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

Ancient mitochondrial DNA variants may affect autism risk, lead to metabolic therapies

Variations in mitochondrial DNA (mtDNA) originating during ancient times may play a significant role in autism spectrum disorders (ASD), a new study reports.

Mitochondria are the "power plants" of cells. They contain their own DNA, which codes for genes controlling cellular energy production, and these genes exchange signals with nuclear DNA.

Douglas Wallace discovered in 1980 that human mtDNA (unlike nuclear DNA) is inherited only through the mother. Since then, he and his team have reconstructed patterns of worldwide human migrations over hundreds of millennia, identifying haplogroups—groups defined by differences in their mtDNA—that represent major branch points in evolution.

In the current study, Wallace and his team, including lead researcher Dimitra Chalkia, analyzed the mtDNA of 1,624 individuals with ASD and 2,417 of their parents and siblings. Participants came from 933 families participating in the Autism Genetic Resource Exchange.

The researchers found that participants in haplogroups designated as I, J, K, X, T, and U—collectively representing approximately 55 percent of the total European population—had an elevated risk of ASD compared to the most common European haplogroup, HHV. Asian and Native American haplogroups A and M also had an increased ASD risk.

Wallace says these findings demonstrate that "a person's vulnerability to ASD varies according to their ancient mitochondrial lineage." He notes that mtDNA haplogroups originated in different areas and adapted to local environments. Later changes, such as migration or dietary changes, could create a mismatch between a mtDNA haplotype and an individual's environment, resulting in a greater risk for certain diseases.

Wallace's team also notes that mtDNA's role in energy production is crucial, and that the brain is particularly vulnerable to even mild energy deficiencies because of its high mitochondrial energy demand. Studies by the team have shown that mitochondrial dysfunction can alter the balance between inhibition and excitation in the brain, a phenomenon seen in autism and other neuropsychiatric disorders (see related article on page 1).

Wallace comments, "There may be a bioenergetic threshold," theorizing that individuals vulnerable to ASD because of their mtDNA variants may be pushed over this threshold by environmental insults or the presence of other gene variants linked to ASD.

He also notes that mtDNA variants may help to explain why more males than females develop ASD. Leber hereditary optic neuropathy (LHON), a condition known to result from mtDNA mutations, also affects more males than females. Wallace speculates that estrogen may increase beneficial antioxidant activity, helping to protect females from mtDNA-associated diseases.

Wallace concludes that the findings of the study may help lead to therapeutic approaches. "There is increasing interest in developing metabolic treatments for known mtDNA diseases such as LHON," he says. "If ASD has a similar etiology, then these same therapeutic approaches may prove beneficial for ASD."

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"Association between mitochondrial DNA haplogroup variation and autism spectrum disorders," Dimitra Chalkia, Larry N. Singh, Jeremy Leipzig, Maria Lvova, Olga Derbeneva, Anita Lakatos, Dexter Hadley, Hakon Hakonarson, and Douglas C. Wallace, *JAMA Psychiatry*, August 23, 2017 (online). Address: Douglas Wallace, wallaced1@email.chop.edu.

—and—

"Altered mitochondria associated with increased autism risk," news release, Children's Hospital of Philadelphia, August 23, 2017.

Experiment points to excitatory-inhibitory imbalance in ASD

A new study offers strong evidence that autism spectrum disorders (ASD) involve an imbalance in signaling by excitatory and inhibitory neurons in one region of the brain.

In 2011, Karl Deisseroth and colleagues found that activating excitatory neurons in the prefrontal cortex caused mice to lose interest in socializing with other mice, indicating that over-excitation in this brain region can contribute to social impairments. In the new study, Deisseroth and his team—including lead author Aslihan Selimbeyoglu—explored the effects of altering the excitatory-inhibitory balance in the brains of mice with a mutation corresponding to a mutation associated with ASD in humans.

In this study, the researchers used mice lacking both copies of CNTNAP2. These mice are less sociable and more hyperactive than typical mice. In addition, like humans with the equivalent mutation, they have a shortage of a type of inhibitory neurons called parvalbumin neurons.

Deisseroth and his team used a technique called optogenetics to insert genes for two types of light-sensitive proteins, or opsins, into two sets of neurons in the medial prefrontal cortex of the mice. Using an implanted optical fiber that delivered a pulse of blue light, the researchers were able to alter the responses of the neurons. One type of opsin caused inhibitory parvalbumin neurons to become more active, while the other type made excitatory pyramidal neurons less active. In both interventions, the researchers found that the mice became significantly more sociable and less hyperactive.

The researchers, who have previously used optogenetic interventions to reduce anxiety, depression, and obsessive-compulsive symptoms in mice, conclude, "This study highlights the potential for modulating neural circuits in the brain as a strategy for treating autism."

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"Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice," Aslihan Selimbeyoglu, Christina K. Kim, Masatoshi Inoue, Soo Yeun Lee, Alice S. O. Hong, Isaac Kauvar, Charu Ramakrishnan, Lief E. Fenno, Thomas J. Davidson, Matthew Wright, and Karl Deisseroth, *Science Translational Medicine*, Vol. 9, Issue 401, August 2, 2017. Address: Karl Deisseroth, deissero@stanford.edu.

—and—

"Autism may reflect excitation-inhibition imbalance in brain," Bruce Goldman, Stanford University, August 2, 2017.

—and—

"Scientists use light to turn off autism symptoms in mice," Nicholette Zeliadt, *Scientific American*, August 3, 2017.

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Single brain scan predicts ASD with high accuracy

A single brain scan can identify autism spectrum disorders (ASD) in six-month-old children with a remarkable degree of accuracy, according to a new study.

The study, by Robert Emerson and colleagues, involved 59 six-month-olds at high risk for ASD because their older siblings had the condition. The researchers used a type of scan called functional connectivity magnetic resonance imaging (fcMRI) to analyze how different brain areas connected with each other.

Focusing on brain connections linked to features of autism—including language, social behavior, and repetitive behaviors—the researchers identified 974 connections in the infants' brains that could be used to predict an ASD diagnosis by 24 months of age. Using a "machine learning" program to refine their results, they predicted that nine of the infants would develop ASD.

Emerson comments, "When the classifier determined a child had autism, it was always right. But it missed two children. They developed autism but the computer program did not predict it correctly, according to the data we obtained at six month of age."

The researchers say, "These findings have clinical implications for early risk assessment and the feasibility of developing early preventive interventions for ASD."

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"Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age," R. W. Emerson, C. Adams, T. Nishino, H. C. Hazlett, J. J. Wolff, L. Zwaigenbaum, J. N. Constantino, M. D. Shen, M. R. Swanson, J. T. Elison, S. Kandala, A. M. Estes, K. N. Botteron, L. Collins, S. R. Dager, A. C. Evans, G. Gerig, H. Gu, R. C. McKinstry, S. Paterson, R. T. Schultz, M. Styner, B. L. Schlaggar, J. R. Pruett, Jr., and J. Piven, *Science Translational Medicine*, Vol. 9, No. 393, June 7, 2017. Address: Robert Emerson, remerson@med.unc.edu.

—and—

"Special brain scans may predict autism in high-risk babies," MedlinePlus, June 7, 2017.

—and—

"A single brain scan has been used to accurately predict autism at just 6 months old," Mike McRae, Science Alert, June 8, 2017.

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Low brain pH may play a role in autism, other conditions

Autism spectrum disorders (ASD) and psychiatric conditions such as schizophrenia and bipolar disorder may involve an acid/alkaline imbalance in the brain, according to a new study.

Hideo Hagihara and colleagues say that low brain pH (indicating greater acidity) has been reported in postmortem studies of individuals with bipolar disorder, schizophrenia, and ASD. However, they say, this was believed to be an artifact caused by secondary factors such as antipsychotic use.

To determine whether low brain pH might instead be a primary feature of a number of psychiatric disorders, the researchers first conducted a meta-analysis of datasets from 10 postmortem studies of individuals with bipolar disorder or schizophrenia. They found that both groups of patients had low brain pH levels, even when the researchers factored in variables such as age at death, postmortem interval, and history of antipsychotic use.

Next, the researchers investigated brain pH levels using five mouse models of psychiatric disorders including schizophrenia, bipolar disorder, and ASD. In all five models, brain pH was significantly lower than in controls. In addition, the researchers detected elevated levels of lactate in the brains of the mice and found that the higher the lactate was, the lower the pH level was. They note that the increase in lactate may explain the decreased brain pH levels, because lactate acts as a strong acid.

The researchers comment that "brain acidosis influences a number of brain functions, such as anxiety, mood, and cognition." In addition, they say, acidosis may affect the structure and function of several types of brain cells including GABAergic neurons and oligodendrocytes. "Alterations in these types of cells have been well-documented in the brains of patients with schizophrenia, bipolar disorder, and ASD," they say, "and may underlie some of the cognitive deficits associated with these disorders."

The researchers say that based on the assumption that low brain pH is an artifact, researchers have typically attempted to match postmortem samples based on tissue pH. In the process, they say, they may have obscured pathological features associated with changes in pH, such as neuronal hyper-excitation and inflammation.

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"Decreased brain pH as a shared endophenotype of psychiatric disorders," Hideo Hagihara, Vibeke S. Catts, Yuta Katayama, Hirotaka Shoji, Tsuyoshi Takagi, Freesia L. Huang, Akito Nakao, Yasuo Mori, Kuo-Ping Huang, Shunsuke Ishii, Isabella A. Graef, Keiichi I. Nakayama, Cynthia Shannon Weickert, and Tsuyoshi Miyakawa, *Neuropsychopharmacology*, August 4, 2017 (epub prior to print publication). Address: Tsuyoshi Miyakawa, Division of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan, miyakawa@fujita-hu.ac.jp.

—and—

"Increased brain acidity in psychiatric disorders," news release, Fujita Health University, August 7, 2017.

Intensive early intervention for ASD saves money, study finds

Intensive early intervention for children with autism spectrum disorders (ASD) is highly cost-effective, a new study reports.

Zuleyha Cidav and colleagues evaluated the Early Start Denver Model (ESDM), which involves a developmental curriculum and set of teaching procedures carried out by therapy teams and parents, either in a clinic or in the child's home. The researchers analyzed costs for 21 children participating in ESDM, comparing them to the costs for 18 children participating in community care.

The researchers say, "During the intervention, children who received the ESDM had average annualized total health-related costs that were higher by about $14,000 than those of children who received community-based treatment. The higher cost of ESDM was partially offset during the intervention period because children in the ESDM group used fewer applied behavior analysis (ABA)/early intensive behavioral intervention (EIBI) and speech therapy services than children in the comparison group. In the postintervention period, compared with children who had earlier received treatment as usual in community settings, children in the ESDM group used fewer ABA/EIBI, occupational/physical therapy, and speech therapy services, resulting in significant cost savings in the amount of about $19,000 per year per child."

Senior study author David Mandell says, "We wanted to show what the short term payoff would be if payers invested in early intensive treatment for children with autism. Much to our surprise, we found that the entire additional cost associated with high-quality intervention as opposed to traditional community services, which often are not as intensive or of as high quality, was completely offset within two years."

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"Cost offset associated with Early Start Denver Model for children with autism," Zuleyha Cidav, Jeff Munson, Annette Estes, Geraldine Dawson, Sally Rogers, and David Mandell, *Child & Adolescent Psychiatry,* Vol. 56, No. 9, September 2017, 777-83. Address: Zuleyha Cidav, zcidav@upenn.edu.

—and—

"High quality early intervention for children with autism quickly results in cost savings," Science Daily, August 8, 2017.

EDITORIAL: Stephen M. Edelson, Ph.D.

The Autism Research Institute: Our Standard of Excellence

I was fortunate to know Dr. Bernard Rimland for nearly 30 years, and worked closely with him for more than 20 years. From the time he established the Autism Research Institute, he held ARI to the highest standard possible. As we celebrate ARI's 50th anniversary year (1967-2017), I would like to share his values—and ours—with you. These are the cornerstones of our philosophy at ARI.

Integrity. Dr. Rimland was tireless in his quest to increase knowledge about autism. Identifying the causes of and interventions for autism was, and still is, a primary concern of ARI.

At the same time, countless parents and professionals worldwide depend on ARI to provide accurate information. To do this, we comb the science literature, talk with experts in the field and related areas, and listen to the concerns of those on the spectrum and their parents. We then share this knowledge in our newsletters, webinars, websites, social media, books, and other venues.

We are mindful of the need to advance the field of autism while supporting those on the autism spectrum and their families. Like most organizations, we carefully contemplate how to best direct our funds and energy. Dr. Rimland always asked: "What is in the best interest of the autism community?"—never "What is in the best interest of ARI?" Following this simple principle, solutions always present themselves.

Dr. Rimland insisted on keeping ARI completely independent of outside influence. Unlike most moderate- and large-scale autism non-profits, ARI does not accept contributions from government agencies, pharmaceutical and insurance companies, and businesses that provide autism-related services and products. For many years, Charity Navigator has awarded ARI its highest, four-star rating based on our transparency, accountability, and sound fiscal management.

Innovation. Dr. Rimland never accepted the status quo. His award-winning 1964 book *Infantile Autism* shattered the prevailing belief that autism was due to maternal emotional neglect. During the 1960s, he changed the course of the field by emphasizing the importance of genetics, the environment, and neurology in relation to autism. Over the next 30 years, he expanded his focus to include nutrition, restricted diets, behavior modification (or ABA), sensory interventions, medical co-morbidities, and adults on the spectrum.

Today, ARI continues to invest in innovative research projects that have the potential to revolutionize our ideas about the causes and treatment of autism. Frequently, we fund small-scale investigational studies, ranging from $5,000 to $30,000, that are designed to examine cutting-edge ideas. If the results are encouraging, the investigator then has science-based pilot data that will increase the likelihood of obtaining financial support from larger funding agencies. Since we feel that there is an urgency to help those on the spectrum, we do our best to minimize delays in the review and funding process.

Excellence. As many of us know, individuals on the autism spectrum and their family members often feel unheard and struggle to receive appropriate support from professionals, government agencies, and insurance companies. Dr. Rimland wanted ARI to be a forum where barriers faced by the autism community are discussed and actively addressed.

Today, ARI's Board of Directors, staff, and I continue to be attentive to the needs of our constituents. We are aided by an outstanding Scientific Advisory Panel that includes many top researchers in the field, hailing from such universities and hospitals as Arizona State University, Boston University, Cleveland Clinic, Massachusetts General Hospital, UC Davis, UCLA, UC San Diego, the University of Arkansas, the University of Chicago, and the University of South Carolina. All of these scientists are active within the organization, participating in our webinars, writing and editing articles for us, reviewing grant proposals, and attending our think tanks.

Empowerment. Because there are no guarantees that any given treatment for autism will be beneficial, those on the spectrum or their caregivers often need to make difficult treatment decisions. To empower them to make informed decisions, we disseminate science-based information on our website, through our webinars, and in our publications. Often, parents share our information with professionals to make them better aware of the biomedical issues affecting individuals with autism.

Hope. Hope for the future is fundamental in light of the many challenges faced by individuals on the spectrum and their families. We are aware of the dangers of giving false hope, but at the same time, we oppose the idea of giving no hope.

One way ARI provides hope for the future is by reporting on promising treatments. We published a popular book, *Treating Autism: Parent Stories of Hope and Success*, which we later followed up with an expanded edition. The book contains articles written by parents who successfully used various interventions to help treat their children's behaviors and medical co-morbidities. We have also published books on the biomedical treatment approach (five editions), the Specific Carbohydrate Diet, and nutritional supplements. Recently, we were instrumental in the publication of the book titled *Understanding and Treating Self-Injurious Behavior in Autism*.

Another way ARI encourages hope is to inform the medical community about the best treatments for those on the autism spectrum. We publish a bimonthly e-newsletter for obstetricians, pediatricians, and nurses, outlining the latest peer-reviewed research that is relevant to their practice. Connecting physicians to improved standards of care is crucial to our mission. In joint providership with the Cleveland Clinic, we continue to offer complimentary CME-certified online education to amplify understanding of the medical nature of the disorder.

Community. Since day one, we have always taken the perspective that "we are all in it together." Dr. Rimland cared about people worldwide. He would often say that a child with autism in Japan was just as important as a child with autism in San Diego. He had ARI's diagnostic checklist translated into 40 different languages, added the word "International" to the title of our science newsletter, the *Autism Research Review International*, and lectured on autism throughout the world.

Over the years, we have made a concerted effort to develop open lines of communication with all organizations within the autism community. We do this through social media platforms, conferences, think tanks, in-person meetings, and conference calls.

ARI continues to support the international autism community. We are a member of the United Nations (NGO, non-government organization), communicate with autism organizations worldwide on a regular basis, have translated many of our articles as well as our popular Autism Treatment Evaluation Checklist (ATEC) into different languages, and have helped sponsor an annual international conference in Eastern Europe for the past five years.

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The vision that Dr. Rimland established for the Autism Research Institute 50 years ago is the same vision that guides our work today. As a result, professionals, individuals with autism spectrum disorders, and their families worldwide can rely on ARI for cutting-edge research, unbiased and accurate information, practical help, and powerful advocacy.

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Research Updates

Kids with ASD have hypermasculine faces

Children with autism spectrum disorders (ASD) appear to have more masculine facial features than neurotypical children, a new study reports.

Diana Weiting Tan and colleagues used a computer algorithm to create a gender scale for a sample of 3-D facial images, ranging from very masculine to very feminine. The researchers then compared the facial features of 54 boys and 20 girls with ASD to the features of 102 neurotypical boys and 113 neurotypical girls, determining each child's score. All of the children were prepubescent.

The researchers report, "For each sex, increased facial masculinity was observed in the ASD group relative to [the] control group." Analyses also revealed that increased facial masculinity in the ASD group correlated with the presence of more social and communication difficulties.

Previous research by the same group found an association between a more masculine facial profile and increased exposure to prenatal testosterone. The researchers conclude that while evidence for the association between ASD and prenatal testosterone exposure is mixed, their findings provide further support for the idea that autism may involve "hypermasculinization."

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"Hypermasculinised facial morphology in boys and girls with autism spectrum disorder and its association with symptomatology," Diana Weiting Tan, Syed Zulqarnain Gilani, Murray T. Maybery, Ajmal Mian, Anna Hunt, Mark Walters, and Andrew J.O. Whitehouse, *Nature Scientific Reports*, August 24, 2017 (free online). Address: Diana Weiting Tan, Neurocognitive Development Unit, School of Psychological Science, University of Western Australia, Perth, 6009, Western Australia, Australia.

—and—

"Computer algorithm links facial masculinity to autism," news release, University of Western Australia, August 25, 2017.

— AUTISM.JOBS —

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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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Peer mentoring helps students with ASD navigate college

Peer mentoring can benefit college students with autism spectrum disorders (ASD), according to new research.

Choo Ting Siew and colleagues evaluated the effects of one semester of one-on-one peer mentoring on 10 young adults with ASD attending a university in Australia. Participants received mentoring from postgraduate students with backgrounds in psychology, speech pathology, occupational therapy, or social work.

The researchers administered a battery of tests to the participants before and after the semester, and conducted semi-structured interviews at the end of the semester. They report that overall, participants reported high levels of satisfaction with the program. The researchers add, "They also reported increased perceived social support and decreased general communication apprehension following participation in [the program]."

Interviews with participants found that they appreciated having constant, stable support from peers. In addition, they enjoyed the flexible, individualized assistance their mentors provided.

While students with ASD often struggle in college, the students in the mentoring program passed nearly 94% of their academic assessments and achieved "distinction" or "high distinction" on nearly 63% of their assessments. Their failure rate was only 2.9%. All study participants re-enrolled in the second semester.

The researchers caution that their findings are preliminary, and involve only a small number of individuals. However, they note that York University in Canada and Sheffield Hallam University in the U.K., which offer peer mentoring programs for students with ASD, are also seeing promising results.

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"A specialist peer mentoring program for university students on the autism spectrum: a pilot study," Choo Ting Siew, Trevor G. Mazzucchelli, Rosanna Rooney, and Sonya Girdler, *PLOS ONE*, July 13, 2017 (online). Address not listed.

Rates of pathological video gaming high for adults with ASD

Adults with autism spectrum disorders (ASD) are at higher risk for pathological video game use than their neurotypical peers, according to a new study. The study is consistent with earlier research showing that children and adolescents with ASD are more likely than neurotypical peers to engage in problematic game use.

Christopher Engelhardt and colleagues asked 119 adults with and without ASD to fill out forms measuring their daily hours of video game use, the percentage of their free time they spent playing video games, and their symptoms of pathological game use (for instance, a preoccupation with gaming, "withdrawal" symptoms if they tried to quit, a decline in health or hygiene due to excessive gaming, and lying to others about the amount of time spent gaming). The researchers say that adults with ASD reported significantly more symptoms of video game pathology than their neurotypical peers reported. In addition, they spent more hours per day playing video games and spent a higher percentage of their free time gaming. For both the ASD and neurotypical groups, the motive of "escapism" was associated with higher rates of gaming pathology.

The researchers say, "Adults with ASD are already at risk for poor outcomes, including reduced engagement in social and community activities, education, and employment. Excessive or pathological use of video games may exacerbate these difficulties, displacing time that could be spent on social, occupational, or other recreational activities. Furthermore, given evidence from the general population, pathological game use may exacerbate core or co-occurring symptoms among adults with ASD, particularly worsening mood, anxiety, irritability, and social isolation." They note, however, that adults with ASD experience some benefits from gaming, including reduced stress and more social connections.

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"Pathological game use in adults with and without autism spectrum disorder," Christopher R. Engelhardt, Micah O. Mazurek, and Joseph Hilgard, *PeerJ*, June 26, 2017 (online). Address: Micah O. Mazurek, mazurekm@health.missouri.edu.

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Research Updates

Gene mutations after conception may play major role in autism

Genetic mutations occurring after conception may play a significant role in autism spectrum disorders (ASD), a new study reports.

Many cases of autism involve *de novo* (spontaneous, non-inherited) mutations that occur in a parent's sperm or egg or arise after fertilization. Mutations that occur after fertilization are called *post-zygotic* mutations, or PZMs. The later PZMs occur during development, the fewer cells carry them, and the more difficult they are to detect.

Using previously analyzed gene sequencing data collected from nearly 6,000 families, Elaine Lim and colleagues resequenced some of the DNA using three separate sequencing technologies in parallel. The researchers classified 7.5% of *de novo* mutations in individuals with ASD as PZMs. Of these, they report, 83% were not identified in the original analysis.

Some of the PZMs detected by the researchers affected genes known to be associated with autism or other neurodevelopmental disorders, while others affected genes known to be active in brain development but not previously associated with ASD. While some mutations reduced the effects of genes, others increased these effects.

Comparing their sequencing data to gene expression data from brain autopsies, the researchers found that PZMs in individuals with ASD occur disproportionately in genes expressed in the amygdala. Lim says, "This was exciting to us, in that the amygdala has been proposed as an important region of the brain in autism."

Senior study author Christopher Walsh adds, "We have known that PZMs are an important cause of epilepsy, but this work provides the best evidence so far that they are relevant to autism as well."

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"Rates, distribution and implications of postzygotic mosaic mutations in autism spectrum disorder," Elaine T. Lim, Mohammed Uddin, Silvia De Rubeis, Yingleong Chan, Anne S. Kamumbu, Xiaochang Zhang, Alissa M. D'Gama, Sonia N. Kim, Robert Sean Hill, Arthur P. Goldberg, Christopher Poultney, Nancy J. Minshew, Itaru Kushima, Branko Aleksic, Norio Ozaki, Mara Parellada, Celso Arango, Maria J. Penzol, Angel Carracedo, Alexander Kolevzon, Christina M. Hultman, Lauren A. Weiss, Menachem Fromer, Andreas G. Chiocchetti, Christine M. Freitag, Autism Sequencing Consortium, George M. Church, Stephen W. Scherer, Joseph D. Buxbaum, and Christopher A. Walsh, *Nature Neuroscience*, July 17, 2017 (online). Address: Elaine T. Lim, Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, MA 02115.

—and—

"Late-breaking mutations may play an important role in autism," news release, Boston Children's Hospital, July 17, 2017.

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Intranasal oxytocin more helpful for those with low initial levels

Intranasal administration of oxytocin—a hormone that enhances social behavior in animals—may improve social deficits in some children with autism spectrum disorders (ASD), according to a small study.

In the double-blind, placebo-controlled study involving 32 children with ASD, Karen Parker and colleagues administered intranasal oxytocin spray or a placebo spray to participants twice daily for four weeks. The researchers measured the children's blood oxytocin concentrations and assessed their behavior at the beginning and end of the study.

The researchers found that oxytocin administration resulted in improvements in social behavior, and that children with the lowest initial levels of oxytocin benefitted the most from receiving the hormone. Oxytocin administration did not affect stereotypical behavior or anxiety.

Parker comments, "Our results suggest that some children with autism will benefit from oxytocin treatment more than others, and that blood oxytocin levels might be a biological sign that will allow us to predict if a child will respond maximally or not."

As in several previous studies, children in the placebo group showed some improvement, although to a lesser degree than those receiving oxytocin. Interestingly, children who had low oxytocin levels at baseline benefited more from the placebo than those with higher oxytocin levels. In addition, their bodies' production of oxytocin rose slightly. The researchers say, "This finding is consistent with the notion that increased endogenous oxytocin secretion (perhaps caused by enhanced social interactions during the trial) may underlie the social improvement in placebo-treated participants."

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"Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism," Karen J. Parker, Ozge Oztan, Robin A. Libove, Raena D. Sumiyoshi, Lisa P. Jackson, Debra S. Karhson, Jacqueline E. Summers, Kyle E. Hinman, Kara S. Motonaga, Jennifer M. Phillips, Dean S. Carson, Joseph P. Garner, and Antonio Y. Hardan, *Proceedings of the National Academy of Sciences*, July 2017 (epub prior to print publication). Address: Karen J. Parker, kjparker@stanford.edu.

—and—

"Oxytocin improves social abilities in some kids with autism," news release, Stanford University School of Medicine, July 10, 2017.

—and—

"Oxytocin nasal spray may boost social skills in children with autism," *Scientific American*, July 11, 2017.

Eye movements offer clues about symptoms in autism

The eye movements of individuals with autism spectrum disorders (ASD) may offer insight into their symptoms, a preliminary study suggests.

In a series of experiments, Edward Freedman and John Foxe tracked the saccades (rapid eye movements) of individuals with ASD as they viewed a target appearing in different locations on a screen. The researchers designed the experiment so that the participants' focus would frequently "overshoot" the intended target.

Neurotypical individuals efficiently adjusted their eye movements when they repeated the task. However, individuals with ASD continued to miss the target, suggesting that the sensory motor controls in the cerebellum responsible for eye movement were impaired in this group.

The researchers note that accurate saccades are crucial for navigating, understanding, and interacting with the world. Thus, they say, the visual abnormalities seen in individuals with ASD may help to explain the communication and social deficits they experience.

"If these deficits do turn out to be a consistent finding in a sub-group of children with ASD," Freedman says, "this raises the possibility that saccade adaptation measures may have utility as a method that will allow early detection of this disorder." They note that saccade adaptation can be accurately measured in children as young as 10 months of age.

While the researchers' findings are preliminary, they say their results are consistent with those reported in two other recent studies. In one study, researchers found differences in the rate of adaptation in subjects with high-functioning autism compared to neurotypical participants or those with Asperger's disorder, as well as a small change in velocity during adaptation in the neurotypical participants but not in those with an ASD. In the other study, researchers found that the rates of adaptation in individuals with ASD were slower than in neurotypical participants.

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"Eye movements, sensorimotor adaptation and cerebellar-dependent learning in autism: toward potential biomarkers and subphenotypes," Edward G. Freedman and John J. Foxe, *European Journal of Neuroscience*, July 12, 2017 (epub prior to print publication). Address: Edward G. Freedman, Department of Neuroscience, The Del Monte Institute for Neuroscience, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, ed_freedman@urmc.rochester.edu.

—and—

"Eye test could help diagnose autism," news release, University of Rochester Medical Center, July 24, 2017.

Ketogenic, GFCF diets appear to benefit children with ASD

Both a modified Atkins diet and a gluten-free, casein-free diet appear to be valuable interventions for young children with autism spectrum disorders (ASD), a new study by researchers in Egypt concludes.

In the six-month study, Omnia El-Rashidy and colleagues divided 45 children between 3 and 8 years of age, all diagnosed with ASD, into three groups:

- One third of the children ate the modified Atkins diet (MAD), a less restrictive version of the ketogenic diet (which is high in fat, contains moderate protein, and drastically reduces carbohydrate intake). On this diet, the children obtained approximately 60% of their calories from fat sources, 30% from proteins, and 10% from carbohydrates.
- One third of the children ate a gluten-free, casein-free (GFCF) diet.
- One third of the children—the control group—ate a basic balanced diet.

Five children in the MAD group dropped out of the study before completion. The remaining children in this group exhibited significant improvement on the Childhood Autism Rating Scale (CARS) and the speech, social, and cognitive parameters of the Autism Treatment Evaluation Checklist (ATEC).

No children in the GFCF diet group dropped out. This group also improved their scores on the CARS, and on ATEC subscores of speech/language/communication and behavior.

Overall, the children in the MAD group improved more than those in the GFCF group, exhibiting a higher percentage of positive changes. Children in the control group exhibited no significant changes.

The researchers' findings are consistent with a growing body of research indicating that both ketogenic-style and GFCF diets can benefit many children with autism. However, El-Rashidy and colleagues note that large-scale studies are needed to confirm their results.

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"Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study," Omnia El-Rashidy, Farida El-Baz, Yasmin El-Gendy, Randa Khalaf, Dina Reda, and Khaled Saad, *Metabolic Brain Disease*, August 14, 2017 (online). Address: Khaled Saad, ksaad8@yahoo.com.

People with autism are less surprised by the unexpected

Individuals with autism spectrum disorders (ASD) may overestimate the volatility of the world around them, a new study suggests.

Rebecca Lawson and colleagues enrolled 24 adults with ASD and 25 neurotypical adults in their study. Participants completed a task that involved learning to anticipate certain pictures appearing on a computer screen after hearing either a high or low sound.

The adults with autism performed the task successfully overall. However, they overestimated the volatility of the task, and thus were less able to form expectations about upcoming pictures. The more severe the symptoms of participants with ASD were, the less surprised they were by an unexpected picture.

Lawson comments, "When we're uncertain about our own beliefs, such as under volatile conditions, we're driven more by our senses than our prior expectations. If people with autism are more often expecting volatility, that could help explain their propensity to sensory overload, enhanced perceptual functioning and context insensitivity." She adds that the research "represents an important advance in our understanding of how people with autism see the world differently."

The researchers also found that measures of learning and surprise were associated with changes in pupil size. These changes, they say, are believed to reflect the function of neuromodulating brain chemicals such as noradrenaline.

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"Adults with autism overestimate the volatility of the sensory environment," Rebecca P. Lawson, Christoph Mathys, and Geraint Rees, *Nature Neuroscience*, July 31, 2017 (online). Address: Rebecca P. Lawson, Wellcome Trust Centre for Neuroimaging, 12 Queen Square, London WC1N 3BG, rebecca.lawson@ucl.ac.uk.

—and—

"People with autism are less surprised by the unexpected," news release, University College London, July 31, 2017.

Survey Gauges Treatment 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/

Individuals with autism less susceptible to biased decisions

The reduced sensitivity to contextual clues displayed by many people with autism spectrum disorders (ASD) may make them more efficient at making high-level decisions than their neurotypical peers, according to a new study.

In the study, George Farmer and colleagues asked 90 adults with ASD and 212 neurotypical controls to participate in an online decision-making task. The researchers' goal was to study the *attraction effect*, which they explain "arises when people choose between two options, A and B, that 'trade off' two dimensions—for example, two USB drives that respectively have lower capacity but higher longevity and higher capacity but lower longevity. When the choice set includes a third, 'decoy' option that is fractionally worse than A on both dimensions, people very rarely choose the decoy, but its presence boosts the tendency to choose A rather than B—and vice versa if the decoy targets option B."

In the experiment, participants evaluated 10 groups of products. In each group, two products (A and B) appeared along with a "decoy." Participants viewed each A-and-B pair twice—once with the decoy designed to target Product A, and once with it designed to target Product B.

The researchers say that if participants made decisions based purely on reason, the decoy items would be irrelevant and participants would make the same choice each time they viewed products A and B. If the decoys were effective, however, participants would switch their choice when the decoy changed, favoring the product targeted by the decoy in each group.

The researchers report, "People with autism spectrum conditions made fewer context-induced preference reversals than did neurotypical individuals. That is, they made more conventionally rational decisions."

In a second experiment, the researchers recruited members of the general population to perform the same task, comparing individuals with the highest and lowest scores on the Autism-Spectrum Quotient (which measures levels of autistic traits in neurotypical individuals). Participants with the most autistic traits made more consistent choices in the task than those with the fewest autistic traits, although the difference was less pronounced than in the experiment involving individuals with ASD.

Farmer comments, "These findings suggest that people with autism might be less susceptible to having their choices biased by the way information is presented to them—for instance, via marketing tricks when choosing between consumer products."

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"People with autism spectrum conditions make more consistent decisions," George D. Farmer, Simon Baron-Cohen, and William J. Skylark, *Psychological Science*, June 2017 (free online). Address: William J. Skylark, Department of Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, United Kingdom, wjm22@cam.ac.uk.

—and—

"Adults with autism make more consistent choices," news release, Association for Psychological Science, June 27, 2017.

Study renews questions about maternal antidepressants, ASD

In the wake of three studies showing no link between maternal antidepressant use and autism (see ARRI Vol. 2, 2017), a more recent study raises questions about the possibility of a small association.

In the new study, Dheeraj Rai and colleagues used a range of analyses to explore data from more than 250,000 individuals between 4 and 17 years of age, including more than 5,000 with autism. All of the individuals lived in Stockholm between 2001 and 2011.

The researchers divided the individuals into three groups: those born to mothers who did not take antidepressants and did not have any psychiatric disorder, those born to mothers who took antidepressants during pregnancy, and those born to mothers with psychiatric disorders who did not take antidepressants during pregnancy.

The researchers found that of the 3,342 children exposed to antidepressants during pregnancy, 4.1% received an autism diagnosis, compared to 2.9% of unexposed children of mothers with a history of psychiatric disorder. Using fathers as a control, the researchers found that there was no increased risk of autism in children whose fathers took antidepressants during mothers' pregnancies.

The researchers emphasize that the absolute risk of autism they detected was small, and that more than 95% of women in the study who took antidepressants during pregnancy did not have children with autism. They estimate that "if a causal link were robustly established, and if no pregnant women took antidepressants during pregnancy, only 2% of autism cases in this population would be prevented."

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"Antidepressants during pregnancy and autism in offspring: population based cohort study," D. Rai, B. K. Lee, C. Dalman, C. Newschaffer, G. Lewis, and C. Magnusson, *British Medical Journal*, July 19, 2017 (online). Address: Dheeraj Rai, Centre for Academic Mental Health, School of Social and Community Medicine, University of Bristol, Bristol BS8 2BN, UK, dheeraj.rai@bristol.ac.uk.

—and—

"Study points to link between antidepressant use in pregnancy and autism in children," news release, *British Medical Journal*, July 19, 2017.

Study offers clues about eye avoidance in ASD

New research indicates that individuals with autism spectrum disorders (ASD) avoid eye contact not because they lack interest in interacting socially, but because making eye contact causes them to experience unpleasant arousal in the brain's subcortical system.

Nouchine Hadjikhani and colleagues enrolled 23 individuals with ASD and 20 controls in their study, which used functional magnetic resonance imaging (fMRI) to measure brain responses. The researchers asked participants to view faces under two conditions. In the first condition they viewed the faces freely, while in the second condition they were asked to look at a cross located in the eye region of each face.

The researchers found that the two groups responded similarly during free viewing. However, participants with ASD exhibited over-activation of the face processing components of the subcortical system when they focused on the eye area.

The researchers say that constraining gaze to the eyes had the greatest effect on the amygdala in the group with ASD. The difference between the group with ASD and the controls was strongest for fearful faces, but also occurred when participants viewed happy faces. The researchers say, "This shows that the subcortical system in ASD over-reacts not only to threat-related stimuli, but also to stimuli that should be considered as positively engaging and socially rewarding."

Hadjikhani says, "The findings demonstrate that, contrary to what has been thought, the apparent lack of interpersonal interest among people with autism is not due to a lack of concern. Rather, our results show that this behavior is a way to decrease an unpleasant excessive arousal stemming from overactivation in a particular part of the brain."

Based on the study's findings, Hadjikhani says that forcing individuals with autism to focus on other people's eyes may be misguided. Instead, she says, "An approach involving slow habituation to eye contact may help them overcome this overreaction and be able to handle eye contact in the long run, thereby avoiding the cascading effects that this eye-avoidance has on the development of the social brain."

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"Look me in the eyes: constraining gaze in the eye-region provokes abnormally high subcortical activation in autism," Nouchine Hadjikhani, Jakob Åsberg Johnels, Nicole R. Zürcher, Amandine Lassalle, Quentin Guillon, Loyse Hippolyte, Eva Billstedt, Noreen Ward, Eric Lemonnier, and Christopher Gillberg, *Nature Scientific Reports*, June 9, 2017 (free online). Address: Nouchine Hadjikhani, nouchine@nmr.mgh.harvard.edu.

—and—

"Mass. General researchers explore why those with autism avoid eye contact," news release, Massachusetts General Hospital, June 15, 2017.

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Conducting and sponsoring research on the causes of and best treatments for autism (more than $400,000 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.

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