Tan, and Fathima Kodakkadan, *Journal of Autism and Developmental Disorders*, October 7, 2021 (epub prior to print publication). Address: Steven Stagg, Anglia Ruskin University, East Road, Cambridge, CB1 PT1, UK, steven.stagg@aru.ac.uk.

—and—

"Autistic children struggle with hidden emotions," news release, Anglia Ruskin University, October 8, 2021.

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.

Two new studies suggest no significant association between epidural anesthesia and ASD

Two new studies indicate that there is no significant association between the use of epidural anesthesia during delivery and the odds of a child developing an autism spectrum disorder (ASD).

The studies, along with a previous one by Elizabeth Wall-Wieler in 2021 (see ARRI 2021, No. 2), reached conclusions that differed from a 2020 study by Chunyuan Qiu and colleagues (see ARRI 2020, No. 4). In the 2020 study, researchers found that epidural analgesia given to women during vaginal delivery may increase the risk of autism spectrum disorders (ASD) in their children.

One of the new studies, by Gillian Hanley and colleagues, examined data on 388,254 children born in British Columbia. The researchers detected a small association between epidurals and autism, with 1.53% of epidural-exposed children and 1.26% of unexposed children receiving a later ASD diagnosis. However, further analyses cast doubt on this association. For instance, when the researchers analyzed data from women who had multiple children, including at least one child with ASD and one without, they found that these women were no more likely to have had an epidural when giving birth to the child with ASD than they were when giving birth to a child without it.

The second new study, by Anders Pretzmann Mikkelsen and colleagues, analyzed data from 479,178 children in Denmark. In this study, which controlled for a family history of autism and for a maternal history of psychiatric disorders, the researchers found an incidence rate of 23.1 cases of autism per 10,000 person-years in the epidural-exposed group, compared to 18.5 per 10,000 person-years in the unexposed group. This, they say, indicates that "maternal exposure to epidural analgesia during labor was not significantly associated with autism spectrum disorder in offspring."

In the earlier study in April 2021, Wall-Wieler and colleagues found that 2.1% of children exposed to epidurals later received a diagnosis of ASD, compared with 1.7% of children not exposed to epidurals. However, when the researchers controlled for a wide variety of variables, they no longer detected an association between ASD and epidural exposure.

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"Association of epidural analgesia during labor and delivery with autism spectrum disorder in offspring," Gillian E. Hanley, Celeste Bickford, Angie Ip, Nancy Lanphear, Bruce Lanphear, Whitney Weikum, Lonnie Zwaigenbaum, and Tim F. Oberlander, *Journal of the American Medical Association*, September 28, 2021 (online). Address: Gillian Hanley, gillian.hanley@vch.ca.

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"Association of labor epidural analgesia with autism spectrum disorder in children," Anders Pretzmann Mikkelsen, Iben Katinka Greiber, Nikolai Madrid Scheller, and Øjvind Lidegaard, *Journal of the American Medical Association*, September 28, 2021 (online). Address: Anders Pretzmann Mikkelsen, Department of Gynaecology and Obstetrics, Juliane Marie Centre, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark, anders.mikkelsen@regionh.dk.

—and—

"No link between epidurals and autism, two studies confirm," Laura Dattaro, Spectrum News, September 28, 2021.

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"Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring," Chunyuan Qiu, Jane C. Lin, Jiaxiao M. Shi, Ting Chow, Vimal N. Desai, Vu T. Nguyen, Robert J. Riewerts, R. Klara Feldman, Scott Segal, and Anny H. Xiang, *JAMA Pediatrics*, October 12, 2020 (online). Address: Anny H. Xiang, Department of Research and Evaluation, Kaiser Permanente Southern California, 100 South Los Robles Avenue, Pasadena, CA 91101, anny.h.xiang@kp.org.

EMDR Study

The Johnson Center for Child Health and Development is conducting a study of Eye Movement Desensitization and Reprocessing (EMDR) for addressing anxiety and post-traumatic stress. Participants will be ages 18 or older, have an autism diagnosis, and have experienced traumatic or adverse events. Participants must be within traveling distance of the research location in Austin, TX.

For more information, call (512) 732-8400 or email info@johnson-center.org.

Pupil responses to non-social stimuli: an early clue to ASD?

Infants who later develop autism spectrum disorders (ASD) show a strong "alerting" response to certain nonsocial sounds, according to a new study.

Maja Rudling and colleagues studied 99 ten-month-old infants, 68 of whom were at elevated risk for ASD due to having a sibling with ASD. At follow-up at 36 months of age, 18 children in the elevated-risk group were diagnosed with autism.

Using pupil dilation as a measure of attentional alerting, the researchers measured the infants' responses to two stimuli: speech directed toward them, and the sound of running water. "Compared to infants without diagnosis," the researchers found, "the infants who were subsequently diagnosed with autism had larger pupil dilation when listening to nonsocial sounds, while reactivity to speech was strikingly similar between groups. In the total sample, more pupil dilation to the nonsocial sound was associated with higher levels of autistic symptoms."

The researchers note that at the neural level, pupil size is considered to be a marker of activity in the locus coeruleus (LC), a key structure for regulating the neurotransmitter norepinephrine. "In turn," they say, "LC activity has been associated with psychological processes related to attention orienting, sensory processing, and selectivity. These processes have been implicated in autism, and atypical LC activity has been proposed as one underlying mechanism of autistic development."

The researchers say their findings suggest that certain nonsocial sounds may cause atypical norepinephrine activity in infants who subsequently develop ASD. "If these atypical responses generalize to other environmental stimuli," they say, "it could have cascading consequences for learning and development."

They conclude, "These findings may have important theoretical and clinical implications." In particular, they say, "our results suggest that during social interaction with infants with an elevated likelihood of autism, one may promote development by minimizing task-irrelevant background sounds. This principle is well known in intervention for older children with autism, but to our knowledge it has not been emphasized in [prediagnostic] intervention trials so far."

The researchers note that their results need to be replicated because their study was small, involved children already at risk for ASD, and tested only one type of nonsocial sound.

—

"Larger pupil dilation to nonsocial sounds in infants with subsequent autism diagnosis," Maja Rudling, Pär Nyström, Sven Bölte, and Terje Falck-Ytter, *Journal of Child Psychology and Psychiatry*, September 13, 2021 (free online). Address: Maja Rudling, Department of Psychology, Uppsala University, Box 1225, 751 42 Uppsala, Sweden, maja.rudling@psyk.uu.se.

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Survey explores sexuality in adolescents, adults with ASD

Individuals with autism spectrum disorders (ASD) are less likely to identify as heterosexual and more likely to identify with other sexual orientations than are those without ASD, according to a new study.

Elizabeth Weir and colleagues used an anonymous online self-report survey to study the sexual activity, sexual orientation, and sexual health of 1,183 autistic and 1,203 non-autistic adolescents and adults ranging in age from 16 to 90 years. They note that their study is the largest to date to investigate the sexual orientations of adolescents and adults with ASD.

The researchers report, "Our findings bolster previous evidence that autistic individuals identify with a wider range of sexual orientations than others. Our results clarify that autistic males are uniquely more likely to identify as bisexual than other males and autistic females are uniquely more likely to identify as homosexual than other females—suggesting that autistic adults do not conform to the same sex-specific patterns of sexual orientation observed in the general population." The study found that males with ASD were 3.5 times more likely to identify as bisexual than non-autistic males, and females with ASD were three times more likely to identify as homosexual than non-autistic females.

Overall, the researchers say, "[A]utistic individuals are 8.1 and 7.6 times more likely to self-report identifying as asexual or 'other' sexual orientation than non-autistic individuals, respectively."

The researchers also found that 70% of males with ASD and 76% of females with ASD engage in sexual activity, compared to 89% of both non-autistic males and females. There were no differences between individuals with and without ASD when it came to the likelihood of contracting a sexually transmitted infection (STI) or the age at which the individuals first engaged in sexual activity.

The researchers conclude, "Providers should... be aware that autistic individuals may be more likely to identify with a wider spectrum of genders and sexualities, and their language should be affirming and inclusive of all these identities, particularly when discussing sexual education, sexual health, and consent." In addition, they say, given that individuals with ASD are as likely to contract an STI as their non-autistic counterparts, "improving sexual education and ensuring regular gynecological/sexual health appointments for autistic adolescents and adults across the spectrum should remain a priority."

—

"The sexual health, orientation, and activity of autistic adolescents and adults," Elizabeth Weir, Carrie Allison, and Simon Baron-Cohen, *Autism Research*, September 2021 (free online). Address: Elizabeth Weir, Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK, emw60@cam.ac.uk.

—and—

"Autistic individuals are more likely to be LGBTQ+," news release, University of Cambridge, September 20, 2021.

Microbiome differences in ASD may be due to restricted diets

(continued from page 2)

Yap says. "The microbiome is strongly affected by the environment, which is why we designed our study with two comparison groups."

The researchers found only limited evidence for a direct association of autism with the microbiome. However, they did detect a highly significant association of autism with diet. Their analysis showed that an ASD diagnosis was associated with a less diverse diet and poorer dietary quality. A higher degree of autistic traits was also associated with a less diverse diet.

They conclude that the findings of their study "support a model whereby ASD-related restricted interests are associated with less diverse diet[s], and in turn reduced microbial taxonomic diversity and looser stool consistency."

However, the researchers note that their study could not rule out microbiome contributions prior to ASD diagnosis or the possibility that diet-related changes in the microbiome could have a feedback effect on behavior. In addition, while they excluded individuals taking antibiotics at the time of stool collection, they could not account for prior antibiotic use.

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"Autism-related dietary preferences mediate autism-gut microbiome associations," Chloe X.Yap, Anjali K. Henders, Gail A. Alvares, David L.A. Wood, Lutz Krause, Gene W. Tyson, Restuadi Restuadi, Leanne Wallace, Tiana McLaren, Narelle K. Hansell, Dominique Cleary, Rachel Grove, Claire Hafekost, Alexis Harun, Helen Holdsworth, Rachel Jellett, Feroza Khan, Lauren P. Lawson, Jodie Leslie, Mira Levis Frenk, Anne Masi, Nisha E. Mathew, Melanie Muniandy, Michaela Nothard, Jessica L. Miller, Lorelle Nunn, Gerald Holtmann, Lachlan T. Strike, Greig I. de Zubicaray, Paul M. Thompson, Katie L. McMahon, Margaret J. Wright, Peter M. Visscher, Paul A. Dawson, Cheryl Dissanayake, Valsamma Eapen, Helen S. Heussler, Allan F. McRae, Andrew J.O. Whitehouse, Naomi R. Wray, and Jacob Gratten, *Cell*, November 11, 2021 (online). Address: Jacob Gratten, jacob.gratten@mater.uq.edu.au.

—and—

"Gut microbiota differences seen in people with autism may be due to dietary preferences," news release, Cell Press, November 11, 2021.

—In Memoriam—

Dr. Michael Rutter, who died on October 23 at the age of 88, was an early giant in the field of autism. Like Dr. Bernard Rimland, Dr. Rutter helped to overturn the idea that autism was due to bad parenting. In addition, his research into twins provided important insights into genetic influences on autism. He also was one of the first researchers to be interested in the remarkable strengths and talents of individuals on the autism spectrum.

Dr. Rutter's 1981 textbook, *Child and Adolescent Psychiatry*, had a profound effect on the field of autism research and treatment. He also helped to develop the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview in collaboration with Dr. Catherine Lord. He was a professor of developmental psychopathology at the Institute of Psychiatry, King's College London, retiring only recently. In addition, he was a consultant psychiatrist at the Maudsley Hospital. He was knighted in 1992.

Dr. Rutter's important contributions in many areas of autism research significantly advanced the field. He will be greatly missed.

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•

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

•

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

•

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