

# ***Inside the Institute***

*Newsletter for the Carolina Institute for Developmental Disabilities*

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## Can CRISPR/Cas9 Help Cure Angelman Syndrome?

We all have a gene called UBE<sub>3</sub>A, and when the copy we inherit from our mother works normally, our brain develops properly. When it doesn't, the result is Angelman Syndrome, a neuro-genetic disorder that mainly affects the nervous system and includes symptoms such as severe intellectual and developmental disabilities, seizures, and problems with speech, balance, movement, and sleep.

The UNC School of Medicine lab of Mark Zylka, PhD, director of the UNC Neuroscience Center, W.R. Kenan, Jr. Distinguished Professor of Cell Biology and Physiology, and member of the Carolina Institute for Developmental Disabilities (CIDD) and UNC Autism Research Center, has figured out exactly how to edit the genome so that the copy of UBE<sub>3</sub>A we inherit from our fathers can replace the version we inherit from our mothers.

Watch our latest UNC Science Short to learn how the Zylka Lab is using CRISPR/Cas9 gene editing technology as the basis for a one-time treatment to cure people with Angelman Syndrome. This work is funded through a grant from the Angelman Syndrome Foundation.

[Watch UNC Science Short: Can CRISPR/Cas9 Help Cure Angelman Syndrome?](#)

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## Bradley Allf Wins Brain Awareness Video Contest

BrainFacts.org, a public information initiative, selected Bradley Allf's video "I Think, Therefore I Sleep" as the 2018 winner of its Brain Awareness Video Contest. Allf created the video as a technician in the lab of Graham Diering, PhD, Assistant Professor of Cell Biology and Physiology and member of the CIDD.

When you sleep, a lot is happening. If you can't sleep or if you decide to forego sleep, your brain pays the price in ways you likely do not fully comprehend. The lab of Graham Diering, PhD, in the department of cell biology and physiology, studies the mechanisms of sleep – precisely what happens in our brains as we sleep, why it's important, and what can be learned in order to ultimately help people with conditions such as Alzheimer's disease, schizophrenia, autism, and others.

The video titled "I Think, Therefore I Sleep," created by lab technician Bradley Allf in the Diering lab, explains the purpose of sleep and how it affects brain function. Specifically, it explores one process by which sleep is thought to play a role in properly regulating synapses – the junction between neurons.

For this work, Allf won first place in the Brain Awareness Video Contest, sponsored by BrainFacts.org, which is a public information initiative funded by the Society of Neuroscience (SfN), the Kavli Foundation, and the charitable foundation Gatsby. Allf won \$1,000 and travel expenses, two-nights lodging, and registration fees to attend the SfN conference in San Diego in November.

[Watch Video: I Think, Therefore I Sleep](#)



## Can Genetic Therapy Help Kids with Angelman Syndrome Overcome Seizures?



Ben Philpot, PhD

*The UNC School of Medicine lab of Ben Philpot, PhD, discovered key details for how a deficiency in the gene *UBE3A* affects the brain and how replacing it could benefit children with the neuro-genetic disorder.*

Angelman syndrome is a genetic disease with no cure. Children grow up with severe intellectual disabilities and a range of other problems, arguably the worst of which are epileptic seizures. Now scientists at the UNC School of Medicine have found evidence that genetic therapy may prevent the enhanced seizure susceptibility.

[Published in the \*Journal of Clinical Investigation\*](#), the research marks the first time scientists were able to reduce seizure susceptibility in mice by activating a dormant copy of the *UBE3A* gene so it could replace the faulty mutant version. While replacing the faulty gene in juveniles reduced seizures, replacing the faulty gene in adult mice had no effect.

The UNC scientists also found evidence that the loss of this gene in Angelman syndrome promotes seizures by impairing the normal activity of inhibitory neurons – cells that normally keep brain circuits from being overstimulated.

“These findings should be very useful in the development and testing of therapies for Angelman syndrome,” said senior author Benjamin D. Philpot, PhD, Kenan Distinguished Professor in the Department of Cell Biology and Physiology, associate director of the UNC Neuroscience Center, and member of the UNC Autism Research Center and Intellectual and Developmental Disabilities Research Center (IDDR) .



Bin Gu, PhD

Angelman syndrome, named for the pediatrician who first described it in 1965, afflicts roughly one in 20,000 people, which implies that there are more than 16,000 people with the syndrome in the United States alone. The syndrome is caused by the loss of function of a single gene, *UBE3A*, but with an odd twist: the mutant or deleted copy of *UBE3A* is the one inherited from the patient’s mother. This maternal copy is crucial in neurons because – for reasons still unknown – the paternal copy of *UBE3A* is silenced in these cells via a mechanism called genomic imprinting.

*UBE3A* encodes a protein that works in an important cellular waste-disposal and gene-regulating system. Precisely how the absence of this protein in neurons causes Angelman syndrome has never been clear. Even so, scientists have been working on candidate therapies to restore *UBE3A* activity in neurons, thereby preventing or reversing some or all of the features of the disease. Among these features is epilepsy, which afflicts about 90 percent of Angelman syndrome patients, who typically do not respond well to standard anti-seizure medications.

Some aspects of the disease reflect abnormal prenatal and early postnatal development, and may never be reversible with treatments that start years after birth. But epilepsy often doesn’t start in Angelman patients until age 2 or 3, suggesting that early life replacement of *UBE3A* might cure it or prevent it. Philpot and colleagues decided to investigate how early the gene reinstatement needed to take place. They took advantage of an Angelman syndrome mouse model, in which researchers inserted a working copy of the *UBE3A* gene that would lie dormant in brain cells until scientists turned it on with a chemical switch.

The scientists found that switching on *UBE3A* failed to prevent or reverse the high susceptibility to seizures in adult Angelman mice. However, switching on the gene when the mice were just three weeks old made them as resistant to seizures as ordinary mice.

“Three weeks of age for a mouse corresponds to early childhood for a human, so this suggests that there may be a window of opportunity in childhood for the prevention of Angelman syndrome epilepsy,” said first author Bin Gu, PhD, a postdoctoral researcher in the Philpot Lab who performed most of the key experiments.

Another big question for Angelman syndrome researchers has to do with the neurons affected by the disease. Philpot wondered, to treat the condition successfully, would *UBE3A* activity need to be restored in all types of neurons or just in some?

*Continued on page 16*



## New NC-Based Study to Advance Research Through Free and Expanded Newborn Screening



*Cynthia M. Powell, MD, is Early Check Lead Investigator for the team from UNC.*

Early Check, a new research study, led by RTI International and a group of distinguished partners, is now available for newborn babies in North Carolina. Early Check is a free screening study designed to identify children with rare health conditions before symptoms appear and will study the benefits of early treatments. New and expectant mothers may enroll in the program online from their second trimester until 4 weeks after their child’s birth.

"We are enrolling participants now and hope to offer every baby born in North Carolina the opportunity to participate in this unique study," said Don Bailey, PhD, Distinguished Fellow at RTI International and principal investigator for Early Check.

Currently, the North Carolina State Laboratory of Public Health performs newborn screening for all babies born in the state. Early Check staff located in the NC state Lab will perform the additional Early Check screenings. "The North Carolina State Laboratory of Public Health is excited to be advancing the science of public health through our partnership with RTI," said Scott J. Zimmerman, DrPH, MPH, director of the North Carolina State Laboratory of Public Health.

After receiving the mother’s consent, Early Check reuses the same blood sample taken for regular newborn screening to test for two additional rare conditions: fragile X syndrome—the leading inherited cause of intellectual disability, and spinal muscular atrophy—a serious neuromuscular disease that may cause early death among infants. These conditions are not currently included in standard newborn screening in North Carolina.

"There is not enough evidence that early treatment changes outcomes for fragile X syndrome and for spinal muscular atrophy," said Lisa Gehtland, M.D., a physician and public health analyst at RTI and the project director. "We hope that Early Check test results will provide key evidence that could enable additions to standard newborn screening for these rare but serious conditions and others we might add in the future."

For the extra tests, RTI is working in partnership with the following organizations to make the Early Check study possible: North Carolina State Laboratory of Public Health, University of North Carolina at Chapel Hill, Duke University, Wake Forest School of Medicine.

Cynthia Powell, MD, professor of Pediatrics and Genetics, Director of the Medical Genetics Residency Program, and new IDDRC Investigator, is Early Check Lead Investigator for the team from the University of North Carolina at Chapel Hill.

"We understand that parents will be concerned if confirmatory testing determines that their child has one of the conditions. But the results will also help determine the severity of the condition, and the appropriate next steps. For SMA, a form of muscular dystrophy, rapid confirmatory testing is important as for the most severe form, early treatment can help prevent rapid decline in muscle strength. A positive result in an infant may have implications for many other family members. So, families who participate in Early Check and have a positive screen will receive genetic counseling. Additional genetic counseling will be provided to parents of infants who are confirmed to have one of the conditions," Powell said.

Primary funding for Early Check has been provided by the National Institutes of Health (NIH), National Center for Advancing Translational Sciences (NCATS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development, The John Merck Fund, CureSMA, and Asuragen. NCATS is the funding agency for the North Carolina Translational and Clinical Sciences (NC TraCS) Institute -- the UNC-Chapel Hill home for the NIH's Clinical and Translational Sciences Awards (CTSA) Program.

Additional information about the research program and enrollment criteria is available at [www.EarlyCheck.org](http://www.EarlyCheck.org)



## Piloting an Early Intervention Program for Infants with Fragile X Syndrome

Starting in October of 2018, researchers at RTI, in collaboration with UNC, Duke, Wake Forest, and the NC State Public Health Laboratory, all birthing parents in NC will be offered free voluntary expanded newborn screening for fragile X syndrome (FXS) as part of Early Check (*see page 2*). Babies with a documented diagnosis of FXS will be eligible for Part C Community-based Early Intervention due to an established condition. In North Carolina, identification of these infants at birth will provide families with access to a family coordinator through the Early Intervention program who will connect with the family on a regular basis and make referrals to specific providers (e.g., physical therapist, speech/language pathologist) when the child begins to show symptoms warranting those services. Although earlier access to these services may in itself make a difference for these children, the timing, quality, and dosage of these services will differ across the state and will depend on the emergence of symptoms. However, it is expected that the greatest impact will come from a more intensive intervention that is implemented *presymptomatically*.

Through funding from the John Merck Fund, Drs. Lauren Turner-Brown (UNC) and Anne Wheeler (RTI) will lead a team of clinical researchers in developing and testing a two-phase intensive intervention focused on improving the sensitivity of parents and their effectiveness in addressing emerging atypical behavior of infants with FXS.

The intervention, called Parents and Infant with Fragile X Intervention (PiXi) will consist of two phases, combining parent education about FXS and early intervention programs (phase 1), direct parent coaching around parent-child interaction based on an empirically based parent-mediated early intervention (phase 2, *i*-BASIS-VIPP), and repeated comprehensive assessments of family and child functioning. Evidence of benefit from earlier diagnosis of FXS has significant implications for newborn screening policy and the possibility of earlier screening for other IDD conditions.

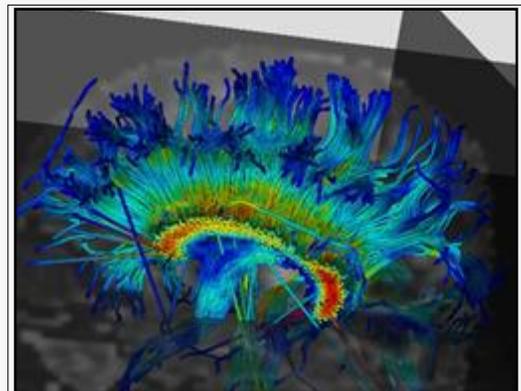
## Pilot Study of a Remotely Administered Developmental Assessment



NCTraCS funded a pilot study to test the validity of a remotely administered developmental assessment battery for infants who are at-risk for intellectual and developmental disabilities (IDD). Existing tools rely on parent report or in-person direct interactions with the infant, methods that require extensive resources to implement. The study is co-led by Anne Wheeler and Katherine "Casey" Okoniewski at Research Triangle International (RTI) and Heather Hazlett at CIDD, working together with the tool's developer at Purdue University, Bridgette Tonson. Participants will be recruited from a funded state-wide newborn screening initiative, Early Check (*see page 2*), and will be enrolled if they have a confirmed diagnosis of an *FMR1* premutation. Participants will complete a remote developmental assessment (RDA) and measures of language, heart activity, visual attention, temperament, mother-child interaction, unstructured play, and responses to social presses will also be collected. Longitudinal follow-up will include a direct developmental assessment to provide validation data of the RDA. If successful, the study will provide support for remote developmental assessments that can be used in research to help reduce travel burden and increase engagement.

## Study of White Matter in Angelman Syndrome

IDDRC investigators Ben Philpot and Heather Hazlett were awarded an RO1 from NICHD to continue their work examining white matter dsymorphology in Angelman syndrome (AS). Dr. Philpot's team will work to understand the developmental trajectory of white matter deficits in AS model mice, and when reinstatement of *UBE3A* in neurons can work best to provide recovery of functioning. Dr. Hazlett, partnering with CIDD new faculty Mark Shen, will investigate whether the white matter deficits observed using neuroimaging in children with AS can be correlated with their motor functioning, suggesting the possibility for use as a treatment biomarker. The project is planned to start in December and will work closely with the CIDD Angelman Clinic and AS support groups for recruitment.



Above: an example of white matter projections of the corpus callosum in an adult brain.

## Brain Development in Infants with Down Syndrome

Investigators at the CIDD will participate in a new study funded by NIH's INCLUDE initiative. This project will study brain development in infants with Down syndrome, starting in the first year of life. Infants will be seen in the first year of life, as young as 6 months old, and followed with brain MRI scans and developmental assessments until age 2. The study is led by Dr. Kelly Botteron at Washington University in St. Louis and includes partnering sites across the United States. The study is a companion project to the IBIS Early Prediction study, (Dr. Joseph Piven as co-PI with Dr. John Pruett at Wash Univ) which is planned to start in 2019. This study represents a large effort to understand early brain development in Down syndrome. With the newly funded school-age study (led by Dr. Heather Hazlett – *see story below*), the research team hopes to characterize the brain and behavioral phenotype of children with Down syndrome across the first decade of life. There is currently no large study like this in Down syndrome, and this work will provide important information that can provide the foundation for new approaches for intervention. Enrollment at the UNC site will kick off in early 2019.

## Brain Development in School-Aged Children with Down Syndrome



A new study to characterize brain development in school-aged children with Down syndrome has been funded by the NIH. The award is part of NIH's new INCLUDE initiative to increase research focused on Down syndrome. The project is led by CIDD psychologist Heather Hazlett, PhD, and provides supplemental funding to the ongoing NIH Autism Center of Excellence (ACE) Network directed by UNC (Principal Investigator, Joseph Piven, MD). The UNC team, along with collaborators across the U.S., will be enrolling a sample of children (7-11 years old) with Down syndrome. Children will receive cognitive and behavioral assessments along with a brain MRI scan. Brain metrics such as volume, surface morphology, and white matter tracts will be examined and the team will be able to compare children with Down syndrome to groups of children with typical development and autism. The UNC team will be starting enrollment in November and recruiting from the North Carolina region.



## Yen-Yu Ian Shih Included in Third Annual Class of Yang Family Biomedical Scholars

The UNC School of Medicine has named Yen-Yu Ian Shih, PhD, associate professor of Neurology, as a recipient of the third annual Yang Family Biomedical Scholars Award. Shih, who has been at the UNC School of Medicine since 2012, is the director of the Center for Animal MRI and director of the Small Animal MRI Core Facility at the Biomedical Research Imaging Center (BRIC); is a member of the UNC McAllister Heart Institute, the UNC Bowles Center for Alcohol Studies, the UNC Lineberger Comprehensive Cancer Center, and the Intellectual and Developmental Disabilities Research Center (IDDRC); and is an adjunct faculty member in the UNC-NC State Joint Department of Biomedical Engineering and faculty member of UNC-Chapel Hill's Neurobiology Curriculum.

Shih's laboratory carries out a diversified program of cutting-edge biomedical research in two main areas: understanding the link between brain activity and blood flow, including this link's relation to stroke progression, and understanding the role of stimulating a small population of neurons in the rodent brain. The physiology of such "neurovascular coupling" remains one of the most puzzling questions in both basic and human neuroscience and is at the foundation of the widespread use of functional MRI (fMRI) to study the human brain. His research accomplishments have garnered him a revered national and international reputation. Among his honors are the Ellen Schapiro & Gerald Axelbaum Investigator and Young Investigator Awards from the Brain & Behavior Research Foundation.

With the Yang Scholars program, the UNC School of Medicine aims to establish a community of its brightest and most promising young tenured faculty. The award recognizes faculty that have made significant scholarly contributions to their field while also receiving national recognition for their research.

## Joseph Piven Honored with Ruane Prize for Autism Research

*At an awards dinner in New York City this past month, Joseph Piven was named co-recipient of the Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research by the Brain and Behavior Research Foundation.*

Joseph Piven, MD, director of the Carolina Institute for Developmental Disabilities, received the Brain and Behavior Research Foundation's prestigious Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research. The award includes a \$50,000 prize, which Piven will share with co-recipient Ami Klin, PhD, director of the Marcus Autism Center in Atlanta. The award was initiated in 2000 by philanthropists Joy and William Ruane to recognize important advances in understanding and treating early-onset brain and behavior disorders.

Piven is the Thomas E. Castelloe Distinguished Professor of Psychiatry and Pediatrics and executive committee member of the UNC Autism Research Center at the University of North Carolina at Chapel Hill. Since 2002 he has led an NIH Autism Center of Excellence at UNC Chapel Hill, a program that supports large-scale research aimed at elucidating our understanding of autism spectrum disorder.

He is an expert on the causes and mechanisms underlying neurodevelopmental disorders such as autism. His current primary focus is in leading the multi-center 'Infant Brain Imaging Study (IBIS)' on brain and behavior development in infants at high risk for later development of autism.

Last year, [three papers](#) on which Piven was senior author, were in the top 10 research papers of 2017, according to the autism advocacy group Autism Speaks.



*Dr. Joseph Piven*

## Yen-Yu Ian Shih Earns \$3.8-Million NIH BRAIN Initiative Grant

*Yen-Yu Ian Shih will use cutting-edge neuroscience tools to improve the understanding of fMRI signal in a brain area called striatum.*



*The Shih Lab. Dr. Yen-Yu Ian Shih, back row, center*

Yen-Yu Ian Shih, PhD, associate professor of neurology and member of the UNC Biomedical Research Imaging Center, was awarded a four-year, \$3.8-million BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative grant from the National Institutes of Health.

It is the eighth such grant issued to UNC School of Medicine researchers since the initiative was launched in 2013 and the third for the Shih lab. Shih, who is also director of the UNC Center for Animal MRI, became a Yang Family Biomedical Scholar (*see page 4*) earlier this year for his work on functional magnetic resonance imaging, or fMRI.

For this BRAIN Initiative Study, Shih's lab will investigate the use of fMRI to study the striatum, a region of the brain involved in cognition, motivation,

reward, sensorimotor function, as well as several neurological and neuropsychiatric disorders, such as addiction, obsessive-compulsive disorder, schizophrenia, Parkinson's disease, and major depression. The scientific community's understanding of human brain function has been heavily influenced by fMRI – a technique that measures neuronal activity indirectly through blood oxygenation changes. But more and more scientific reports have indicated that scientists' interpretation of fMRI data could have been wrong in some brain areas, leading scientists to miscalculate the actual neuronal processes.

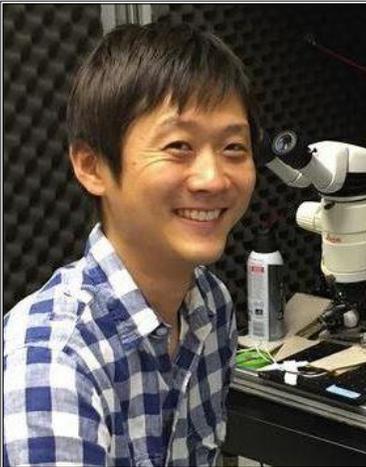
In this project, the Shih lab will use cutting-edge neuroscience tools to stimulate and record cellular activity as well as neurotransmitter release in the striatum during fMRI to uncover the mechanism by which fMRI signal is formed in this brain area. This information would help scientists better understand the brain function using noninvasive fMRI tools. "We have observed significant overgrowth in the striatum, specifically the caudate nucleus, in children with fragile X syndrome, starting in infancy," noted Dr. Heather Hazlett. "The new project by Dr. Shih using fMRI to examine the striatum has great promise to help us better understand the underlying neuropathology of this brain region and lay the groundwork for possible treatment studies."

## Hyejung Won Receives 2018 NARSAD Young Investigator Grant



The Brain & Behavior Research Foundation announced the awarding of its Young Investigator Grants valued at more than \$13.8 million to 200 of the world's most promising young scientists. The grants, awarded annually, support the work of early-career scientists with innovative ideas for groundbreaking neurobiological research seeking to identify causes, improve treatments and develop prevention strategies for psychiatric disorders.

New IDDRC Investigator, Hyejung Won, PhD, received the grant for research in genetic regulation. She hypothesizes that portions of the genome that confer unusual risk impact psychiatric conditions through complex gene regulatory networks. Dr. Won's project aims to unravel the gene regulatory landscape of the human brain to discover biological mechanisms of how risk variants drive gene expression patterns underlying psychiatric disorders. Dr. Won will utilize brain enhancer maps and statistical algorithms to prioritize regulatory variants that may underlie or indicate psychiatric conditions, then leverage chromatin interaction maps and other methods to assign schizophrenia risk variants to potential target genes. The functional relationship between non-coding variants and target genes will be explored.



## Hiroyuki Kato Selected for 2018 Class of Pew Scholars

The Pew Charitable Trusts named 22 early-career researchers as the 2018 class of Pew scholars in the biomedical sciences. The scholars, including Hiroyuki Kato, PhD, of the UNC Neuroscience Center and IDDRC, will receive four-year grants to advance their explorations of biological mechanisms underpinning human health and disease. Dr. Kato, an assistant professor in the department of psychiatry and a member of the UNC Neuroscience Center, will study how animals process sounds and the behavior elicited by different calls.

The scholars—all of whom have held assistant professor positions for three years or less—enter a vibrant community of researchers who have received awards from Pew since 1985. Current scholars meet annually to discuss their research, and exchange ideas with peers in fields outside of their own. This year's scholars were selected from 184 nominations, each submitted by a leading academic or research institution in the United States. The 2018 awardees are working to solve biomedical puzzles including the development of cancers

linked to viruses, how brain circuits enable verbal communication, and the ways in which the body senses and responds to external stimuli. The results of their research could provide new scientific foundations for potential treatments of metastatic cancer, infectious diseases, and psychiatric disorders.



## Juan Song Honored with 2018 Hettleman Prize

New IDDRC Investigator, Juan Song, PhD, has been awarded the Phillip and Ruth Hettleman Prizes for Artistic and Scholarly Achievement by Young Faculty. Dr. Song, who came to Carolina in fall 2013, leads a research team trying to understand how the healthy adult brain regenerates and to apply basic learned principles to the degenerated or injured brain to promote regeneration upon neuronal loss.

The birth of new neurons, a process called neurogenesis, is important for normal learning and memory, stress response and mood regulation. By understanding how neuronal circuitry and signaling mechanisms regulate the birth of new neurons in the adult hippocampus – an area of the brain critical to memory formation – Song's team hopes to create therapeutic interventions for brain injuries, degenerative diseases and mood disorders by targeting these adult-born neurons. At UNC, Song has developed a reputation both as "an innovative and fearless investigator" and a "model of friendship and collegiality" whose work blends

exceptional experimental skills with originality and creativity, said Henrik G. Dohlman, chair of the pharmacology department.

When Song was a postdoctoral fellow at Johns Hopkins University, she studied how neural stem cells create new neurons and how these new neurons contribute to specific brain functions. Building on these findings, Song and her team at UNC have published 13 research articles in some of the most prestigious scientific journals. On Nov. 2, 2017, *Cell Stem Cell* journal published a Song lab paper later selected as one of the journal's best eight articles of the year. "I have worked with some high-achieving individuals over the years, including several Nobel laureates and National Academy members," Dohlman said. "Even in this distinguished comparison group, I consider Dr. Song to be one of the most ambitious."

## Michael Sidorov Receives NIH Pathway to Independence Award & 2018 PARE Award



New IDDRC Investigator, Michael Sidorov, PhD, has been awarded an NIH Pathway to Independence Award (K99/R00) from the National Eye Institute to study how anterior cingulate cortex encodes visual input and is modified by visual experience. Anterior cingulate cortex is a prefrontal region involved in many higher-order processes, including cognitive control, error detection, and pain perception. In mice, this region receives direct input from visual areas and responds to very basic visual stimuli. However, it is not known if, and how, anterior cingulate uses this visual information to generate predictions and shape behavior. To address these questions, Dr. Sidorov will electrically record neural activity as awake mice view visual sequences on a monitor. He will train mice to expect "familiar" sequences of four visual stimuli, and will describe how neurons and networks within anterior cingulate cortex change as mice learn that they have seen a sequence before.

Given the importance of high-level, prefrontally-encoded behaviors to the autism phenotype, sensory processing in prefrontal circuits remains understudied. Therefore, Dr. Sidorov will characterize dysfunction in anterior cingulate microcircuits, and will investigate associated behavioral phenotypes, in two related single-gene mouse models of autism: Angelman syndrome and Dup15q syndrome. These autism-like disorders are caused by reciprocal loss or gain of function mutations in the UBE3A gene. The five year award provides training and funding for two years while Dr. Sidorov continues his postdoctoral fellowship working with Dr. Ben Philpot, followed by an additional 3 years of funding as he launches his independent research career.

Dr. Sidorov, who completed the T32 Post-Doctoral Research Training Program at the CIDD, has also been named a 2018 PARE Award Winner. The Postdoctoral Awards for Research Excellence (PARE) is given by UNC-Chapel Hill's Office of Postdoctoral Affairs in recognition of the research promise demonstrated by individual postdoctoral scholars. The awards are open to postdoctoral scholars in all disciplines.



## Stephanie Fox Receives CIDD Trainee Travel Award

Psychology Postdoctoral Fellow, Stephanie Fox, PhD, has been awarded the CIDD Trainee Travel Award, which will provide funds for her to attend the Association of University Centers on Disabilities (AUCD) 2018 Annual Conference in Washington, DC. At the conference, Stephanie will be presenting information about the Hearing and Development and Behavior Medicine Clinics of the Carolina Institute for Developmental Disabilities. Her conference presentations discuss the importance of a multidisciplinary team approach to evaluating and treating individuals with intellectual and developmental disabilities (I/DD). Additionally, her presentations emphasize the necessity to train emerging leaders in the field to increase access to high quality services for individuals with I/DD. The AUCD annual conference will take place in November 2018.



## Shannon Sweeney Awarded the Dashiell-Thurstone Prize

Shannon Sweeney, a graduating senior in Psychology and Neuroscience, is a recipient of the 2018 Dashiell-Thurstone Prize. The Dashiell-Thurstone Prize is awarded each year for the best senior honors thesis, as judged by a faculty committee. This award is named in memory of two significant figures in the life of the Department of Psychology: John Dashiell, who founded the Department in 1920, and Leon Thurstone, who founded the Psychometric Research Laboratory in 1953, which later became a significant component of the Department. Sweeney, working with her mentors at the CIDD, Drs. Heather Hazlett, Joseph Piven, and Jessica Cohen, won for her outstanding senior honors thesis, "Cerebellar Volumes in School-Age Boys with Autism Spectrum Disorder and Fragile X Syndrome." Sweeney was honored at the Psychology and Neuroscience Commencement Ceremony on May 13, 2018.

## Study Confirms Link Between Maternal Phthalate Levels, Risk of ADHD in Children



Dr. Stephanie Engel

A recently published study of mothers and children in Norway has confirmed an association between high phthalate concentrations in maternal urine and increased risk of attention-deficit hyperactivity disorder (ADHD) in children.

The study, led by new IDDRC Investigator, Stephanie M. Engel, PhD, professor of epidemiology in the University of North Carolina at Chapel Hill's Gillings School of Global Public Health, investigated growing concerns over whether prenatal phthalate exposure might impact children's neurodevelopment. Samantha Drover, a doctoral student studying epidemiology in the Gillings School, joined Engel and colleagues from Duke University, The Norwegian Institute of Public Health and Harvard University in this research.

The full study, titled "Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort," was published online May 10 by the journal *Environmental Health Perspectives*.

According to the Centers for Disease Control and Prevention, "Phthalates are a group of chemicals used to make plastics more flexible and harder to break. They are used in hundreds of products, such as storage containers, detergents, automotive plastics, raincoats and personal-care products like soaps, shampoos and nail polishes. People are exposed to phthalates by eating and drinking foods that have been in contact with products containing phthalates. Once phthalates enter a person's body, they are converted into breakdown products (metabolites) that pass out quickly in urine."

"Phthalates are ubiquitous in consumer products, and exposure also can occur through the diet," Engel said. "It is very difficult for individuals to meaningfully change their exposure to phthalates, but where regulations exist, they have been effective at reducing population exposure to these compounds."

In recent years, research on children's prenatal exposure to phthalates has linked high exposure levels with externalizing behaviors and executive functioning defects suggestive of ADHD. To learn more about this association, the researchers undertook an investigation into whether prenatal exposure was associated with clinically confirmed ADHD in a population-based, nested case-control study of the Norwegian Mother and Child Cohort (MoBa) between the years 2003 and 2008. Investigators measured phthalate metabolite levels in urine samples collected mid-pregnancy; they obtained ADHD case information by linking MoBa and the Norwegian National Patient Registry.

Subsequent modeling revealed that increasing quantities of di-2-ethylhexyl phthalate metabolites (DEHP) in maternal urine were associated with a steadily increasing risk of ADHD in children. Children of mothers who were in the highest quintile for DEHP had almost three times the odds of receiving an ADHD diagnosis compared to children whose mother's DEHP levels were in the lowest quintile. There were no significant variations to this trend based on sex, preterm delivery or maternal thyroid function.

"There is growing concern that phthalates might have neurotoxic effects, with increasing evidence of behavioral and cognitive associations coming from a number of independent studies," Engel said. "Our study is unique in that we had both a biomarker of prenatal exposure and a clinically diagnosed developmental outcome, which strengthens confidence in these measures. We need more research into the developmental impacts of these and other endocrine-disrupting exposures, but it also may be worthwhile to consider whether more health-protective regulations are warranted." Additional research is needed, the authors concluded, to evaluate potential biological mechanisms linking phthalates to ADHD.

### Benefits of Broccoli Extract in Young Men with Autism

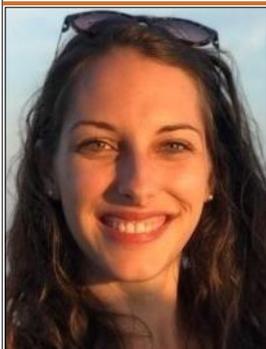
Research study to explore possible benefits of a broccoli extract supplement (sulforaphane) for young men 13-30 years of age with autism. If you or someone you know may be interested in participating in this study, please contact: Jessica Blanks 919-962-8462 or [Jessica.Blanks@cidd.unc.edu](mailto:Jessica.Blanks@cidd.unc.edu). For more information, follow this link to the digital brochure:

<http://www.cidd.unc.edu/docs/sulforaphanestudybrochure.pdf>



## Welcome T32 Postdoctoral Trainees

The CIDD T32 Postgraduate Research Training Program develops researchers with expertise in both the biological basis and clinical manifestations of neurodevelopmental disorders. This broad-based and integrated perspective enables researchers to better relate across disciplines and maximizes the potential for major research advances in understanding the pathogenesis and treatment of these disorders.



**Jessica Girault, PhD**, received her doctorate in Neuroscience from UNC Chapel Hill under the mentorship of Dr. John Gilmore. Dr. Girault's thesis work characterized the associations between brain structural maturation and cognitive development during infancy and toddlerhood in a large cohort of children with longitudinal brain imaging and behavioral assessment data. During her thesis work, Dr. Girault explored the usefulness of neuroimaging phenotypes as biomarkers of dimensional cognitive outcomes and became interested in using novel analytic techniques to probe brain-cognition associations with the goal of understanding the neurobiological mechanisms that contribute to variation in cognitive and behavioral outcomes across individuals. Dr. Girault joined the T32 program to work under the co-mentorship of Dr. Joseph Piven and Dr. Kathleen Gates to investigate how neuroimaging can be used to derive biologically-based subgroups of infants and toddlers at high familial risk for autism spectrum disorder (ASD) and use this information to help parse the heterogeneity in cognitive and behavioral profiles in ASD.



**Rebecca Grzadzinski, PhD**, received her doctorate in Clinical Psychology from Teachers College, Columbia University under the mentorship of Dr. Catherine Lord. Dr. Grzadzinski's research has focused on behavioral definitions of Autism Spectrum Disorder (ASD), measurement of ASD symptoms over time, and comorbid psychiatric symptoms. During her doctoral studies, she worked closely with Dr. Lord and colleagues to develop a treatment response measure for children with ASD called the Brief Observation of Social Communication Change (BOSCC)-- an observation-based measure of subtle symptom changes in children with ASD that aims to assist intervention researchers with identifying efficacious treatments. Dr. Grzadzinski joined the T32 program to work with Dr. Hazlett at the CIDD and Dr. Watson in the Speech and Hearing Sciences department. Through the Infant Brain Imaging Study (IBIS; Hazlett) and Early Development Project (Watson), Dr. Grzadzinski will study sensory and motor profiles in infancy and toddlerhood that predict later diagnoses of ASD and differential responses to treatment. This research will

add to the field's understanding of early behaviors that are related to later neurodevelopmental disorders, contribute to identifying maximally effective interventions, and promote the development of individualized treatments for children with ASD.



**Hanqian Mao, PhD**, received her bachelor of science in biotechnology from East China Normal University, where she studied single nucleotide polymorphism in human patients susceptible to systemic lupus erythematosus. For her graduate work at Duke University, Dr. Mao focused on posttranscriptional regulation of embryonic neurogenesis, and pursued her PhD under the mentorship of Dr. Debra Silver. Dr. Mao's thesis work characterized the role of RNA binding proteins in regulating the proliferation and differentiation of neural stem cells in mouse models. For her post-doctoral work at UNC, Dr. Mao is mentored by Dr. Mark Zylka, where she applies her expertise in molecular and cellular biology with *in vivo* mouse modeling to determine the efficacy of genomic editing therapy in treating Angelman syndrome. The goal of her research is to identify potential therapeutic strategy to mitigate the behavioral deficits in human patients, and perhaps prevent the manifestation of symptoms through early genetic intervention of patients.



**John Shorter, PhD**, received his doctorate in genetics from North Carolina State University under Dr. Trudy Mackay. Dr. Shorter studied the genetic architecture of gene interaction networks. Underlying genetic variation in certain genes may mask the effects of other genes through epistatic interactions. This was true for genes associated with aggressive behavior in a Genome Wide Association study (GWA), as natural genetic variation at one locus masked the effects of genes at another locus in one population but not another. The inability of replication in GWA in different populations is likely due to differing allelic variants, differing allele frequency, and epistatic interactions. This result has implications in GWA studies that make generalized claims using a single homogenous population. Currently, Dr. Shorter is in the department of genetics with Dr. Pardo Manuel de Villena working on experimental models of human disease. As a postdoc at UNC, Shorter has worked on understanding infertility and genetic incompatibilities using the Collaborative Cross mouse population. He is now working to understand the genetic factors influencing epilepsy as a CIDD T32 postdoctoral fellow. It is estimated that 30% of

individuals with seizures are refractory to existing drug treatment. The goal of his research is to identify genetic variants that lead to increased sensitivity to seizure, then repurpose or develop anti-epileptics to treat refractory seizures.

# NC-LEND Trainees and Fellows, 2018-2019

## Leadership Education in Neurodevelopmental and Related Disabilities

LEND is an interdisciplinary leadership training program funded by the U.S. Maternal and Child Health Bureau to prepare professionals for leadership roles that enable them to direct and facilitate culturally/linguistically-competent and family-centered interdisciplinary efforts, including systems change, to improve the health status of infants, children, and adults who have, or are at risk for developing, autism spectrum disorders or related developmental disabilities.



**Salma Baig** is a doctoral student in UNC's School Psychology program, serving as the psychology trainee at CIDD. Her interests are cultural competency across evaluations and interventions for neurodevelopmental and psychiatric disorders. Ms. Baig hopes to serve in the identification of children with comorbid disorders across all minority populations. Her LEND mentor is Dr. Jean Mankowski.



**Kendyl Cole** is a masters student in occupational therapy. Her interests include addressing transition services, sexual health education, and supporting community participation and development for individuals with I/DD. Her LEND mentor is Dr. Linn Wakeford.



**Tina Braimah** is a LEND Parent Fellow, Certified Nurse Midwife, and owner of a home birth midwifery practice. She is mother of 4 children—her youngest child has Down Syndrome. Ms. Braimah's interests include becoming a stronger advocate for her daughter and making midwifery care more accessible to all women. Her LEND faculty mentor is Ms. Ann Palmer.



**Anna Coleman** is a Self-Advocacy trainee interested in helping high school students with disabilities learn how to advocate for themselves. She is an Ambassador for the Special Olympics and a competitive runner. Her LEND mentor is Ms. Deb Zuver.



**Meredith Braza** is a graduate student in UNC's Doctor of Audiology program. She is interested in research to improve the early hearing detection and intervention of infants born preterm and/or with neurodevelopmental conditions. Her LEND faculty mentor is Dr. Jack Roush.



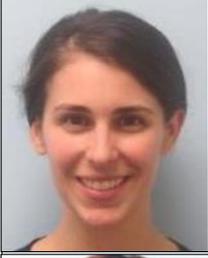
**Chelsea DeAngelis** is a second year masters student in the public health nutrition program at UNC. Her primary interest includes nutrition as a supplemental form of therapy for autism. Her LEND faculty mentor is Dr. Heather Wasser.



**Sheila A. Brown** is a Captain in the US Air Force and student in the Doctoral of Nursing Practice program. She is interested in helping parents identify signs and symptoms of developmental delay and disability to maximize their child's development and growth through early intervention programs. Her LEND mentor is Dr. Rob Christian.



**Jenna Duerr** is a graduate student in UNC's Doctor of Audiology program. She is interested in children with developmental disabilities who use cochlear implants. Her LEND faculty mentor is Dr. Jack Roush.



**Kelly Caravella** is a psychology intern at UNC, in the CIDD track. She is completing her PhD in Clinical-Community Psychology at the University of South Carolina and is interested in the longitudinal development of social communication in young children with genetic syndromes. Her LEND mentor is Dr. Jean Mankowski.



**Aimee Durrett** is a masters student in the Genetic Counseling program at UNC-Greensboro. She is interested in the role of genetics in intellectual and developmental disabilities and how to better advocate for individuals living with I/DD and their families. Her LEND mentor is Ms. Jennifer Mathews.



**Meng-Ting Chen** is a 5th-year PhD student in school psychology interested in neuropsychological assessment and rehabilitation. Her research focuses on the executive functioning and the gender differences among individuals with ASD. Her LEND mentor is Dr. Pete Duquette.



**Demi Eckhoff** is a MPH/RD student in nutrition interested in nutrition for people with I/DD and other disabilities, as well as public health related nutrition issues. She hopes to serve as a self and professional advocate for individuals living with I/DD. Her LEND mentor is Dr. Heather Wasser.

## NC-LEND Trainees and Fellows, 2018-2019 *continued*



**Crisma Emmanuel** is a PhD student in nursing interested in health equity and health care experiences of people with ASD. She hopes to serve as a researcher and advocate for individuals and family Service Details as they utilize both acute and long-term healthcare services. Her LEND mentor is Dr. Rob Christian.



**Gregory Hudson** is a Self-Advocacy trainee. His goal as a leader is to advocate for people to get the support they need. His LEND faculty mentor is Ms. Deb Zuver.



**Stephanie Fox, PhD** is a psychology post-doctoral fellow at the CIDD interested in differential diagnosis of intellectual/developmental disabilities, interdisciplinary diagnostic assessment, and family-focused interventions for individuals with ASD. Her LEND mentor is Dr. Jean Mankowski.



**Senyene Eyo Hunter, MD, PhD** is a 5th year Pediatric Neurology resident. She has a special interest in epilepsy and strives to optimize care for patients with neurodevelopmental disabilities. She is also interested in researching the genetic basis of neurological and metabolic disorders. Her LEND mentor is Dr. Rob Christian.



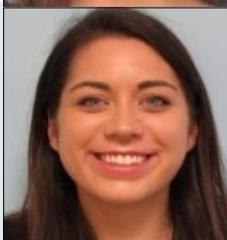
**Sarah Furlong** is a PhD student in clinical psychology interested in assessment of cognitive functions after surgery, traumatic brain injury, or other unique circumstances, as well as the diagnosis of ASD in school-age children. Her LEND mentors are Dr. Pete Duquette and Dr. Laura Hiruma.



**Liz Jaramillo** is a doctoral student in Speech and Hearing Sciences. She is interested in cross-cultural work and the global epidemiology of speech and hearing disorders, including autism. Her LEND mentor is Dr. Becky Pretzel.



**Rachel Greene** is a 5<sup>th</sup> year student in the Clinical Psychology program interested in assessing and treating co-occurring psychiatric disorders in individuals with ASD across the lifespan. Her LEND mentor is Dr. Pete Duquette.



**Paige Landau** is a doctoral student in the School Psychology program. Her interests involve neurodevelopmental disorders across the lifespan with a special interest in working with children with epilepsy and traumatic brain injury. Her mentor is Dr. Jean Mankowski.



**Rahma Hida** is a third-year student in the school psychology doctoral program at North Carolina State University. She is interested in evidence-based interventions and internationalization. Her LEND mentor is Dr. Whitney Griffin.



**Chelsea Lasky, PT, DPT** is a pediatric physical therapist resident. She graduated from Boston University before working for two years as a pediatric physical therapist serving children birth to 21 years. Her interests include early power mobility and adaptive sports. LEND mentor is Dr. Jean Mankowski.



**Emily Holding** is a doctoral student in the School Psychology program interested in neurodevelopmental disorders in pediatric populations. She hopes to conduct evaluations to identify children with complex developmental disorders and provide therapeutic services for these children and their families. Her LEND mentor is Dr. Pete Duquette.



**Heather Lauria** is a Doctor of Nursing Practice Family Nurse Practitioner student and Registered Nurse in Neurology/Neurosurgery interested in advocacy and access to healthcare for individuals with neuro-developmental disabilities. Her LEND mentor is Dr. Rob Christian.



**Maggie Holland, PT, DPT** is a pediatric physical therapy resident at Duke University interested in helping children with developmental disabilities optimize their movement and independence to fully participate in family and community life. Her LEND mentor is Dr. Jean Mankowski.



**Denise Pascarelli** is a LEND Parent Fellow interested in gaining knowledge and advocacy skills to help families and those living with I/DD live meaningful, productive and joyous lives. Her LEND mentor is Ms. Ann Palmer.

## NC-LEND Trainees and Fellows, 2018-2019 *continued*



**Alex Alvarez Rivas** is a MSW student. As a native Spanish speaker, she is especially passionate about working with Spanish speaking and/or immigrant populations with developmental disabilities and promoting equity in mental health care and resource access for these groups. Her LEND mentor is Ms. Sherry Mergner.



**Christine South** is a MS student in speech-language pathology interested in early identification of ASD and the impact of social inequality on access to intervention services. Her LEND mentor is Ms. Margaret DeRamus.



**Courtney Schlachter** is a graduate student in the Doctor of Audiology program interested in pediatric audiology and early intervention. She hopes to work on an interdisciplinary team serving children with hearing loss and I/DD. Her LEND mentor is Dr. Jack Roush.



**Amy Spicer** is a graduate student in the Doctor of Audiology program. She has a B.S. in Communication Sciences and Disorders and is interested in early intervention and working with children with profound hearing loss and multiple disabilities. Her LEND mentor is Dr. Jack Roush.



**Jill Sirko** is a LEND Family Fellow. Her daughter was born with a rare genetic condition and complex communication needs. Ms. Sirko's interests include promoting augmentative and alternative communication and literacy for every child. She is currently a parent educator at the Exceptional Children's Assistance Center. Her LEND mentor is Ann Palmer.



**Cheryl Walfall-Flagg** is a LEND Parent Fellow and mother of 3 sons: a pre-teen with I/DD, a teen with I/DD, and a college freshman. Her goals include supporting her boys to live the best lives possible, supporting other parents and individuals by sharing her experience and knowledge, and being a voice within the community. Her LEND mentor is Ms. Ann Palmer.



## UNC SPARK Continues to Help Move Research Forward!

The SPARK study aims to speed up research and advance the understanding of autism. Enrollment is done entirely online and saliva collection kits are sent directly to participants in the mail. So far, more than 3600 participants (individuals and their family members) have enrolled in SPARK through UNC. More than 2500 saliva kits have been returned for DNA analysis.

SPARK just released their second Snapshot data report highlighting information collected from families and individuals enrolled in SPARK. Snapshot 2 is a data report gathered from information provided by independent adults with autism who are participating in SPARK. This information is self-reported. In this report, an "independent adult with autism" is defined as an individual with autism who is at least 18 years old and who does not have a legal guardian. Data in this report include demographic and diagnostic data, as well as self-reported information on lifestyle, mental health, gender and sexuality, housing, and employment. You can find Snapshot 2 here: <http://cidd.unc.edu/Registry/Research/Docs/39.pdf>

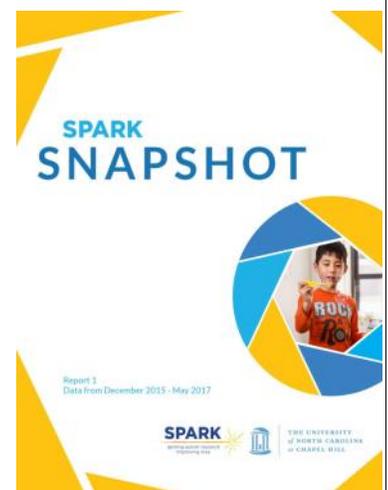


Data from December 2015 to April 2018



In case you missed the first Snapshot, Snapshot 1 is a data report on the first 18 months of SPARK. It's a compilation of interesting findings from information as reported by families and individuals enrolled in SPARK. This includes demographic and diagnostic data, information on pregnancy, birth history and associated conditions, as well as reported past genetic testing information. You can find Snapshot 1 here: <http://cidd.unc.edu/Registry/Research/Docs/33.pdf>

If you would like to learn more about or join UNC SPARK, please visit [www.SPARKforAutism.org/UNC](http://www.SPARKforAutism.org/UNC) or contact UNC SPARK Study Coordinator, Corrie Walston, MS at 919-966-6795 or [walstonc@email.unc.edu](mailto:walstonc@email.unc.edu)



## Study Finds a Role for an Autism Candidate Risk Factor NrCAM in Developmental Spine Pruning

The Maness Lab has published a new paper in *Cerebral Cortex*, 2018, 1-15, "Temporal Regulation of Dendritic Spines Through NrCAM-Semaphorin3F Receptor Signaling in Developing Cortical Pyramidal Neurons." Authors are Vishwa Mohan, Chelsea S. Sullivan, Jiami Guo, Sarah D. Wade, Samarpan Majumder, Amit Agarwal, Eva S. Anton, Brenda S. Temple, and Patricia F. Maness.

Excess dendritic spines and excitatory connections that are not pruned between early childhood and adolescence could be main problems underlying autism. Our goal is to understand the molecular mechanisms involved in spine pruning and find promising targets for therapeutic agents. Neuron-glia related cell adhesion molecule NrCAM is a newly identified negative regulator of spine density that genetically interacts with Semaphorin3F (Sema3F) and is implicated in autism spectrum disorders (ASD). We generated a novel conditional knockout mouse that allowed us to delete NrCAM from the pyramidal neurons at different developmental time points.

This work reveals a temporal function for NrCAM in regulating Semaphorin-mediated dendritic spine pruning in pyramidal neurons in developing neocortex. Deletion of NrCAM around adolescence resulted in elevated dendritic spine density in the cerebral cortex, whereas deleting it around early adulthood did not affect spine density. This underscores the importance of NrCAM during developmental spine pruning phase that happens around adolescence. Here we identified a novel mechanistic role for NrCAM in promoting oligomeric clustering of Sema3F receptor subunits through a molecular interface with Npn2, and by interaction with PDZ scaffold proteins such as SAP102. NrCAM-induced receptor clustering induces PlexA3's intrinsic Rap-GTPase activating protein (GAP) activity, which in turn inhibits Rap1 GTPase and inactivates  $\beta$ 1-integrins in the dendritic membrane.

These results define a novel developmental function for NrCAM in Sema3F receptor signaling that limits dendritic spine density on cortical pyramidal neurons during adolescence. As a result, balance between excitatory and inhibitory synapses develops, which is necessary for brain circuits to function properly.

*This research was funded by National Institute of Health grants (MH113280, MH101605, NS 090029, P30 CA016086) and pilot award (2KR361203) from North Carolina Translational and Clinical Science Institute (NC TraCS).*

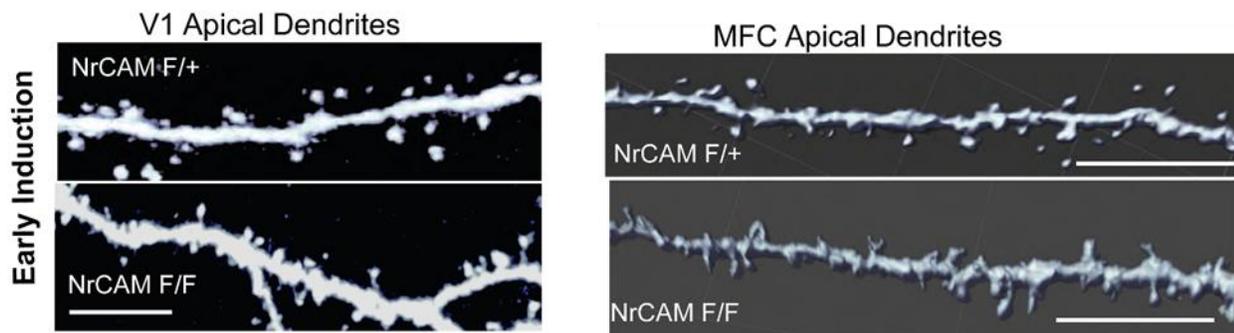


Figure representing the increased number of dendritic spines in NrCAM knockout (NrCAM F/F) compared to control mice (NrCAM F/+) in the pyramidal neurons of visual and medial frontal cortex.

### The UNC CIDD INVESTIGATOR FORUM Presents:



**Margaret Sheridan, PhD**

Assistant Professor, Dept. of Psychology and Neuroscience  
University of North Carolina at Chapel Hill

**"How Dimensions of Adversity Contribute to Risk for Psychopathology"**

Tuesday, December 4

12:15 PM - 1:30 PM

Bioinformatics Building, 1<sup>st</sup> floor auditorium (Room 1131)

130 Mason Farm Road, Chapel Hill

To view the 2019 schedule go to: <http://www.cidd.unc.edu/Education/InvestigatorForum/2018-2019InvestigatorForum.aspx>

Questions contact: Angela Cousin 919-843-8641 | [Angela.Cousin@cidd.unc.edu](mailto:Angela.Cousin@cidd.unc.edu)

# Angelman Syndrome: Bellwether for Genetic Therapy in Autism



The following commentary written by Matt Judson, research associate in the UNC Neuroscience Center, and Benjamin Philpot, associate director of the center, professor of neuroscience at UNC, and member of the CIDD, was originally published on Spectrum [www.spectrumnews.org](http://www.spectrumnews.org) October 16, 2018.



Matthew Judson, PhD

The ongoing discovery of autism-associated genes is coinciding with an explosion in technologies for gene editing and an ever-improving capacity to deliver therapeutic genes to the brain. This convergence carries with it new hopes for unique genetic therapies for autism and other conditions with strong genetic underpinnings. But the success of genetic therapies is not guaranteed. Even if disrupted genes can be replaced, repaired or otherwise restored, the fix may come too late. Genetic therapies may need to be implemented before neural insults even arise.

Perhaps the best way to tackle this concern is to attempt to treat an autism-related condition in which the therapeutic target — for instance, the causative gene — is discrete and well defined. Angelman syndrome is an ideal candidate.

Angelman syndrome is a neurodevelopmental condition characterized by intellectual impairment and motor dysfunction. Although its features overlap with those of autism, unlike most other forms of autism, it is caused by the dysfunction of a single gene, UBE3A. Due to the unusual regulation of UBE3A expression in neurons, Angelman syndrome is uniquely amenable to a variety of therapeutic approaches, ranging from adding the UBE3A gene back into neurons to turning on a dormant copy of the gene.

In the past few years, researchers have developed sensitive and reliable biomarkers that can be used to monitor the syndrome's progression and a person's response to treatment. And despite the condition's low prevalence of about 1 in 12,000 people, the clinicians who treat the syndrome are a tight-knit group. There are registries of [contact information](#) for and [data on individuals](#) with Angelman syndrome that will facilitate clinical trials. This combination of factors makes Angelman syndrome exceptionally tractable for therapeutic intervention.

A number of pharmaceutical companies have recognized these advantages and are actively advancing genetic therapies for the syndrome. It is not a matter of whether there will be clinical trials of genetic therapy for Angelman syndrome, but when.

## Two tactics:

There are two main strategies for these therapies; each one has risks and benefits. Typically, only the maternal copy of the UBE3A gene is active in neurons; the copy that is inherited from the father is silenced during development. People with Angelman syndrome usually carry mutations in the maternal copy of the gene, leading to a near-complete loss of UBE3A activity in neurons. This rare situation suggests two strategies for restoring UBE3A function. The most direct approach is to introduce a healthy copy of UBE3A into neurons. This transfer could be achieved using adeno-associated viruses, which can carry new genes to cells. Other approaches involve unsilencing the dormant paternal copy of UBE3A.

Adeno-associated viruses could be used to deliver genes encoding molecules that either destroy or block production of the RNA that silences paternal UBE3A. Small molecules and nucleotide fragments that bind to this RNA have already been shown to work — both in mice and in neurons derived from people with Angelman syndrome — suggesting that reactivation of paternal UBE3A is a viable approach. Given these promising opportunities, clinical trials for genetic therapy in Angelman syndrome seem inevitable. Their success hinges on sufficient distribution in the brain and proper timing of drug delivery.

## Location, location, location:

Because UBE3A is expressed in almost all neurons, an ideal genetic therapy for Angelman syndrome would reach the entire brain. Unfortunately, small molecules, nucleotide fragments and viral genetic therapies are unlikely to reinstate UBE3A expression uniformly across the brain.

Complicating matters, spatially biased reactivation of the gene could be worse than no reactivation at all. Our 2017 work demonstrates that selective reinstatement of UBE3A in excitatory, glutamatergic neurons worsens seizures in a mouse model of Angelman syndrome by boosting excitation in the brain. Introducing UBE3A into neurons that dampen brain activity can prevent the mice's increased susceptibility to seizures. Although this is an extreme example, any strategy for genetic therapy would need to account for the cell types and brain regions in which UBE3A reinstatement is most likely to occur.

*Continued on next page*

## Angelman Syndrome: Bellwether for Genetic Therapy in Autism

### *continued from previous page*

Even if researchers achieve spatially unbiased therapeutic delivery, a sufficient proportion of neurons must re-express UBE3A to alleviate features of the syndrome. The minimal requirement is unclear, but studies of people missing UBE3A in only a subset of neurons indicate that expression of the gene in as little as 10 percent of cells can be therapeutic.

UBE3A expression is likely to be much more important during development than in adulthood. Accordingly, mouse studies indicate that reinstating the gene in an embryo or newborn maximizes the therapeutic benefit. Later intervention may fail to fully address the earliest emergent features of the syndrome, including motor problems.

If begun early enough, genetic therapies for Angelman syndrome may not need to continue throughout life; targeting a critical window of development could be sufficient, although this window has yet to be defined.

#### **Safety concerns:**

Small-molecule or nucleotide therapies, on the other hand, may require repeated administration to sustain paternal UBE3A unsilencing throughout a critical developmental window. Ongoing treatment sparks safety concerns such as toxicity and off-target effects. These concerns, however, are offset by the opportunity to adjust dosing and, if adverse consequences arise, to discontinue treatment.

An unmutated copy of the UBE3A gene, once delivered, could not be turned off if it proved to produce harmfully high amounts of its protein product. And genetically delivered nucleases that destroy the silencing RNA could have off-target effects that accumulate over time. Furthermore, the viruses used to deliver these genetic therapies are likely to trigger an immune response, which would limit the ability to use them for any second-chance therapies.

The fact that Angelman syndrome occurs early in life presents its own set of challenges. First, there are significant regulatory and safety concerns for treating children who have a non-life-threatening condition. Second, drug dosing and delivery is inherently more challenging in children than it is in adults, and toxicities often vary by age. And repeated dosing to sustain UBE3A activity could be particularly risky in children. However, repeated delivery of nucleotides to treat spinal muscular atrophy has proven safe for use, even in infants.

The key timing and drug-delivery requirements for therapeutic efficacy in Angelman syndrome apply to most neurodevelopmental conditions. So the results of the inevitable clinical trials for genetic Angelman therapies should help guide strategies for trials in other similar single-gene brain conditions. They may also serve as a bellwether for treating more genetically complex forms of autism.

## Can Genetic Therapy Help Kids with Angelman Syndrome Overcome Seizures?

### *continued from page 2*

Philpot's team removed functional UBE3A from excitatory neurons – which trigger activity in connected neurons – and observed that the resulting mice were unaffected. Then they blocked the gene just in inhibitory neurons, whose activity normally quiets and regulates connected neurons, thereby preventing the neural hyperactivity that can trigger seizures. With UBE3A gone from the inhibitory neurons, the mice became even more susceptible to seizures than if UBE3A were absent from all neurons.

"This result implies that if you want to limit epilepsy in Angelman syndrome, you'll need at least to restore the function of UBE3A in inhibitory neurons," Philpot said.

The researchers gained another clue to the mechanism of Angelman syndrome seizures when they examined the brains of the seizure-prone mice, particularly in an area of the brain known as the hippocampus. They detected an abnormal accumulation of perineuronal nets (PNNs) – structures that surround neurons and block them from making new connections. Abnormal PNN formation has previously been linked to seizures. The scientists found that the abnormal PNN deposition did not occur in the young mice where UBE3A activity had been restored.

"We can now think of these abnormal PNNs as biomarkers for enhanced seizure susceptibility," Philpot said. "We now want to determine if these structures actually cause seizure susceptibility, for example by disrupting the connections that inhibitory neurons normally would make in this brain region."

Philpot and collaborators at UNC, along with other researchers elsewhere, are working on potential Angelman syndrome treatments, including drugs that would activate the previously silenced paternal copy of UBE3A in brain cells.

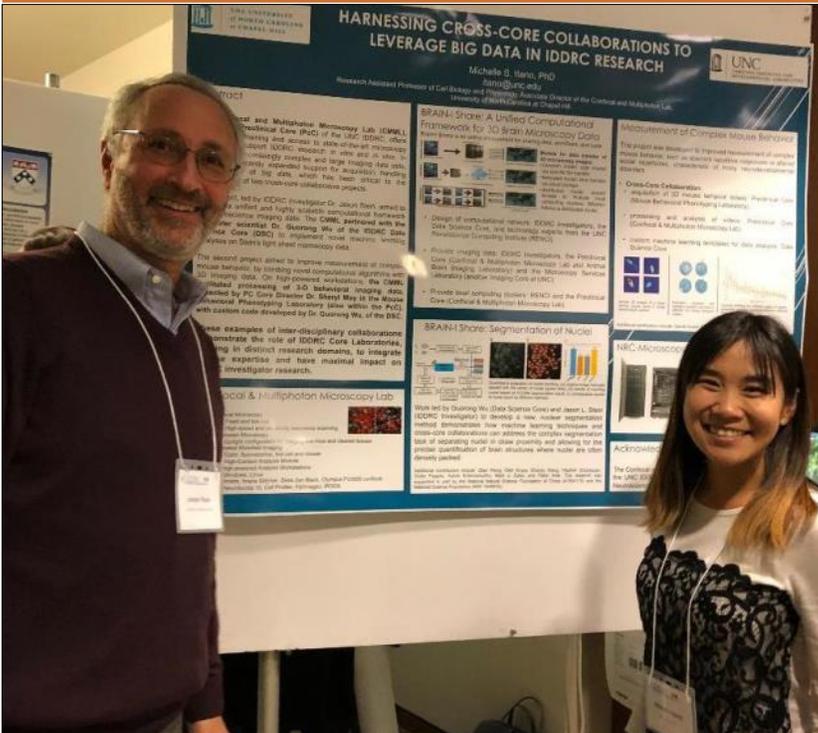
*The American Epilepsy Society, the Angelman Syndrome Foundation, and the National Institutes of Health funded this research.*



## CIDD Community Talk Series Presents:

**Natalie Wood Riche**, North Carolina Department of Justice – Outreach Specialist  
**"Popular Teen Apps Crash Course: A Guide for Parents of Children with Special Needs"**

A "crash course" on social media apps and tips to protect your child online!  
Wednesday, December 5 at 6:30PM to 8:00PM in the CIDD Castelloe Conference Room 101  
To RSVP or for more information, please contact: Debbie Reinhartsen at (919) 966-4138 or  
[Debbie.Reinhartsen@cidd.unc.edu](mailto:Debbie.Reinhartsen@cidd.unc.edu)



Pictured above left to right: CIDD and UNC IDRC Director, Joe Piven, and Michelle Itano, Assistant Professor of Cell Biology and Physiology and Director of the Confocal and Multiphoton Microscopy Lab of the IDRC/Neuroscience Center PreClinical Core. This Core lab is a collaborative effort supported by both the CIDD IDRC and UNC Neuroscience Center. Drs. Piven and Itano are pictured at the annual meeting of the IDRCs at Boston Children's Hospital with Dr. Itano's poster presentation entitled 'Harnessing Cross-Core Collaborations to Leverage Big Data in IDRC Research.' Ayse Belger, Director of the IDRC Clinical Translational Core and Director of FPG, and Gabriel Dichter, Associate Director of the IDRC, also attended the meeting.

This past Spring, CIDD representatives who support the NC Postsecondary Education Alliance (NC PSEA), participated in the South East Postsecondary Education Alliance (SE PSEA) conference in Memphis. Pictured left to right are Deb Zuver, Education Consultant and director of NC PSEA, McCafferty S. Kermon, Advocacy Faculty, Robert Evans, LEND trainee in advocacy, Tamira White, LEND trainee in transition and doctoral candidate.

## Your Support



The programs of the Carolina Institute for Developmental Disabilities provide innovative, high-quality clinical, research, and training activities supporting individuals with developmental disabilities. Now, more than ever, we need well-trained practitioners, teachers, and researchers. State funds pay only part of the costs to recruit and retain the best faculty and support the unique training and programs that are the hallmarks of the Carolina Institute for Developmental Disabilities experience. It is private funds that sustain and enhance these extraordinary opportunities for students, patients, families, and faculty. We can't do it without you!

A gift to the Carolina Institute for Developmental Disabilities is an investment in the lives of thousands and in the future of our communities. Join us by giving today. To make a donation by credit card, please visit the Medical Foundation of North Carolina's gifting page and choose "Carolina Institute for Developmental Disabilities:" [Click Here](#). Email [info@cidd.unc.edu](mailto:info@cidd.unc.edu) or call 919-966-5171 for more information about supporting the Carolina Institute.

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