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Skin cell study provides intriguing clues about ASD

Researchers report that in a subgroup of children with autism, brain cells grow unusually fast and have too few connections between them.

M. C. Marchetto and colleagues collected skin cell samples from children with autism who also had enlarged brains. (Between 20 and 30 percent of children with autism exhibit brain overgrowth.) The researchers reprogrammed the skin cells to produce precursor cells found in the developing brain.

The researchers found that the cells from autistic individuals grew at a faster rate than those from controls, and that these cells activated their genes in a different pattern. Genes related to cell growth were more active in the samples from the group with autism, leading to more cells with less connectivity. This, the researchers say, can lead to an enlarged head and faulty neural networks that cannot properly transmit signals.

Marchetto and colleagues found that the abnormal genes in the samples from individuals with autism belonged to the Wnt signaling pathway. The researchers had previously discovered that mice lacking Wnt genes display symptoms resembling autism, including social anxiety and repetitive behavior.

"Interestingly," the researchers say, "defects in neuronal networks could be rescued by insulin growth factor 1 (IGF-1), a drug that is currently in clinical trials for ASD." The researchers do not yet know whether IGF-1 acts by altering the Wnt pathway.

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"Altered proliferation and networks in neural cells derived from idiopathic autistic individuals," M. C. Marchetto, H. Belinson, Y. Tian, B. C. Freitas, C. Fu, K. C. Vadodaria, P. C. Beltrao-Braga, C. A. Trujillo, A. P. D. Mendes, K. Padmanabhan, Y. Nunez, J. Ou, H. Ghosh, R. Wright, K. J. Brennand, K. Pierce, L. Eichenfield, T. Pramparo, L. T. Eyler, C. C. Barnes, E. Courchesne, D. H. Geschwind, F. H. Gage, A. Wynshaw-Boris, and A. R. Muotri, *Molecular Psychiatry*, July 5, 2016 (online). Address: Anthony Wynshaw-Boris, anthony.wynshaw-boris@case.edu.

—and—

"Scientists uncover common cell signaling pathway awry in some types of autism," *Science Daily*, August 26, 2016.

iPad games help diagnose ASD, offer insight into origins

Simple iPad games may help clinicians diagnose autism in the future, according to a new study.

Currently, the diagnosis of autism tends to focus on social, emotional, and language deficits. However, Anna Anzulewicz and colleagues note that disruption of normal movement patterns "is a cardinal feature of ASD and is becoming increasingly recognized as a likely primary deficit in ASD etiology."

To determine if they could identify children with autism by analyzing their movement patterns, the researchers used iPads, which have touch-sensitive screens and embedded inertial movement sensors, to record the movements of 37 young children with autism and 45 age- and gender-matched neurotypical controls as they played games. All of the children were between three and six years of age. They played two games, one involving a sharing activity and the other involving free-form coloring.

The researchers report that the movement patterns of children with autism "consisted of greater forces at contact and with a different distribution of forces within a gesture." In addition, they say, "gesture kinematics were faster and larger, with more distal use of space." Analysis of the children's motor patterns identified autism with up to 93% accuracy.

Study coauthor Jonathan Delafield-Butt says, "This study is the first step toward a validated instrument. Interestingly, our study goes further in elucidating the origins of autism, because it turns out that movement is the most important differentiator in the gameplay data. In other words, it is not social, emotional, or cognitive aspects of the gameplay that identify autism. Rather, the key difference is in the way children with autism move their hands as they touch, swipe, and gesture with the iPad during the game. This unexpected finding adds new

continued on page 2

Oxytocin may not work correctly in "stress buffer" role in ASD

In children with autism spectrum disorders (ASD), the hormone oxytocin may not protect well against stress, according to a new study.

Oxytocin is currently being tested as a treatment for ASD because it facilitates social behavior. However, Blythe Corbett and colleagues note that it also serves as a "stress buffer," rising when people are exposed to stressors that elevate levels of the hormone cortisol.

To examine the interplay of cortisol and oxytocin in ASD, Corbett and colleagues administered a single low dose of hydrocortisone (pharmaceutical cortisol) or a placebo to 14 children with high-functioning ASD and 11 neurotypical controls in a double-blind, crossover experiment. All of the children were between 8 and 12 years of age.

The researchers report that cortisol and oxytocin levels were comparable in children with ASD and controls at baseline. However, the two groups responded very differently to the cortisol challenge. In the neurotypical group, levels of oxytocin rose after hydrocortisone administration, indicating that it played a stress-buffering role. In the children with ASD, however, oxytocin levels remained unchanged or even decreased in response to the challenge.

The researchers comment, "While oxytocin has been tied to the social ability of children with ASD, the diminished moderating effect of oxytocin may play a contributory role in the heightened stress often observed in children with ASD especially during social interactions. In other words, in addition to [these children] experiencing heightened stress in response to novel and changing situations, it appears that oxytocin does not assist in ameliorating stress once activated."

(See related story on page 4.)

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"Comparing oxytocin and cortisol regulation in a double-blind, placebo-controlled, hydrocortisone challenge pilot study in children with autism and typical development," Blythe A. Corbett, Karen L. Bales, Deanna Swain, Kevin Sanders, Tamara A. R. Weinstein, and Louis J. Muglia, *Journal of Neurodevelopmental Disorders*, Vol. 8, No. 32, 2016 (online). Address: Blythe Corbett, Department of Psychiatry and Behavioral Sciences, Vanderbilt University, PMB 40, 230 Appleton Place, Nashville, TN 37203, blythe.corbett@vanderbilt.edu.

iPad games help diagnose autism, offer insight into its origins

(continued from page 1)

impetus to a growing scientific understanding that movement is fundamentally disrupted in autism, and may underpin the disorder."

Delafield-Butt adds that movement analysis is much simpler than standard techniques used for diagnosing autism. "This is potentially a major breakthrough for early identification of autism, because no stressful and expensive tests by clinicians are needed," he says. "Early detection is important as this can allow parents and children to gain access to a range of services support. This new 'serious game' assessment offers a cheaper, faster, fun way of testing for autism." He notes, however, that more work is needed to confirm the group's findings.

The researchers say an earlier study by a different group also identified autism-specific motor patterns, achieving an accuracy of 96% in identifying individuals with autism. The researchers say the fact that two different studies using different paradigms and technologies achieved similar results is a strong indication that abnormal movements are a key biological marker for autism.

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"Toward the autism motor signature: Gesture patterns during smart tablet gameplay identify children with autism," Anna Anzulewicz, Krzysztof Sobota, and Jonathan T. Delafield-Butt, *Nature Scientific Reports*, August 24, 2016 (online). Address: Jonathan Delafield-Butt, jonathan.delafield-butt@strath.ac.uk.

—and—

"New iPad game could help diagnose autism in children," news release, University of Strathclyde, August 30, 2016.

ARI Survey: Seniors with Autism Spectrum Disorder

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 the online form.

We invite you to complete the survey on quality of life issues associated with senior adults on the autism spectrum. We hope the results from this survey will provide much insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers. We anticipate that this study will also inspire others, as well as better inform the autism community, government agencies, and other welfare and health-related organizations about such quality of life issues.

Once the data from this survey are collected and analyzed, we will send responders a summary report of the findings.

Website: ASDSeniorSurvey.com

Inner ear defect may impair language processing in ASD

Researchers have detected an inner anomaly in children with autism spectrum disorders (ASD) that may impair their ability to recognize speech.

Loisa Bennetto and colleagues enrolled 35 children with high-functioning autism and 42 age-matched neurotypical controls in their study. All participants were boys between 6 and 17 years of age with hearing classified as normal.

The researchers tested the participants using miniature speaker/microphone earplugs that detect tiny sound emissions made by the inner ear's outer hair cells in response to tones or clicks. If the cells are not working correctly, the earplugs fail to detect an emission.

> Bennetto and colleagues found that children with ASD had difficulty responding to sounds in a specific frequency (1-2 kHz) that is important for speech. In addition, they found that the degree of impairment correlated with the severity of ASD symptoms.

The researchers found that children with ASD had impaired responses to sounds in a specific frequency (1-2 kHz) that is important for processing speech. In addition, they found that the degree of impairment correlated with the severity of ASD symptoms.

"Auditory impairment has long been associated with developmental delay and other problems, such as language deficits," Bennetto comments. "While there is no association between hearing problems and autism, difficulty in processing speech may contribute to some of the core symptoms of the disease."

Bennetto and her colleagues say their finding may pave the way for earlier diagnosis of autism and "can inform the development of approaches to correct auditory impairment with hearing aids or other devices that can improve the range of sounds the ear can process."

See related story on page 4.

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"Children with autism spectrum disorder have reduced optoacoustic emissions at the 1 kHz mid-frequency region," Loisa Bennetto, Jessica M. Keith, Paul D. Allen, and Anne E. Luebke, *Autism Research*, July 12, 2016 (epub prior to print publication). Address: Anne E. Luebke, University of Rochester Medical Center, 601 Elmwood Avenue, Box 603, Rochester, NY 14642, anne_luebke@urmc.rochester.edu.

—and—

"Hearing test may identify autism risk," news release, University of Rochester, July 25, 2016.

Immune system molecule may affect social behavior

A new study by researchers at the University of Virginia reports surprising evidence that the immune system directly affects social behavior.

"The brain and the adaptive immune system were thought to be isolated from each other, and any immune activity in the brain was perceived as sign of a pathology," study coauthor Jonathan Kipnis says. "And now, not only are we showing that they are closely interacting, but some of our behavior traits might have evolved because of our immune response to pathogens. It's crazy, but maybe we are just multicellular battlefields for two ancient forces: pathogens and the immune system. Part of our personality may actually be dictated by the immune system."

Last year, the researchers discovered that meningeal vessels directly link the brain with the lymphatic system, disproving the accepted idea that the brain was "immune privileged" and did not have a direct connection to the immune system. Their new study indicates that in mice, one specific immune system molecule—interferon gamma—plays a crucial role in social behavior.

Normally, the immune system produces interferon gamma in response to infections. When the researchers blocked the molecule in mice, regions of the brain became hyperactive and the mice became less social.

The researchers note that social behavior is critical for the survival of a species, but social behavior also exposes the members of the species to infection. "So you need to be social," lead author Anthony Filiano says, "but [when you are] you have a higher chance of spreading pathogens. The idea is that interferon gamma, in evolution, has been used as a more efficient way to boost social behavior while boosting an anti-pathogen response."

The researchers say that anomalies of the immune system may be one cause of the social deficits in disorders such as autism and schizophrenia. While the researchers stress that interferon gamma is likely to be only one factor in these disorders, Kipnis says that their finding "has potentially very important clinical implications."

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"Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour," Anthony J. Filiano, Yang Xu, Nicholas J. Tustison, Rachel L. Marsh, Wendy Baker, Igor Smirnov, Christopher C. Overall, Sachin P. Gadani, Stephen D. Turner, Zhiping Weng, Sayeda Najamussahar Peerzade, Hao Chen, Kevin S. Lee, Michael M. Scott, Mark P. Beenhakker, Vladimir Litvak, and Jonathan Kipnis, *Nature*, July 13, 2016 (online). Address: Jonathan Kipnis, Center for Brain Immunology and Glia, School of Medicine, University of Virginia, Charlottesville, Virginia 22908.

—and—

"Shocking new role found for the immune system: controlling social interactions," news release, UVA School of Medicine, July 13, 2016.

EDITORIAL: Stephen M. Edelson, Ph.D.

Revisiting auditory integration training—and an important new research finding

Since the 1970s, the Autism Research Institute (ARI) has shown interest in an auditory-based intervention referred to as Berard auditory integration training (AIT).

Over our near-50-year history, parents would sometimes contact ARI to find out how to treat their children's severe hearing sensitivity. Such painful hearing can be associated with rather severe behavioral issues, such as head and ear banging as well as violent tantrums.

After receiving numerous reports from parents worldwide, Dr. Bernard Rimland started recommending that they contact Dr. Guy Berard, a physician practicing in Annecy, France. Dr. Rimland even traveled to Annecy to meet Dr. Berard and to learn more about this intervention.

Briefly, AIT involves listening to filtered music for two half-hour sessions a day for 10 consecutive days. The most common improvements reported by parents include a reduction in sound sensitivity, improvement in attention and listening, and a decrease in behavioral issues.

Initially, AIT was simply referred to as "auditory training." But because there already was a device called an auditory trainer, which is similar to a hearing aid, Dr. Rimland and I came up with the term "auditory integration training." The term is still used today.

Annabel Stehli, a mother who brought her daughter to Annecy for AIT, was so impressed with her daughter's dramatic improvement that she wrote a popular book titled *The Sound of a Miracle*. *Reader's Digest* published a summary of the book, and *Women's Day* and the television show *20/20* also covered stories on AIT. At one time *60 Minutes* planned to produce an exposé on AIT; but after meeting Dr. Rimland and then spending a week with me, they decided not to air their story.

Prior to the book's publication, Dr. Rimland anticipated much media attention would be focused on AIT. He contacted Dr. Berard and convinced him to help us conduct a series of research studies. Dr. Berard flew to San Diego, and spent two weeks discussing research with us and teaching us the method. He also gave us one of his AIT devices.

During the 1990s, Dr. Rimland and I conducted three double-blind controlled studies on AIT. *All three documented a reduction in behavioral problems.* In one study, we found a dramatic improvement in a specific brain wave, referred to as the P3 (also known as P300), which is associated with auditory processing, and possibly retrieval from memory of auditory information.

Around the late 1990s, AIT became a controversial intervention. Many people began offering AIT who were poorly trained, charged a great deal of money, and made unsubstantiated claims. In addition, facilitated communication (FC) was popular at the same time; and many people who were using FC were also trying AIT. As a result, the two methods were grouped together and labeled as "questionable."

In addition, five less-than-optimal studies were published showing no improvement as a result of AIT. Given that these studies are still cited as "proof" that AIT is ineffective, I thought it is important, for the record, to briefly describe their shortcomings

Bettison (1996). This study evaluated AIT using a beta version of a new AIT device. The device processed the sound output differently than the one developed by Dr. Berard, and the device was still going through rather extensive modifications.

Gillberg et al. (1997). This study involved only nine participants, and the authors concluded that no benefits resulted from AIT. A reanalysis of their raw data by Dr. Rimland and me revealed a significant reduction on one of their measures. Later, Gillberg et al. (1998) admitted that "... a moderate reduction in sensory problems may have occurred."

Mudford et al. (2000). These researchers employed a crossover experimental design which is typically used when the behaviors under investigation return to baseline after the intervention is removed. This design is inappropriate for studying AIT because research conducted by ARI found that improvements from AIT may last *at least* nine months. Furthermore, Anabel Stehli's daughter continued to show benefits from her one AIT session 25 years later.

It is important to mention that the study's authors could not explain why they found significant decreases in ear covering and hyperactivity in the control phase of their study. Most likely, these improvements could easily be explained by examining the behavior of participants who received AIT during the first phase of the crossover and then the placebo in the second phase. That is, the benefits of AIT almost certainly continued to occur and spilled over into the control phase. The authors declined to reanalyze the data because they stated this would increase the likelihood of statistical error when conducting an additional analysis of the data. However, when conducting research, scientists are expected to examine their data in ways that best describe the phenomenon under investigation and not to ignore plausible explanations of the results, even if this may mean recanting their original conclusions.

Yencer (1998). The follow-up assessment in this study was administered four weeks after the last AIT listening session. Research has shown that improvement is often first observable somewhere between six and eight weeks following the final AIT session.

Zollweg et al. (1997). In this study, the volume level was played as high as 122 decibels (dB), which is much higher than OSHA's daily permissible exposure levels and has the potential to cause hearing damage. The recommended dB level for AIT is 80. In addition, 25% of the device's filters were set incorrectly. And finally, only one-third of the participants had autism, and there is no indication in the literature that AIT may be beneficial for those with other developmental disabilities.

Due to these poorly conducted studies and AIT's association with FC in the 1990s, interest in AIT within the research and autism communities has diminished over the last 15 years.

(Note: Numerous other studies, mostly supporting the benefits of AIT, have also been published in journals and presented at conferences. However, they lack scientific rigor, such as not including a control group for comparison and relying on the ratings of "non-blinded" evaluators.)

An important new study on the efficacy of AIT was recently published by Estate Sokhadze, Manuel Casanova, Allan Tasman, and Sally Brockett in *Applied Psychophysiology and Biofeedback* (online, 29 August 2016). Drs. Casanova and Sokhadze run one of the top psychophysiological autism research laboratories in the world, and Dr. Casanova is a well-published and highly regarded neurologist.

These researchers measured participants' evoked potentials prior to, during, and after receiving AIT. Evoked potentials are brain waves that occur soon after the presentation of a stimulus. In this study, the stimulus was auditory-based.

The results revealed improvements in both early and late processing of auditory information. In addition, the researchers detected a decrease in hyperactivity, irritability, and repetitive behaviors. These results replicate the findings published by ARI in the 1990s regarding the effects of AIT on auditory processing (i.e., the P3) and behavior. Drs. Sokhadze and Casanova plan to conduct a more elaborate follow-up study.

We all know that the field of autism research and treatment has been rife with controversy. Many approaches—from Bruno Bettelheim's parent-blaming psychoanalysis in the 1960s to FC, which actually led to the

continued on page 7

Research Updates

Vitamin D may protect against diabetes caused by antipsychotic drugs

Many individuals with autism take atypical antipsychotic medications, which are linked to a greatly increased risk for diabetes. A new study indicates that a simple intervention—supplementation with vitamin D—can reduce this risk.

Reviewing information from the U.S. Food and Drug Administration's Adverse Event Reporting system, Takuya Nagashima and colleagues noted that patients who had coincidentally been prescribed vitamin D while taking the antipsychotic drug quetiapine were less likely to develop elevated blood glucose levels. The researchers confirmed this effect in mice, finding that those administered vitamin D in conjunction with quetiapine had significantly lower blood sugar than those receiving quetiapine alone.

"Interestingly," Dr, Nagashima says, "vitamin D on its own doesn't lower diabetes risk, but it certainly defends against the insulin-lowering effects of quetiapine." Through further research, his team discovered that it does this by inhibiting quetiapine-induced downregulation of a gene called Pik3r1, which plays a critical role in regulating insulin.

"Based on the current results," the researchers say, "we propose a novel vitamin D/antipsychotic combination pharmacotherapy in which vitamin D can efficaciously safeguard against antipsychotic-induced hyperglycemia accompanied by insulin resistance."

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"Prevention of antipsychotic-induced hyperglycaemia by vitamin D: a data mining prediction followed by experimental exploration of the molecular mechanism," Takuya Nagashima, Hisashi Shirakawa, Takayuki Nakagawa, and Shuji Kaneko, *Nature Scientific Reports*, May 20, 2016 (online). Address: Shuji Kaneko, skaneko@pharm.kyoto-u.ac.jp.

—and—

"Unusual combo reduces health risk from atypical antipsychotic," news release, Kyoto University, June 2, 2016.

Voice recognition impaired in ASD

Individuals with high-functioning autism (HFA) have difficulty processing voices, a new study from Germany indicates.

The study, conducted by Stefanie Schelinski and colleagues, involved 16 individuals with HFA and 16 controls matched for gender, age, handedness, and IQ. The researchers evaluated participants' performance on a variety of tests:

- A voice discrimination test, in which participants listened to two sentences and had to determine whether they were spoken by the same person or not.
- A voice-face learning test, in which participants heard the voices of three male and three female speakers, with each voice paired with a face, and then had to match the faces to the voices; and two similar experiments in which voices were paired with names or colors.
- A famous voice recognition test, in which participants listened to the voices of famous and non-famous people and had to categorize each voice as being familiar or not.
- Acoustic processing tests to measure participants' ability to discriminate vocal pitch and timbre.
- Tests to evaluate participants' musical pitch discrimination and musical instrument recognition.
- A test to measure participants' ability to recognize faces.

The researchers report that participants with HFA had more difficulty than controls in determining whether two consecutive sentences were spoken by the same or different speakers. In addition, they had more difficulty learning unfamiliar voices. This was true whether they learned the voices together with a face, a name, or a color. However, the HFA group had no trouble recognizing famous voices.

The researchers also found that participants with HFA had difficulty in discriminating vocal pitch (the highness or lowness of a tone) but not vocal timbre (sound characteristics independent of pitch or loudness). HFA participants and controls performed similarly on the musical pitch and musical instrument recognition tests. In the HFA group, difficulties in recognizing unfamiliar voices were associated with difficulties in recognizing unfamiliar faces.

Schelinski and colleagues conclude, "Lifelong perceptual impairments with vocal information might significantly exacerbate difficulties with social interaction—a core feature of ASD." A dual impairment in voice and face recognition may be particularly limiting, they add, since individuals would be unable to use one skill to compensate for impairments in the other.

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"Voice identity processing in autism spectrum disorder," Stefanie Schelinski, Claudia Roswandowitz, and Katharina von Kriegstein, *Autism Research*, July 12, 2016 (epub prior to print publication). Address: Stefanie Schelinski, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstraße 1a, 04103 Leipzig, Germany, schelinski@cbs.mpg.de.

Long-term oxytocin use may damage DNA

While research indicates that administering the hormone oxytocin to individuals with autism may promote social behavior, a new study raises concerns about its safety.

Daniela Leffa and colleagues injected rats with three different doses of oxytocin or a placebo once a day for either 21 or 56 days. Then, using a technique called a comet assay, they assessed the status of the rats' hippocampal DNA. The researchers detected significantly increased numbers of cells with DNA damage after 21 days, and said that DNA damage intensity was "significantly increased after both treatment lengths at most of the doses."

Leffa and colleagues say their findings indicate that additional clinical and preclinical studies evaluating the safety of long-term oxytocin administration are necessary.

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"DNA damage after chronic oxytocin administration in rats: a safety yellow light?" Daniela D. Leffa, Francine Daumann, Adriani P. Damiani, Arlindo C. Afonso, Maria A. Santos, Thayara H. Pedro, Renan P. Souza, and Vanessa M. Andrade, *Metabolic Brain Disease*, August 2016 (online). Address: Daniela D. Leffa, Laboratório de Biologia Celular e Molecular, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense (UNESC), Avenida Universitaria, 1105 Bloco S, Criciuma, SC 88806-100, Brazil, daniela_leffa@hotmail.com.

Research Updates

Pilot study: no link detected between mycotoxins, ASD

Exposure to mycotoxins, which are environmental contaminants produced by fungi, can cause developmental and neurological problems. However, a recent pilot study found no association between mycotoxin exposure and autism spectrum disorders (ASD).

Jennifer Duringer and colleagues compared 25 individuals with ASD (ranging in age from 5 to 20 years) to 29 controls, screening the participants for 87 urinary mycotoxins using mass spectrometry. In all, they detected four mycotoxins: zearalenone, zearalenone-4-glucoside, 3-acetyldeoxynivalenol, and altenuene. Nine study participants (17%) tested positive for one mycotoxin. "Each compound," the researchers say, "was… generally evenly distributed between both the ASD and control groups." This finding held true when they adjusted for several variables.

While Duringer and her colleagues detected no association between mycotoxin exposure and ASD, they note that they measured only current mycotoxin levels. "Urinary sampling across multiple time points in the mother and children in the earlier years would provide a more thorough evaluation of mycotoxin exposure and possible association with ASD incidence," they say.

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"No association between mycotoxin exposure and autism: A pilot case-control study in school-aged children," Jennifer Duringer, Eric Fombonne, and Morrie Craig, *Toxins*, July 20, 2016 (free online). Address: Eric Fombonne, Department of Psychiatry, Institute for Development & Disability, Oregon Health & Science University, 840 SW Gaines Street, Portland, OR 97239, fombonne@ohsu.edu.

Induced labor does not appear to raise ASD risk, large-scale study shows

Inducing labor does not appear to raise the risk of autism in children, according to a new study.

Anna Sara Oberg and colleagues reviewed data on all live births in Sweden between 1992 and 2005. The researchers followed more than one million of these births through 2013 to determine which children received neuropsychiatric diagnoses. In addition, they analyzed records for the children's siblings and maternal first cousins and evaluated factors pertaining to the mothers' health.

In their initial evaluation of unrelated individuals, the researchers detected an association between induced labor and autism spectrum disorders (ASD), similar to an association detected in a 2013 study. However, when they compared siblings discordant for induction (one sibling having experienced induced labor, while the other did not), the association disappeared.

The researchers conclude, "Our findings suggest that concern for ASD should not factor into the clinical decision about whether to induce labor."

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"Association of labor induction with offspring risk of autism spectrum disorders," Anna Sara Oberg, Brian M. D'Onofrio, Martin E. Rickert, Sonia Hernandez-Diaz, Jeffrey L. Ecker, Catarina Almqvist, Henrik Larsson, Paul Lichtenstein, and Brian T. Bateman, *JAMA Pediatrics*, July 25, 2016 (online). Address: Anna Sara Obert, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts 02115.

—and—

"Study finds induced labor not associated with risk for autism spectrum disorders," news release, Harvard T. H. Chan School of Public Health, July 25, 2016.

Folic acid associated with better response to structured teaching

Children with autism spectrum disorders (ASD) who took supplemental folic acid while participating in a TEACCH-style structured educational program showed greater improvement than children who did not take the nutrient, a study from China reports.

Caihong Sun and colleagues assigned 44 children to the folic acid group and 22 to a control group. Children in the intervention group took 400 micrograms of folic acid twice a day. The children in both groups participated in three months of structured education based on the TEACCH model.

Before and after the study, the researchers assessed the children using the Autism Treatment Evaluation Checklist (ATEC), the Psychoeducational Profile (PEP-3), the Autism Behavior Checklist (ABC), and the Childhood Autism Rating Scale (CARS). They also measured folic acid levels, homocysteine levels, and glutathione metabolism in 29 of the folic acid-treated children and 29 neurotypical controls.

The researchers report that folic acid intervention was associated with greater improvements in sociability, verbal and preverbal cognitive ability, receptive language, affective expression, and communication on the ATEC and PEP-3. In addition, supplementation increased folic acid levels, which were low at baseline, and reduced levels of homocysteine, which were high initially. (High homocysteine levels can be destructive to cells and cause abnormal DNA methylation.) Supplementation also resulted in normalized glutathione metabolism, which is crucial for protecting against oxidative damage to cells.

The researchers conclude that some children with ASD "could benefit from this simple and safe nutritional supplementation."

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"Efficacy of folic acid supplementation in autistic children participating in structured teaching: an open-label trial," Caihong Sun, Mingyang Zou, Dong Zhao, Wei Xia, and Lijie Wu, *Nutrients*, June 7, 2016 (epub prior to print publication). Address: Wei Xia, xiawei1023@126.com.

Individuals with ASD react differently to human, robot faces

Children and adults with autism spectrum disorders (ASD) process human faces, but not robot faces, in a different way than neurotypical controls, according to a new study.

Corinne Jung and colleagues enrolled eight males with ASD and 12 neurotypical male controls in their study. Participants ranged in age from 7 to 36 years, and participants with ASD who were 22 years of age or younger were matched for age with at least one neurotypical control. The researchers used functional near-infrared spectroscopy (fNIRS) to analyze participants' reactions to human and robot faces.

Jung and her team say, "As predicted, the neurotypical group showed right hemisphere lateralization for the human faces, but the ASD group did not. Remarkably, however, brain activation patterns for the ASD group did not differ from the neurotypical group for the robot faces."

The new findings are consistent with studies showing that individuals with ASD often respond better to robots than to humans. "One possible explanation," the researchers say, "is that individuals with ASD exhibit more lateralized activity for objects and are processing robots more as objects, rather than as people."

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"Atypical asymmetry for processing human and robot faces in autism revealed by fNIRS," Corinne E. Jung, Lars Strother, David J. Feil-Seifer, and Jeffrey J. Hutsler, *PLOS ONE*, July 7, 2016 (online). Address: Corrine E. Jung, Department of Psychology, Program in Neuroscience, University of Nevada Reno, Reno, Nevada 89557, corinnejung@gmail.com.

Wheat sensitivity in people without celiac disease linked to leaky gut, systemic inflammation

Many individuals experience symptoms including bloating, abdominal pain, diarrhea, anxiety, and cognitive problems when they eat foods containing gluten—a condition called non-celiac gluten or wheat sensitivity (NCWS). A new study indicates that NCWS, which affects many people with autism, stems from a "leaky gut" that causes body-wide inflammation.

Peter Green, a co-author of the study headed by Melanie Uhde, says, "Our study shows that the symptoms reported by individuals with this condition [NCWS] are not imagined, as some people have suggested. It demonstrates that there is a biological basis for these symptoms in a significant number of these patients."

In their study, Uhde and her colleagues evaluated 80 people with NCWS, 40 individuals with celiac disease (an autoimmune disease in which gluten exposure causes severe intestinal damage), and 40 healthy controls. They found that people with celiac disease, while they had extensive intestinal damage, did not have elevated blood markers of systemic immune system activation. In contrast, the NCWS group exhibited a marker of intestinal cell damage that correlated with blood markers of acute systemic immune activation.

The researchers say their results indicate that system-wide immune activation in NCWS occurs because microbial and dietary components escape through a weakened intestinal barrier and enter the bloodstream. This, they say, "would be consistent with the generally rapid onset of the reported symptoms in people with NCWS."

The researchers also found that individuals with NCWS who ate a diet free of wheat and related grains for six months normalized their levels of immune activation and intestinal cell damage markers. As a result, these individuals experienced fewer intestinal and non-intestinal symptoms, although the magnitude of change in biological markers did not correlate significantly with the magnitude of change in symptom severity.

Study coauthor Armin Alaedini says, "The data suggest that in the future, we may be able to use a combination of biomarkers to identify patients with NCWS and to monitor their response to treatment."

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"Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease," Melanie Uhde, Mary Ajamian, Giacomo Caio, Roberto De Giorgio, Alyssa Indart, Peter H. Green, Elizabeth C. Verna, Umberto Volta, and Armin Alaedini, *Gut*, July 25, 2016 (online). Address: Armin Alaedini, Department of Medicine, Columbia University Medical Center, 1130 Saint Nicholas Ave., Room 937, New York, NY 10032, aa819@columbia.edu.

—and—

"Columbia researchers find biological explanation for wheat sensitivity," news release, Columbia University Medical Center, July 26, 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/

Prenatal exposure to acetaminophen may raise autism risk

Children exposed to acetaminophen (Tylenol) before birth may have an increased risk for autism spectrum disorders (ASD), according to a new study.

Claudia Avella-Garcia and colleagues recruited more than 2,600 mother-child pairs for their study during the mothers' pregnancies. They evaluated 88 percent of the children at one year of age, and nearly 80 percent at five years of age.

The researchers determined whether mothers took acetaminophen during pregnancy and, if so, whether they took it sporadically or regularly. Of the children in the study, more than 40 percent were exposed to acetaminophen at some time during the first 32 weeks of pregnancy.

Avella-Garcia and her colleagues found that children exposed prenatally to acetaminophen were more likely to exhibit hyperactivity and impulsive behavior at five years of age. In addition, boys persistently exposed to acetaminophen exhibited more symptoms of autism than unexposed boys.

Study coauthor Jordi Julvez says there are several possible explanations for the team's findings. "First of all," he says, "[acetaminophen] relieves pain by acting on cannabinoid receptors in the brain. Since these receptors normally help determine how neurons mature and connect with one another, [the drug] could alter these important processes. It can also affect the development of the immune system, or be directly toxic to some fetuses that may not have the same capacity as an adult to metabolize this drug, or by creating oxidative stress."

The researchers say that the correlation between acetaminophen use and ASDs in boys but not girls may be linked to sex differences in the metabolism of the drug. "Animal studies have suggested that male mice undergo greater toxicity than female mice after being administered a similar dose of acetaminophen," they say.

The researchers' results are consistent with those of an earlier study which reported that mothers who take acetaminophen frequently during pregnancy may be more likely to have children with language and behavior problems. In that study, Ragnhild Eek Brandlistuen and colleagues analyzed data on more than 48,000 women and found that children exposed to prenatal acetaminophen for more than 28 days had poorer gross motor and communication skills. In addition, they exhibited more behavior problems and had higher activity levels.

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"Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms," Claudia B. Avella-Garcia, Jordi Julvez, Joan Fortuny, Cristina Rebordosa, Raquel García-Esteban, Isolina Riaño Galán, Adonina Tardón, Clara L. Rodríguez-Bernal, Carmen Iñiguez, Ainara Andiarena, Loreto Santa-Marina, and Jordi Sunyer, *International Journal of Epidemiology*, June 28, 2016 (epub prior to print publication). Address: Jordi Julvez, Centre for Research in Environmental Epidemiology-PRBB, C. Doctor Aiguader 88, 08003 Barcelona, Spain, jjulvez@creal.cat.

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"Prenatal exposure to paracetamol may increase autism spectrum symptoms," news release, Oxford University Press, July 1, 2016.

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"Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study," Ragnhild Eek Brandlistuen, Elvind Ystrom, Irena Nulman, Gideon Koren, and Hedvig Nordeng, *International Journal of Epidemiology*, October 24, 2013 (online). Address: Ragnhild Eek Brandlistuen, Department of Pharmacy, School of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, 0316 Oslo, Norway, r.e.brandlistuen@farmasi.uio.no.

—and—

"Too much Tylenol in pregnancy could affect child's development, study finds," Kathryn Doyle, Reuters, October 24, 2013.

Large-scale study suggests link between PCBs, autism

Organochlorine chemicals banned decades ago may still be increasing the risk of autism, according to new research.

Kristen Lyall and colleagues conducted a population-based case-control study involving 545 children with autism spectrum disorders (ASD), 181 children with intellectual disability (ID), and 418 controls from the general Southern California population. The researchers used blood samples taken during the mothers' second trimester of pregnancy to analyze levels of exposure to two different classes of organochlorine chemicals: polychlorinated biphenyls (PCBs) and organochlorine pesticides. While production of organochlorine chemicals was banned in the U.S. in 1977, they can remain in the environment and can cross the placenta during pregnancy.

The researchers say that children exposed prenatally to the highest levels of two PCBs in particular—PCB 138/158 and PCB 153—were between 79 and 82 percent more likely to have an ASD diagnosis than those exposed to the lowest levels. Children exposed to the highest levels of two other compounds, PCB 170 and PCB 180, were approximately 50 percent more likely to be diagnosed with ASD compared to children with the lowest prenatal exposure to these PCBs. None of the pesticides were associated with a higher rate of autism diagnosis.

In children with ID but not ASD, the highest exposure to PCBs doubled the likelihood of a diagnosis compared to the lowest exposure.

The researchers note that their study is very large and "is one of the few studies to date examining prenatal exposure to organochlorine chemicals, with exposures assessed from biospecimens collected during pregnancy, in relation to ASD and ID diagnoses." Their findings, they say, "add to potential neurodevelopmental concerns surrounding these chemicals."

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"Polychlorinated biphenyl and organochlorine pesticide concentrations in maternal mid-pregnancy serum samples: association with autism spectrum disorder and intellectual disability," Kristen Lyall, Lisa A. Croen, Andreas Sjödin, Cathleen K. Yoshida, Ousseny Zerbo, Martin Kharrazi, and Gayle C. Windham, *Environmental Health Perspectives*, August 23, 2016 (online). Address: Kristen Lyall, AJ Drexel Autism Institute, Suite 560, 3200 Market Street, Philadelphia, PA, 19104, kld98@drexel.edu.

—and—

"Chemicals banned decades ago linked to increased autism risk today," news release, Drexel University, August 23, 2016.

Correcting metabolic abnormalities can ease depression

A new study reports that depression—a common problem for individuals with Asperger syndrome or high-functioning autism—can often be addressed effectively by correcting metabolic deficiencies.

Lisa Pan and colleagues performed plasma, urine, and cerebrospinal fluid (CSF) profiles on 33 teens and young adults with treatment-resistant depression and 16 controls. They found that 64 percent of the participants who suffered from depression had a deficiency in neurotransmitter metabolism, compared with none of the controls. The most common issue was cerebral folate deficiency (normal serum folate levels and low CSF levels of 5-methyltetrahydrofolate), detected in 12 individuals with depression.

The researchers report that for nearly all individuals with metabolic deficiencies, correcting these deficiencies reduced symptoms of depression—in some cases leading to complete remission. Moreover, the longer treatment lasted, the more the individuals' symptoms improved.

Pan says, "It's really exciting that we now have another avenue to pursue for patients for whom our currently available treatments have failed. This is a potentially transformative finding for certain groups of people with depression."

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"Nonmetabolic disorders: Potentially treatable abnormalities in patients with treatment-refractory depression and suicidal behavior," Lisa A. Pan, Petra Martin, Thomas Zimmer, Anna Maria Segreti, Sivan Kassiff, Brian W. McKain, Cynthia A. Baca, Manivel Rengasamy, Keith Hyland, Nicolette Walano, Robert Steinfeld, Marion Hughes, Steven K. Dobrowolski, Michele Pasquino, Rasim Diler, James Perel, David N. Finegold, David G. Peters, Robert K. Naviaux, David A. Brent, and Jerry Vockley, *American Journal of Psychiatry*, August 9, 2016 (online). Address: Lisa A. Pan, thomasla@upmc.edu.

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"Correcting metabolic deficiencies may improve depression symptoms," news release, University of Pittsburgh Schools of the Health Sciences, August 9, 2016.

TOLL-FREE CALLING CENTER:

The Autism Research Institute maintains a toll-free calling center:

866-366-3361

If you are a parent struggling to find help, our volunteers can help you locate the information and resources you need.

Editorial: Revisiting Auditory Integration Training

(continued from page 1)

jailing of innocent parents—have actively done harm, while other approaches that seemed promising have not held up under careful examination. However, many other approaches that initially were greeted with skepticism, such as applied behavioral analysis and biologically-oriented therapies, have changed the lives of individuals with ASD profoundly for the better.

I urge the research community to re-evaluate past research on AIT and consider studying this intervention in an unbiased, truly scientific manner. With more research, AIT may someday become an accepted, evidence-based intervention.

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References to the studies cited along with a description of other studies evaluating AIT can be found at: www.autism.com/ait.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

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Nov 17:
*Johnson Center Research Update

Dec 2:
*Patient and Family Centered Care: What You Need to Know

Dec 7:
Ask the Nutritionist—Live Q&A

Dec 15:
*Essential Oils—Separating Fact from Fiction

These webinars are offered at 1 p.m. Eastern time (U.S.). Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links.

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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 informational websites on autism in the world.

•

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

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