Researchers at the Carolina Institute for Developmental Disabilities Link Brain Changes in Infancy to Autism

A national research network led by UNC School of Medicine's Joseph Piven, M.D., found that many toddlers diagnosed with autism at 2 years of age had a substantially greater amount of brain fluid at 6 and 12 months of age, before diagnosis is possible.

CHAPEL HILL, NC – "The cerebral spinal fluid (CSF) is easy to see on standard MRIs and points to a potential biomarker of autism before symptoms appear years later," said Piven, cosenior author of the study, the Thomas E. Castelloe Distinguished Professor of Psychiatry, and director of the Carolina Institute for Developmental Disabilities (CIDD). "We also think this finding provides a potential therapeutic target for a subset of people with autism."

The findings, published in *Biological Psychiatry*, point to faulty CSF flow as one of the possible causes of autism for a large subset of people.

"We know that CSF is very important for brain health, and our data suggest that in this large subset of kids, the fluid is not flowing properly," said Mark Shen, Ph.D., CIDD postdoctoral fellow and first author of the study. "We don't expect there's a single mechanism that explains the cause of the condition for every child. But we think improper CSF flow could be one important mechanism."

"Our findings that these brain changes are present before autism unfolds gives us a completely different perspective on this condition. It allows us to consider screening and intervention before the onset of symptoms." Until the last decade, the scientific and medical communities viewed CSF as merely a protective layer of fluid between the brain and



skull, not necessarily important for proper brain development and behavioral health. But scientists then discovered that CSF acted as a crucial filtration system for byproducts of brain metabolism.

Every day, brain cells communicate with each other. These communications cause brain cells to continuously secrete byproducts, such as inflammatory proteins that must be filtered out several times a day. The CSF handles this, and then it is replenished with fresh CSF four times a day in babies and adults.

In 2013, Shen co-led a study of CSF in infants at UC Davis, where he worked with David Amaral, Ph.D., co-senior author of the current *Biological Psychia-try* study. Using MRIs, they found substantially greater volumes of CSF in babies that went on to develop autism. But they cautioned the study was small – it included 55 babies, 10 of whom developed autism later – and so it needed to be replicated in a larger study of infants.

When he came to UNC, Shen teamed up with Piven and colleagues of the Infant Brain Imaging Study



(IBIS), a network of autism clinical assessment sites at UNC, the University of Pennsylvania, Washington University in St. Louis, and the University of Washington.

In this most recent study of CSF, the researchers enrolled 343 infants, 221 of which were at high risk of developing autism due to having an older sibling with the condition. Forty-seven of these infants were diagnosed with autism at 24 months, and their infant brain MRIs were compared to MRIs of other infants who were not diagnosed with autism at 24 months of age.

The 6 month-olds who went on to develop autism had 18 percent more CSF than 6 month-olds who did not develop autism. The amount of CSF remained elevated at 12 and 24 months. Infants who developed the most severe autism symptoms had an even greater amount of CSF – 24 percent greater at six months. Also, the greater amounts of CSF at six months were associated with poorer gross motor skills, such as head and limb control.

"Normally, autism is diagnosed when the child is 2or 3-years-old and beginning to show behavioral symptoms; there are currently no early biological markers," said David G. Amaral, director of research at the UC Davis MIND Institute. "That there's an alteration in the distribution of cerebrospinal fluid that we can see on MRIs as early as six months, is a major finding."

The researchers found that increased CSF predicted with nearly 70 percent accuracy which babies would later be diagnosed with autism. It is not a perfect predictor of autism, but the CSF differences are observable on a standard MRI. "In the future, this sort of CSF imaging could be another tool to help pediatricians detect risks for autism as early as possible," Shen said.

Piven added, "We can't yet say for certain that improper CSF flow *causes* autism. But extra-axial CSF is an early marker, a sign that CSF is not filtering and draining as it should. This is important because improper CSF flow may have downstream effects on the developing brain; it could play a role in the emergence of autism symptoms." The National Institutes of Health, Autism Speaks, and the Simons Foundation funded this research.

Links for More Information

Video Interviews with the Researchers

https://www.youtube.com/watch?v=R8JW00BollI

https://www.youtube.com/watch?v=EIHLShRpKLM

The Full Journal Articles

Early brain enlargement and elevated extra0axial fluid in infants who develop autism spectrum disorder

https://www.ncbi.nlm.nih.gov/pubmed/23838695

Early brain development in infants at high risk for autism spectrum disorder

https://www.ncbi.nlm.nih.gov/pubmed/28202961

The IBIS Network is grateful to participating families. Stay in contact. www. IBISnetwork.org

Important Research Results : UNC Researchers use MRIs to predict which high-risk babies will develop autism as toddlers

This first-of-its-kind study used MRIs to image the brains of infants, and then researchers used brain measurements and a computer algorithm to accurately predict autism before symptoms set in.

CHAPEL HILL, NC – Using magnetic resonance imaging (MRI) in infants with older siblings with autism, researchers from around the country were able to correctly predict 80 percent of those infants who would later meet criteria for autism at two years of age.

The study, published February 15, 2017 in Nature, is the first to show it is possible to identify which infants - among those with older siblings with autism - will be diagnosed with autism at 24 months of age. "Our study shows that early brain development biomarkers could be very useful in identifying babies at the highest risk for autism before behavioral symptoms emerge," said senior author Joseph Piven, MD, the Thomas E. Castelloe Distinguished Professor of Psychiatry at the University of North Carolina-Chapel Hill. "Typically, the earliest an autism diagnosis can be made is between ages two and three. But for babies with older autistic siblings, our imaging approach may help predict during the first year of life which babies are most likely to receive an autism diagnosis at 24 months."

This research project included hundreds of children from across the country and was led by researchers at the Carolina Institute for Developmental Disabilities (CIDD) at the University of North Carolina, where Piven is director. The project's other clinical sites included the University of Washington, Washington University in St. Louis, and The Children's Hospital of Philadelphia. Other key collaborators are McGill University, the University of Alberta, the University of Minnesota, the College of Charleston, and New York University.

"This study could not have been completed without a major commitment from these families, many of whom flew in to be part of this," said first author Heather Hazlett, PhD, assistant professor of psychiatry at the UNC School of Medicine and a CIDD researcher. "We hope to begin work on a similar project to replicate our findings. Parents can contact us about the study via our website. www.IBISnetwork.org."

People with Autism Spectrum Disorder (or ASD) have characteristic social deficits and demonstrate a range of ritualistic, repetitive and stereotyped behaviors. It is estimated that one out of 68 children develop autism in the United States. For infants with older siblings with autism, the risk may be as high as 20 out of every 100 births. There are about 3 million people with autism in the United States and tens of millions around the world.

Despite much research, it has been impossible to identify those at ultra-high risk for autism prior to 24 months of age, which is the earliest time when the hallmark behavioral characteristics of ASD can be observed and a diagnosis made in most children.

For this *Nature* study, Piven, Hazlett, and researchers from around the country conducted MRI scans of infants at six, 12, and 24 months of age. They found that the babies who developed autism experienced a hyper-expansion of brain surface area from six to 12 months, as compared to babies who had an older sibling with autism but did not themselves show evidence of the condition at 24 months of age. Increased growth rate

of surface area in the first year of life was linked to increased growth rate of overall brain volume in the second year of life. Brain overgrowth was tied to the emergence of autistic social deficits in the second year.





Previous behavioral studies of infants who later developed autism – who had older siblings with autism –revealed that social behaviors typical of autism emerge during the second year of life.

The researchers then took these data – MRIs of brain volume, surface area, cortical thickness at 6 and 12 months of age, and sex of the infants – and used a computer program to identify a way to classify babies most likely to meet criteria for autism at 24 months of age. The computer program developed the best algorithm to accomplish this, and the researchers applied the algorithm to a separate set of study participants.

The researchers found that brain differences at 6 and 12 months of age in infants with older siblings with autism correctly predicted eight out of ten infants who would later meet criteria for autism at 24 months of age in comparison to those infants with older ASD siblings who did not meet criteria for autism at 24 months.

"This means we potentially can identify infants who will later develop autism, before the symptoms of autism begin to consolidate into a diagnosis," Piven said.

If parents have a child with autism and then have a second child, such a test might be clinically useful in identifying infants at highest risk for developing this condition. The idea would be to then intervene 'pre-symptomatically' before the emergence of the defining symptoms of autism.

Research could then begin to examine the effect of interventions on children during a period before the syndrome is present and when the brain is most malleable. Such interventions may have a greater chance of improving outcomes than treatments started after diagnosis.

"Putting this into the larger context of neurosci-

ence research and treatment, there is currently a big push within the field of neurodegenerative diseases to be able to detect the biomarkers of these conditions before patients are diagnosed, at a time when preventive efforts are possible," Piven said. "In Parkinson's for instance, we know that once a person is diagnosed, they've already lost a substantial portion of the dopamine receptors in their brain, making treatment less effective."

Piven said the idea with autism is similar; once autism is diagnosed at age 2-3 years, the brain has already begun to change substantially.

"We haven't had a way to detect the biomarkers of autism before the condition sets in and symptoms develop," he said. "Now we have very promising leads that suggest this may in fact be possible."



Colored areas are the regions of overgrowth from **six to 12 months** in infants who were later diagnosed with autism

For this research, NIH funding was provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), and the National Institute of Biomedical Imaging and Bioengineering. Autism Speaks and the Simons Foundation contributed additional support.

The IBIS Network is grateful to participating families. Stay in contact. www. IBISnetwork.org

UNC Brain Imaging Study of Baby Siblings At Risk for Autism

Research Project Update March 2015



The Infant Brain Imaging Study (IBIS) Network is an NIH funded Autism Center of Excellence project and consists of a consortium of 8 universities in the U.S. and Canada.



UNC POLINA INSTITUTE FOR TENTAL DISABILITIES

University of North Carolina at Chapel Hill Children's Hospital of Philadelphia Washington University in St. Louis University of Washington McGill University University of Utah University of Alberta Montreal Neurological Institute University of Minnesota

http://ibis-network.org

About the Study

This research study is examining brain development and behavior in infants who have an older sibling with autism and thus are considered to be at high risk for autism themselves. This is a multi-site study in its 8th year of funding by the National Institute of Health. The study begins following infants as young as 3 months of age and uses some of the most advanced brain imaging technology to examine how brain structure changes during the important period from 6 to 24 months of age. The study also uses developmental and behavioral assessments, parent questionnaires, eye tracking equipment, and genetic testing to assess social communication, repetitive behavior, attention and other behaviors.

Autism Speaks has also provided funding to expand and link the IBIS Network with the Early Autism Risk Longitudinal Investigation (EARLI) to investigate genetic and environmental risk factors for autism from prenatal development through early childhood.

The data gathered in this study will provide important information about early brain development as well as genetic and environmental factors associated with autism.

About the Participants

- 463 Infant siblings of children with autism are enrolled or have completed the study in all sites. 108 of those participated at UNC-CH.
- 191 Infant siblings of typically developing children are currently participating or have completed in all sites. 63 of those participated at UNC-CH.

The IBIS Network is grateful to participating families.

Key Study Publications

Brain volume findings in 6-monthold infants at high familial risk for autism. Hazlett HC, et al. American Journal of Psychiatry. 2012 June; 169 (6) 601-8 http://www.ncbi.nlm.nih.gov/ pubmed/22684595

Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. Wolff JJ, et al. American Journal of Psychiatry. 2012 June; 169 (6) 589-600.

http://www.ncbi.nlm.nih.gov/ pubmed/22362397

Network inefficiencies in autism spectrum disorder at 24 months. Lewis JD, et al. Translational Psychiatry. 2014 May 6; 4:e388

http://www.ncbi.nlm. nih.gov/ pmc/articles/ PMC4035719

Published Results To Date

Brain Imaging Study of Baby Siblings At Risk for Autism Research Update

Findings on Brain

White Matter/Pathway Differ-

ences Paper 1: The research team reported significant differences in brain development of infants who develop ASD and those who do not. They analyzed scans of 92 at-risk infants (all had older siblings with autism). At 24 months, 30 percent of them met criteria for autism spectrum disorders while 70 percent did not. Findings indicate these two groups differed in white matter fiber tract development-white matter fiber tracts are the pathways that connect brain regions. They evaluated 15 fiber tracts and found significant differences in 12 of these pathways in the infants who went on to develop autism compared to infants who did not develop ASD. These findings indicate variances in connectivity and organization within the brain structure and suggest that autism is a whole-brain phenomenon and is not isolated in any one particular region of the brain.



Paper 2: Data from 24 month olds in the study shows that the children who devel-

op autism have significantly less connectivity (efficiency) than the high-risk infants who didn't develop autism and infants with no family history of autism.

Brain Volume Previous studies at UNC have observed larger brain volume and head circumference in children with autism as young as two years of age. The team analyzed brain scans of 6 month olds at high risk for autism (with a sibling with ASD) and compared them to babies who did not have a sibling with ASD. The results so far are inconclusive but the researchers plan to continue to investigate these metrics as more data becomes available.

Findings on Behavior

Repetitive Behavior Evident at 12 Months Restricted interests and repetitive behavior is one of the core features of autism but there is little information about how this behavior manifests in infants and toddlers. The Baby Sibs study is collecting data on repetitive behavior via parent questionnaire and also using a novel behavioral coding approach. One paper reported results from analysis of digital videos of more than 160 12-month old infants participating in 20 minute long, standardized behavioral assessment. The infants who later developed autism show a higher incidence of repetitive movement than the others. A second paper using parent report data yielded similar results. Elevated repetitive behaviors at 12-months may be a 'red flag' for autism.



Parents were able to detect these differences early using a simple, 5-10 minute measure which would make restricted and repetitive behavior a good potential target for early screening and intervention.

Key Study Publications

Repetitive behavior in 12-month olds later classified with autism spectrum disorder. Elison JT, et al. Journal of American Academy of Child Adolescent Psychiatry. 2014 Nov, 53 (11) 1216-24 http://www.ncbi.nlm.nih.gov/ pubmed/25440311

Longitudinal patterns of repetitive behavior in toddlers with autism. Wolff JJ, Journal of Child Psychology and Psychiatry. 2014 UF; 55(8) 945-53. http:// www.ncbi.nlm.nih.gov/ pubmed/24552513

