

Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—www.Autism.com

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

Two studies offer clues about the role of epigenetic changes in autism spectrum disorders

Two new studies are shedding light on the relationship between autism spectrum disorders (ASD) and epigenetic changes.

Epigenetic changes are alterations in gene activity that occur without changes to the DNA itself. These changes, which switch genes on or off, can sometimes be passed on to future generations. The causes of epigenetic changes are wide-ranging and include diet, chemical exposures, stress, disease processes, medications, and prenatal influences.

In the first study, Wenjie Sun and colleagues examined post mortem brain tissue samples from 45 individuals with ASD and 49 controls. They found that the samples from individuals with ASD exhibited a similar set of epigenetic changes, with more than 68% sharing a common pattern of histone acetylation (an epigenetic process that determines

whether a gene is “hidden” or not) at 5,000 gene loci. The researchers say, “This suggests that, despite tremendous heterogeneity in the primary causes of autism, such as DNA mutations and environmental perturbations during development, ASD has molecular features that are commonly shared.”

In the second study, Chang Soon Choi and colleagues injected pregnant mice with valproic acid, an anti-epileptic drug that can cause autistic-like symptoms in prenatally exposed animals and humans. The exposed male offspring exhibited autistic-like social impairments, abnormal marble-burying behavior, increased seizure susceptibility, hyperactivity, and decreased anxiety. When the researchers mated the exposed offspring with unexposed females to produce a second generation, and then mated second-generation males to unexposed females to create a

third generation, the autistic-like behaviors found in the first generation persisted. In addition, the frontal cortices of first- and third-generation mice exhibited an imbalanced expression of excitatory and inhibitory synaptic markers.

The researchers say, “These results open the idea that excitatory/inhibitory imbalance and ASD-like behavioral changes induced by environmental insults in mice can be

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Smartphone app identifies autism with high accuracy

Recently (see ARRI 2016, No. 3), researchers at the University of Rochester announced that they could diagnose autism spectrum disorders (ASD) with up to 93% accuracy using iPad games that measured children’s movement patterns. Now a separate team of researchers at the University at Buffalo are reporting that they have developed a smartphone app that can diagnose ASD with equal accuracy.

Kun Woo Cho and colleagues created an app that tracks the eye movements of children as they look at pictures of social scenes. The researchers tested their app on 32 children ranging from two to 10 years of age, half of whom had an autism diagnosis. While the app is only a prototype, the researchers say that it detected ASD in under one minute with an accuracy of 93.96%.

The researchers say that the eye tracking patterns of children with ASD were more scattered and less focused than those of controls when they viewed the social scenes. Cho says, “We speculate that it is due to their lack of ability to interpret and understand the relationship depicted in the social scene.”

Study coauthor Wenyao Xu says, “The beauty of the mobile app is that it can be used by parents at home to assess the risk of whether a child may have ASD. This can allow families to seek therapy sooner, and improve the benefits of treatment.”

Cho and colleagues presented their findings at the IEEE Wireless Health Conference in October 2016. Address: wenyaoxu@buffalo.edu.

Low vitamin D associated with more autism-related traits

Low levels of vitamin D during prenatal development correlate with a higher level of autism-related traits, according to a new study.

A. A. E. Vinkhuyzen and colleagues analyzed data on the vitamin D (25-hydroxyvitamin D, or 25OHD) status of 4,229 children (measured by cord blood levels at delivery) and their mothers (measured at mid-gestation). They also evaluated the children’s scores on an abridged version of the parent-administered Social Responsiveness Scale (SRS) when the children were approximately six years of age.

The researchers say, “In all analyses, 25OHD deficiency or lower 25OHD concentrations were associated with higher (more impaired) SRS scores.” When the researchers compared children with SRS scores above the suggested cutoff for possible ASD with children below the suggested cutoff, those who were vitamin D-deficient at mid-gestation were 3.8 times more likely to be screened positive than those who had adequate vitamin D levels at mid-gestation. These findings persisted when the researchers controlled for ethnicity, genetic factors, and the season in which the blood samples were taken.

The researchers say, “Because gestational vitamin D deficiency is readily preventable

with safe, cheap and accessible supplements, this candidate risk factor warrants closer scrutiny.” They note that the prevalence of vitamin D deficiency was high in their

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sample, with 16% of mothers being deficient at mid-gestation and 36% of the cord blood samples indicating a deficiency.

“Gestational vitamin D deficiency and autism-related traits: the Generation R Study,” A. A. E. Vinkhuyzen, D. W. Eyles, T. H. J. Burne, L. M. E. Blanken, C. J. Kruithof, F. Verhulst, V. W. Jaddoe, H. Tiemeier, and J. J. McGrath, *Molecular Psychiatry*, November 29, 2016 (epub prior to print publication). Address: J. J. McGrath, Queensland Brain Institute, University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia, j.mcgrath@uq.edu.au.

Researchers investigate associations between autism spectrum disorder and dyspraxia

A new study reveals intriguing connections between autism spectrum disorders (ASD) and dyspraxia.

Dyspraxia is a disorder that affects gross and/or fine motor movements. It is often seen in ASD and also affects approximately 2-6% of the general population.

In the new study, Sarah Cassidy and colleagues analyzed data contributed online by 2,871 adults with ASD and 10,706 controls. The researchers asked participants if they had been diagnosed with dyspraxia. In addition, a large subset of participants in each group completed the Autism Spectrum Quotient (AQ) and the Empathy Quotient (EQ).

The researchers say that nearly 7% of adults with ASD reported a diagnosis of dyspraxia, compared to only 0.8% of controls. In the ASD group, dyspraxia was not significantly related to AQ or EQ scores. However, the researchers say, control group members with dyspraxia reported significantly higher levels of autistic traits and lower levels of empathy than controls without dyspraxia.

The researchers conclude, "These results suggest that motor coordination skills are important for effective social skills and empathy." In addition, they say, their findings indicate that ASD and dyspraxia may overlap, "particularly as both conditions are seemingly associated with

atypical development of neurons within the cerebral cortex."

"Dyspraxia and autistic traits in adults with and without autism spectrum conditions," Sarah Cassidy, Penelope Hannant, Teresa Tavassoli, Carrie

Allison, Paula Smith, and Simon Baron-Cohen, *Molecular Autism*, 2016 (open access). Address: Sarah Cassidy, Centre for Psychology, Behaviour and Achievement, Coventry University, Priory Street, Coventry, CV1 5FB, UK, sarah.cassidy@coventry.ac.uk.

Folinic acid boosts verbal skills in some children with ASD

A new study reports that supplementation with folinic acid, a form of the B vitamin folate, may improve the verbal communication skills of certain children with autism.

Richard Frye and colleagues previously found that children with ASD have a high prevalence of folate receptor autoantibodies. In their new double-blind, placebo-controlled study, the researchers investigated the response of children with and without these autoantibodies to a 12-week trial of supplementation with folinic acid. The study involved 48 children with ASD and language impairment between 3 and 14 years of age. Doses of folinic acid were calculated by weight, with the maximum dose being 50 mg per day.

The researchers report that for children with folate receptor autoantibodies, improvement in verbal communication was significantly greater in those receiving folinic acid compared to the placebo group. For children with biomarkers indicating more normal folate metabolism, there was no significant difference in verbal commu-

nication measures between the two groups. Daily living skills improved significantly in the folinic acid group compared to the placebo group.

The researchers point out that no significant adverse effects occurred in the treated group, saying that "well-tolerated medications that target pathophysiological processes and core symptoms associated with ASD are sorely needed." They also note that their findings are consistent with the idea that children with ASD and folate receptor autoantibodies "may represent a distinct subgroup" who can benefit from treatment with folinic acid.

"Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial," R. E. Frye, J. Slattery, L. Delhey, B. Furgerson, T. Strickland, M. Tippett, A. Sailey, R. Wynne, S. Rose, S. Melnyk, S. Jill James, J. M. Sequeira, and E. V. Quadros, *Molecular Psychology*, October 18, 2016 (epub prior to print publication). Address: R. E. Frye, Autism Research Program, Arkansas Children's Research Institute, Slot 512-41B, 13 Children's Way, Little Rock, AR 72202, REFrye@uams.edu.

Studies offer clues about the role of epigenetics in autism spectrum disorders

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epigenetically transmitted, at least to the third generation." They add that their findings "could help explain the unprecedented increase in ASD prevalence."

"Histone acetylome-wide association study of autism spectrum disorder," Wenjie Sun, Jeremie Poschmann, Ricardo Cruz-Herrera del Rosario, Jonathan Mill, Daniel H. Geschwind, Shyam Prabhakar, et al., *Cell*, Vol. 167, 1385-97, November 17, 2016 (free online). Address: Shyam Prabhakar at prabhakars@gis.a-star.edu.sg.

"Shared epigenetic changes underlie different types of autism," news release, *Cell Press*, November 2016.

"The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy," Chang Soon Choi, Edson Luck Gonzalez, Ki Chan Kim, Sung Min Yang, Ji-Woon Kim, Darine Froy Mabunga, Jae Hoon Cheong, Seol-Heui Han, Geon Ho Bahn, and Chan Young Shin, *Nature Scientific Reports*, November 7, 2016 (free online). Address: Geon Ho Bahn, mompeian@khu.ac.kr.

IN MEMORIAM

Margaret Creedon, Ph.D.

Dr. Margaret Creedon was a true pioneer in the autism field. She was active in the Autism Society of America for many years and directed a major therapeutic treatment center in the Chicago area.

Dr. Creedon spearheaded *simultaneous communication*, a strategy that involves teaching sign language and speech at the same time, and was a major proponent of sensory interventions involving deep pressure, vision, and hearing. She also was deeply concerned about the vulnerability of individuals with autism to physical and sexual abuse, and often provided expert testimony in court cases.

Dr. Creedon assisted ARI with several projects in our adult program as well as our Hard of Hearing/Deaf & Visually Impaired/Blind network, which provides resources to families with children on the autism spectrum.

Karl L. Reichelt, Ph.D., M.D.

Dr. Karl Reichelt was another pioneer in the fields of autism, schizophrenia, and cancer. In collaboration with Paul Shattock, he conducted early and innovative research on the association between autism and opioid peptides in casein and gluten. This line of research provided support for the validity of the gluten-free and casein-free diet.

Dr. Reichelt was a close friend of Dr. Bernard Rimland and an active member of ARI's Defeat Autism Now! program. He provided invaluable input at our think tanks and lectured at our conferences.

In 2004, Dr. Reichelt was awarded Norway's King's Medal of Merit in gold. This medal is rewarded for extraordinary achievements of importance to the country and its citizens.

EDITORIAL: Stephen M. Edelson, Ph.D.

Internal sensory stress and discomfort or pain

Many individuals on the autism spectrum suffer from recurring or chronic discomfort or pain. On occasion, parents and physicians suspect that someone may be suffering from a medical problem, but it can be very difficult to pinpoint the source. As a result, physicians may order laboratory testing, x-rays, and in extreme cases, exploratory surgery.

It is often assumed that these people have difficulty communicating their discomfort or pain verbally or physically (e.g., touching, pointing). However, research on sensory issues, along with reports from adults with autism and their parents, suggests that the lack of expression of discomfort or pain could be a result of diminished or dulled internal sensations. Alternately, internal discomfort or pain may be perceived as being more intense than it is by neurotypical individuals with the same underlying medical problems.

Types of Sensory Processing

Dr. Lucy J. Miller, a pioneering researcher in sensory processing, and her colleagues have demonstrated that those on the spectrum respond to sensory stimulation in distinct ways. Using a standardized procedure to evaluate sensory processing called the Sensory Challenge Protocol, Miller and her colleagues measured sympathetic neural activity associated with various types of external stimulation. Their findings revealed that many on the spectrum were hyposensitive and had a diminished response to sensory sensations. In contrast, others were hypersensitive, exhibiting an enhanced reaction to the same sensory stimuli.

Interoception is a relatively new area of interest among those in the sensory processing field. It refers to the perception of sensory-related stimulation within the body and includes feelings of pain, muscle tension, bladder tension, hunger, and much more. In her new book, *Interoception: The Eighth Sensory System*, Kelly Mahler, M.S., OTR/L, reviews a range of research surrounding interoception and links this research to the common experiences of people with autism. Mahler describes three types of difficulty with interoceptive awareness:

Interoceptive underresponsivity. This refers to hyposensitivity or diminished sensations. Thus, these individuals may feel little or no discomfort or pain while suffering from a medical condition. Consistent with this description, a study by Fiene and Brownlow (2015) involving 74 adults with autism and 228 controls found that those on the spectrum had much lower levels of “sensing internal

bodily states.” At the Autism Research Institute, we have heard reports of people who did not show outward signs of discomfort or pain while suffering from issues such as a ruptured appendix, impacted stools in the gastrointestinal tract, or a severe ear infection.

Interoceptive responsivity. This refers to hypersensitivity or over-responsiveness; thus, internal sensations may actually be enhanced. Dr. Micah Mazurek and her colleagues found that children on the spectrum were over-responsive as well as anxious as

Interoception is a relatively new area of interest among those in the sensory processing field. Interoception refers to the perception of sensory-related stimulation within the body and includes feelings of pain, muscle tension, bladder tension, hunger, and much more.

a result of pain-associated gastrointestinal problems. Furthermore, Dr. Edward Carr and his colleagues found that behavioral challenges in the classroom occurred more often on “sick” days as well as days of menstrual discomfort. The behaviors noted included property destruction, meltdowns, aggression, stereotypies, and self-injurious behavior.

Interoceptive discrimination difficulty. A third type of interoception, termed “discrimination difficulty,” refers to an individual who has a “vague” or “general” feeling of an internal sensation but cannot provide details of this feeling. An example would be someone who feels anxious but is unable to determine that this anxiety is a result of some form of discomfort or pain.

Possible Reasons for Difficulties in Interoception

Research in several areas, including neurology, metabolism, biochemistry, and even nutrition, may shed light on interoceptive challenges. Focuses of investigation include:

Insula. The insula is located deep within the cerebral cortex, within the lateral sulcus. The lateral sulcus separates the temporal and parietal lobes and is known to be responsible for internal sensations, emotional regulation, and autonomic nervous system control. Research on the insula in autism has documented *hypo*-connectivity in some individuals, and *hyper*-connectivity in others. In addition, one study found reduced gray matter in the insula of those with autism.

Minicolumns. Research conducted by Dr. Manuel Casanova and others has documented impaired minicolumns in the neocortex, including sensory regions, in people with autism. Dr. Casanova has suggested different reasons for hypersensitivity and hyposensitivity. Basically, the threshold of reactivity to a sensory stimulus is lower in those with autism. Thus, a relatively weak stimulus would cause more neural firing (i.e., action potential) and lead to increased sensitivity or hyper-reactivity. However, hyposensitivity would occur as a result of additional neural firing (i.e., noise) due to stimulation from adjacent neurons or minicolumns. This would make the stimulus in question less distinguishable and lead to reduced sensitivity or hypo-reactivity (i.e., low signal-to-noise ratio).

Metabolism. There has been much discussion yet little research on the possible connection between mitochondrial impairment and sensory dysfunction. A recent study by Dr. Richard Frye and his colleagues found that a unique form of mitochondrial impairment was related to the occurrence of severe repetitive behaviors. Repetitive behaviors have often been assumed to provide self-stimulation to a hyposensitive sensory system. They may also serve the opposite purpose, reducing sensory input by redirecting one’s attention away from the source of discomfort or pain. ARI is collaborating with Drs. Frye and Miller to further understand the possible relationship between mitochondrial impairment and sensory processing.

Biochemistry. The endorphin theory of autism, originally proposed by Dr. Jaak Panksepp, proposes that endorphins, which are endogenous opiate-like substances, may lead to diminished sensations within the body. As a way to handle severe pain, the body releases endorphins during behaviors such as self-injury, which in turn dampen the pain and lead to pleasurable feelings. Another possibility, proposed by many practitioners and researchers, is a partial breakdown of casein and gluten proteins in an inflamed and “leaky” gut that allows these proteins to seep into the bloodstream. These endorphin-like peptides, casomorphin and gluteomorphin, then circulate throughout the body, leading to a dulling of sensory sensations as well as feelings of pleasure.

Nutrition. Certain deficiencies may lead to sensory hypersensitivity. For example, sound sensitivity may be a result of a magnesium deficiency; bone pain may be caused by

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Research Updates

Elevated rate of celiac disease seen in ASD

Children with autism spectrum disorders (ASD) may have a higher-than-typical rate of celiac disease (CD), a new study from Italy suggests.

Celiac disease is an autoimmune disease in which exposure to gluten damages the intestinal wall. The disease, which causes gastrointestinal symptoms, fatigue, and a wide range of other symptoms, is treated by removing gluten from the diet.

Sara Calderoni and colleagues reviewed data from 382 children who received a diagnosis of ASD and underwent screening for CD. The researchers report that the prevalence of CD in their sample was 2.62%, which is significantly higher than the 1.1% to 1.2% reported in children in the general Italian population.

The researchers note that children with ASD may not show clear signs of CD. Instead, they may express their discomfort via behavioral problems such as anxiety, withdrawal, temper tantrums, oppositional behavior, sleep problems, food selectivity, aggression, and self-injurious acts. “In these cases,” the researchers say, “if a diagnosis of CD is confirmed, the treatment of ASD patients for CD with a gluten-free diet may not only alleviate their CD-related symptoms, but also have a positive impact on associated behavioral problems.”

“Serological screening for celiac disease in 382 pre-schoolers with autism spectrum disorder,” Sara Calderoni, Elisa Santocchi, Teresa Del Bianco, Elena Brunori, Laura Caponi, Aldo Paolicchi, Francesca Fulceri, Margherita Prosperi, Antonio Narzisi, Angela Cosenza, Raffaella Tancredi, and Filippo Muratori, *Italian Journal of Pediatrics*, Vol. 42, No. 1, November 16, 2016. Address: Sara Calderoni, IRCCS Stella Maris Foundation, Viale del Tirreno 331, Pisa 56018, Calambrone, Italy, sara.calderoni@fsm.unipi.it.

Individuals with autism are good candidates for epilepsy surgery

A new study reports that “epilepsy surgery in patients with autism is feasible, with no indication that the comorbidity of autism should preclude a good outcome.”

In the study, M. A. Kokoszka and colleagues analyzed the medical records of 56 consecutive patients with autism who underwent epilepsy surgery. Of these patients,

45 were severely autistic, 27 had significant aggressive or disruptive behaviors, and 30 were nonverbal. In 32 cases, the causes of the epilepsy were known; these causes included structural lesions, medical problems, and developmental and genetic issues.

Twenty-nine of the patients underwent respective treatments, 24 had palliative treatments, and three solely underwent diagnostic subdural electroencephalography. Eighteen patients required more than one surgery.

The researchers followed up with the patients an average of four years later. Three of the patients no longer needed any anti-epileptic drugs, and 24 exhibited reductions in aggression and other aberrant behaviors. Caregivers also reported that most of the patients exhibited improved social and cognitive function. Three patients showed no functional or behavioral changes, while two exhibited worsening seizures and behavioral symptoms.

The researchers note, “The reduction in aberrant behaviors observed in this series suggests that some behaviors previously attributed to autism may be associated with intractable epilepsy, and further highlights the need for systematic evaluation of the relationship between the symptoms of autism and refractory seizures.”

“Epilepsy surgery in patients with autism,” M. A. Kokoszka, P. E. McGoldrick, M. La Vega-Talbot, H. Raynes, C. A. Palmese, S. M. Wolf, C. L. Harden, and S. Ghatan, *Journal of Neurosurgery—Pediatrics*, November 25, 2016 (ePub prior to print publication). Address: Saadi Ghatan, Department of Neurosurgery, Mount Sinai West, 1000 Tenth Ave., Ste. 5G-80, New York, NY 10019, sghatan@chpnet.org.

— AUTISM.JOBS —

The Autism Employment Resource Center

A Free Resource for Job Seekers, Families and Caregivers, Job Coaches, and Employers

At this site, you can discover the advantages of hiring individuals with autism, access practical information designed to help candidates with autism become “job ready,” and learn how to create autism-friendly workplaces.

This database is a searchable collection of autism employment resources with a wealth of practical advice. It includes links to a variety of resources including articles, videos, books and more. Guides highlight key steps in the employment process.

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Reduced asymmetry in ASD may lead to weak central coherence

The hemispheres of the brain may be less specialized in individuals with autism spectrum disorders (ASD) than in neurotypical individuals, a new study indicates.

Ruth Carper and colleagues used a magnetic resonance imaging (MRI) technique known as diffusion tensor imaging to study the brains of 41 participants with ASD and 44 controls, examining how densely connections formed within different regions of white matter. While other studies have examined language-related asymmetries, the researchers note that their study investigated microstructural asymmetries across a large number of fiber tracts.

The researchers report that in controls, the right brain hemisphere had more densely packed connections than the left hemisphere. “This fits with the idea that the right hemisphere has a more integrative function, bringing together many kinds of information,” study coauthor Ralph-Axel Müller says. In contrast, the brain connections in individuals with ASD were more evenly distributed across both hemispheres.

“The idea behind asymmetry in the brain is that there is a division of labor between the two hemispheres,” Müller adds. “It appears this division of labor is reduced in people with autism spectrum disorder.”

Müller says this reduced asymmetry could result in “weak central coherence,” which he compares to “not seeing the forest for the trees.” He notes that this is consistent with the fact that individuals with ASD are often good at detecting details, while having difficulty consolidating information into a coherent whole.

“Reduced hemispheric asymmetry of white matter microstructure in autism spectrum disorder,” Ruth A. Carper, Jeffrey M. Treiber, Shannon Yandall DeJesus, and Ralph-Axel Müller, *Child & Adolescent Psychiatry*, Vol. 55, No. 12, December 2016, pp. 1073-80. Address: Ruth Carper, Brain Development Imaging Laboratory, Department of Psychology, San Diego State University, 6363 Alvarado Ct., Suite 200, San Diego, CA 92120, rcarper@mail.sdsu.edu

—and—

“Division of labor in the brain,” Michael Price, SDSU News Center, November 30, 2016.

Moving?

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Research Updates

Mimicry may aid facial emotion recognition

Asking individuals with autistic traits to mimic the facial expressions of others may improve their ability to recognize emotions, a new study indicates.

Michael Lewis and Emily Dunn administered the Autism-Spectrum Quotient (AQ) to young adults without a diagnosed autism spectrum disorder (ASD) to evaluate their level of autism traits. The individuals then participated in two slightly different experiments, the first involving 46 participants and the second involving 60. In each experiment, half of the participants were told to mimic a facial expression they saw before making a judgment about the emotion being exhibited. The other half of the group viewed the facial expressions without receiving any instructions about mimicking them.

The researchers report that in both experiments, instructing a person to mimic the expression being observed improved facial emotion recognition. Moreover, the improvement was more pronounced for individuals with higher AQ scores (indicating a higher level of autism traits).

While the study involved individuals without an autism diagnosis, the researchers conclude, "If the benefits of instructions to mimic do extend to people with autism spectrum conditions, then this provides a potential intervention in order to improve social communication and empathy in this group."

"Instructions to mimic improve facial emotion recognition in people with sub-clinical autism traits," Michael B. Lewis and Emily Dunn, *Quarterly Journal of Experimental Psychology*, October 13, 2016 (epub prior to print publication). Address: Michael B. Lewis, School of Psychology, Cardiff University, Park Place, Cardiff, CF10 3AT, UK, lewismb@cardiff.ac.uk.

Children conceived in winter more likely to get ASD diagnosis

Autism rates are highest among children conceived in the winter months, according to a large-scale study conducted in Scotland.

D. F. Mackay and colleagues analyzed data on more than 800,000 children, comparing those with and without an autism diagnosis. They found that rates of autism were highest among children conceived between January and March, and lowest among children conceived between July and September. They add, "Seasonal variations were specific to autism spectrum disorder, intellectual dis-

abilities, and learning difficulties (e.g., dyslexia) and were absent for sensory or motor/physical impairments and mental, physical, or communication problems." Overall, they say, seasonality accounted for 11.4% of all cases of autism, intellectual disability, and learning difficulty.

The researchers say that low vitamin D levels during the winter may help to explain their findings. In addition, they say, high rates of influenza during the winter months may play a role.

"Month of conception and learning disabilities: a record-linkage study of 801,592 children," D. F. Mackay, G. C. Smith, S. A. Cooper, R. Wood, A. King, D. N. Clark, and J. P. Pell, *American Journal of Epidemiology*, October 1, 2016 (epub prior to print publication). Address: Jill Pell, Jill.Pell@glasgow.ac.uk.

Study finds that sibling 'cross-disorder' risk is raised for ASD, epilepsy

The risk of developing epilepsy is elevated in younger siblings of children with ASD, a new study reports, and the risk of ASD is elevated if an older sibling has epilepsy.

Jakob Christensen and colleagues analyzed data on all children born in Denmark between 1980 and 2006 who were followed through the end of 2012. Overall, their data included more than 1.6 million children. They report that:

- The overall adjusted hazard ratio (aHR) of epilepsy in younger siblings increased by 70% if an older sibling had ASD.
- The overall aHR of ASD increased by 54% if an older sibling had epilepsy.
- The risk of developing ASD or epilepsy was highest for children whose older siblings had both disorders.

"Cross-disorder" risks were elevated for half siblings as well as full siblings. However, the researchers say, the numbers of half siblings were small and this finding should be interpreted with caution.

The researchers say, "The cross-disorder sibling risk of epilepsy and ASD was increased for the two disorders, which suggests that genes or environmental factors shared by family members may play a causal role in the co-occurrence of ASD and epilepsy."

In addition, they say, "For children with epilepsy and their siblings, it is important to

impose clinical surveillance for ASD—especially in families in which the older sibling has both epilepsy and ASD. A similar surveillance should be imposed in relation to ASD—and again in particular if the older sibling has both ASD and epilepsy."

"Risk of epilepsy and autism in full and half siblings—a population-based cohort study," Jakob Christensen, Morten Overgaard, Erik T. Parner, Mogens Vestergaard, and Dana Schendel, *Epilepsia*, November 8, 2016 (epub prior to print publication). Address: Jakob Christensen, Department of Neurology, Aarhus University Hospital, Norrebrogade 44, DK-8000 Aarhus C, Denmark, Jakob@farm.au.dk.

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Individuals with ASD are less susceptible to “optimism bias” than neurotypical individuals

Neurotypical individuals tend to exhibit a significant “optimism bias” when it comes to forming beliefs about future outcomes in their lives. According to a new study, individuals with high-functioning autism spectrum disorders (ASD) are less susceptible to this bias.

Bojana Kuzmanovic and colleagues say that neurotypical individuals “demonstrate unrealistic optimism, as they tend to overestimate their chances of experiencing positive outcomes, but underestimate their risks of experiencing negative outcomes.” In addition, they say, research indicates that “when people update their beliefs, they tend to take into account good news, but neglect bad news.”

To see if individuals with high-functioning ASD exhibited the same bias, the researchers asked 21 adults with ASD and 21 neurotypical controls to participate in a task measuring optimism bias. The participants were matched for age, gender, years of education, and IQ.

In the task, participants estimated the risk of experiencing adverse events—for instance, a burglary—in the future. The researchers then provided them with statistics regarding the base population rate for each event. (This statistical information was manipulated as part of the study design.) Afterward, participants had the opportunity to adjust their initial estimates based on the information they received. In half of the trials, participants estimated the risks to themselves; in the other half, they estimated the risk to a similar person

of the same age, sex, and socioeconomic background.

“In accordance with previous studies,” the researchers say, “typically developing individuals tended to make larger self-related updates after good news (base rates of adverse events better than expected) than after bad news (base rates worse than expected).” They also were more optimistic when it came to their own outcomes than the outcomes of other people. In contrast, individuals with ASD did not exhibit a significant optimism bias when evaluating the future risks to themselves, and they did not predict risks to themselves more optimistically than risks to others. These findings remained true when the researchers controlled for depressive symptoms.

The researchers note that a cognitive style involving increased rationality may interfere with social functioning, “because the interpretation of complex social situations often requires spontaneous conclu-

sions guided by ambiguous communicative cues and their emotional significance.” However, they note that enhanced rationality may provide substantial benefits as well.

“In contexts such as marketing and politics,” they say, “a smaller susceptibility to emotionally and motivationally significant cues that are non-informative for the actual aim of the decision may be beneficial. Also, enhanced objectivity may be advantageous when planning complex projects, in which overconfidence and the neglect of possible obstacles would foster planning fallacy, and financial and psychological harm.”

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“Brief report: Reduced optimism bias in self-referential belief updating in high-functioning autism,” Bojana Kuzmanovic, Lionel Rigoux, and Kai Vogeley, *Journal of Autism and Developmental Disorders*, October 18, 2016 (online). Address: Bojana Kuzmanovic, Max Planck Institute for Metabolism Research Cologne, Translational Neurocircuitry Group, Gleueler Str. 50 50931 Cologne, Germany, bojana.kuzmanovic@sf.mpg.de.

Study investigates effects of maternal flu infection, vaccine

A large-scale study concludes that maternal influenza infection or flu vaccination during pregnancy does not increase the risk of autism spectrum disorder (ASD) in children, although the research raises possible concerns about first-trimester vaccination.

Ousseny Zerbo and colleagues analyzed information collected on 196,929 children born at Kaiser Permanente Northern California between 2000 and 2010. Reviewing data on the children’s mothers, the researchers identified those who either contracted the flu or had flu shots during pregnancy.

The researchers found that 1,400 mothers developed the flu during pregnancy, and 45,231 received an influenza vaccination. They also identified 3,101 children who received a diagnosis of autism.

The researchers say, “We found no association between ASD risk and influenza infection during pregnancy or influenza vaccination during the second to third trimester of pregnancy.” However, they say, “there was a suggestion of increased ASD risk among children whose mothers received influenza vaccinations early in pregnancy, although the association was insignificant after statistical correction for multiple comparisons.”

The researchers conclude, “While we do not advocate changes in vaccine policy or practice, we believe that additional studies are warranted to further evaluate any potential associations between first-trimester maternal influenza vaccination and autism.”

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“Association between influenza infection and vaccination during pregnancy and risk

of autism spectrum disorder,” Ousseny Zerbo, Yinge Qian, Cathleen Yoshida, Bruce H. Fireman, Nicola P. Klein, and Lisa A. Croen, *JAMA Pediatrics*, November 28, 2016 (free online). Address: Ousseny Zerbo, Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612, ousseny.x.zerbo@kp.org.

—and—
“No association between mother’s flu in pregnancy and increased child autism risk,” *Infection Control Today*, November 2016.

Quotable...

“Neurodevelopment is a complex process governed by both intrinsic and extrinsic signals. While historically studied by researching the brain, inputs from the periphery impact many neurological conditions. Indeed, emerging data suggest communication between the gut and the brain in anxiety, depression, cognition, and autism spectrum disorder (ASD). The development of a healthy, functional brain depends on key pre- and post-natal events that integrate environmental cues, such as molecular signals from the gut. These cues largely originate from the microbiome, the consortium of symbiotic bacteria that reside within all animals. Research over the past few years reveals that the gut microbiome plays a role in basic neurogenerative processes such as the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation and also modulates many aspects of animal behavior.”

G. Sharon and colleagues, in “The central nervous system and the gut microbiome,” *Cell*, November 3, 2016

New Study: Autism Treatment Effectiveness Survey Gauges Improvements, Side Effects

Researchers at Arizona State University are conducting a survey to evaluate the effectiveness of treatments for autism, including medications, nutritional supplements, diets, therapies, and education. The investigators hope to learn which treatments are most effective for different symptoms (language, anxiety, sleep, GI, etc.). Survey results will be posted online for families and clinicians, and published in a scientific journal.

Share your experiences—
take the survey here:
<https://autism.asu.edu/>

Large-scale study raises concerns about effects of first-trimester diagnostic ultrasounds

First-trimester diagnostic ultrasounds may put children with a genetic vulnerability to autism at higher risk for severe symptoms if they develop the condition, a study suggests.

Sara Jane Webb and colleagues evaluated data on 2,644 families included in the Simons Simplex Collection database. The sample included 1,749 children with autism spectrum disorders (ASD) whose profiles contained information on whether or not they had copy number variations (CNV), a risk factor for ASD. Copy number variations are anomalies involving insertions, deletions, inversions, or duplications in areas of the genome.

The researchers found that:

- For the entire sample of children with ASD, exposure to diagnostic ultrasound during the first trimester correlated with

lower social affective symptoms observed by clinicians but worse restrictive and repetitive behaviors as reported by parents.

- For children with CNVs, exposure to first-trimester diagnostic ultrasound correlated with lower nonverbal IQ scores. In addition, there was a trend toward more impaired adaptive behaviors as reported by parents and increased repetitive behaviors as observed by clinicians.
- For male children with CNVs, exposure to first-trimester diagnostic ultrasound was related to lower nonverbal IQ and increased repetitive behaviors as observed by clinicians, as well as trends toward reduced verbal IQ and increased repetitive symptoms as reported by parents.
- There was no correlation between ASD

symptom severity, CNVs, and diagnostic ultrasound exposure during the second or third trimesters.

The researchers conclude, “These data suggest that heterogeneity in ASD symptoms may result, at least in part, from exposure to diagnostic ultrasound during early prenatal development of children with specific genetic vulnerabilities. These results also add weight to ongoing concerns expressed by the FDA about non-medical use of diagnostic ultrasound during pregnancy.”

—
“Severity of ASD symptoms and their correlation with the presence of copy number variations and exposure to first trimester ultrasound,” Sara Jane Webb, Michelle M. Garrison, Raphael Bernier, Abbi M. McClintic, Bryan H. King, and Pierre D. Mourad, *Autism Research*, September 1, 2016 (online). Address: Pierre D. Mourad, Department of Neurological Surgery, Box 356470, University of Washington Seattle, WA 98195, pierre@apl.washington.edu.

—and—

“Prenatal ultrasound tied to autism severity in at-risk kids,” Megan Brooks, *Medscape*, September 21, 2016.

Positive results reported for novel speech training program

A technique called Auditory-Motor Mapping Training (AMMT) may significantly improve the communication skills of minimally verbal children with autism spectrum disorders (ASD), according to a new study.

AMMT combines “sung” speech with the use of specially tuned drums in order to build new connections in the brain. In the procedure, a therapist sings two-syllable words or phrases, using a different pitch for each syllable, while simultaneously tapping on a drum tuned to the same two pitches. Children first listen and then participate in speaking and drumming. The final goal is for the children to produce the words or phrases independently.

The researchers recently tested the therapy on 23 minimally verbal children with ASD, comparing them to seven children with ASD who underwent traditional Speech Repetition Therapy (SRT). All children participated in at least 25 therapy sessions.

Comparing children’s performance after AMMT therapy to their baseline performance, the researchers found that the children exhibited a 19.4% increase in syllables approximated, a 13.8% increase in consonants spoken correctly, and a 19.1% increase in correct vowels. Compared to the SRT group, they produced 29% more syllables approximated, 17.9% more consonants spoken correctly, and 17.6% more correct vowels. A majority of children in the AMMT group showed improvement on each of the three outcome measures, and more children responded to therapy in the AMMT group than in the SRT group. The children’s pre-treatment ability to imitate phonemes, but not their age or baseline performance, correlated significantly with the amount of improvement they exhibited after therapy.

The researchers note that while their study focused on pronunciation, children in the AMMT group experienced gains in a wide range of skills. “Therapists noted that children’s ability to attend to the clinician, participate in turn-taking activities (such as rolling a ball back and forth during breaks), and make specific requests (e.g., snacks, sensory input such as squeezes, favorite motivators, bathroom breaks) improved over the course of treatment,” they say. “In addition, many children learned to associate the target words with their respective pictures, often spontaneously naming them during Step 1. Finally, both parents and clinicians noted an increase in speech-like vocalization on the part of many of the children. That is, participants engaged in more vocal play, an important precursor to speech development in typically developing children. Thus, AMMT may offer additional benefit in the areas of social communication and receptive language, help ‘jumpstart’ the speech development process in some minimally verbal children with ASD, and further improve their ability to intentionally vocalize.”

—
“Auditory-Motor Mapping Training: Comparing the effects of a novel speech treatment to a control treatment for minimally verbal children with autism,” Karen Chenausky, Andrea Norton, Helen Tager-Flusberg, and Gottfried Schlaug, *PLOS One*, November 9, 2019 (free online). Address: Gottfried Schlaug, gschlaug@bidmc.harvard.edu.

—see also—

“Auditory-Motor Mapping Training as an intervention to facilitate speech output in non-verbal children with autism: A proof of concept study,” Catherine Y. Wan, Loes Bazen, Rebecca Baars, Amanda Libenson, Lauryn Zipse, Jennifer Zuk, Andrea Norton, and Gottfried Schlaug, *PLOS One*, September 2011 (free online). Address: cwan@bidmc.harvard.edu.

Editorial: Internal sensory stress and discomfort or pain (continued from page 3)

a vitamin D deficiency; and itchy eyes (which may lead to eye pressing or poking) may be a result of a calcium deficiency.

ARI’s Upcoming Study on Interoception

The Autism Research Institute is currently orchestrating a multidisciplinary study to develop communication strategies that will allow individuals on the spectrum to indicate areas of discomfort and pain. Experts in sensory processing will provide input regarding various means of expression (or lack of expression); behavioral experts in functional communication will help figure out ways to teach individuals how to express themselves; and physicians will provide input regarding the types of medical conditions associated with interoceptive problems.

We hope that by working collaboratively, we can increase awareness of the sensory and medical issues often associated with autism as well as develop a common language to better communicate within the sensory, medical, and behavioral fields. By understanding how those on the autism spectrum react (or fail to react) to a medical condition typically associated with discomfort or pain, physicians will be better able to diagnose and treat these individuals.

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

ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (\$300,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

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

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

Sponsoring one or two major think tanks a year, involving researchers and experienced clinicians.

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