From the director

Despite the challenges of the pandemic, my colleagues at the MIND Institute have continued to work hard to help families affected by neurodevelopmental challenges. Our clinicians transitioned almost seamlessly to telehealth visits in the early stages of the pandemic when in-person visits simply were not safe. Developmental screenings, medication checks, and even therapies were adapted and delivered through telehealth. We have now developed adequate safety procedures and ways to make our young patients comfortable in this new “masked” world, and about half of our clinical visits are again in person.

In terms of research, MIND Institute scientists have continued to make advances, making discoveries about differences in brain development in autism, the role of the maternal immune system in autism, and the early origins of ADHD symptoms in individuals with Down syndrome. MIND Institute faculty even led an effort to create a registry of individuals with the FMR1 premutation that will eventually support research around the world on the causes of, and treatments for, FXTAS and other health challenges. Many staff and faculty also went above and beyond to find new ways of helping families — doing webinars, interviews, and providing online lists of resources about how to deal with the stress of the pandemic, how to adapt to online schooling, and more. Our Child Life Team even figured out a way to do a drive through, social distanced and masked Thank You Party for research families!

You — our donors, supporters, and friends — also stepped up this past year. Philanthropy has helped us launch new initiatives, like the first-in-California inclusive, four-year, residential college program for young people with intellectual disabilities. Gifts from donors also helped us launch a grants program to support new diversity, equity, and inclusion efforts at the MIND Institute.

I have never been prouder of the MIND Institute than I have been over this past year. Thank you for being an integral part of who we are and what we accomplish.

Leonard Abbeduto
Director, UC Davis MIND Institute

A game-changer: new residential college program for students with intellectual disabilities

This fall, UC Davis will enroll 12 extraordinary new students. All will have intellectual disabilities. They’ll be called Redwood SEED (Supported Education to Elevate Diversity) Scholars, part of California’s first four-year residential program for students with intellectual disability associated with conditions such as autism, traumatic brain injury, fragile X syndrome and Down syndrome.

“It’s a game-changer. It’s the only thing like it in the west,” said Beth Foraker, an instructor in the UC Davis School of Education and co-founder of Redwood SEED Scholars.

Foraker has envisioned a program like this for years. Her 21-year-old son Patrick has Down syndrome, and she knows firsthand how limited the post-secondary options are for people like him.

“Ninety-seven percent of adults with intellectual disabilities are living in poverty,” she said. “This is a chance for them to go on to make a living wage, to live an authentic life of true freedom.”

Students in the program will have an opportunity to live on campus, engage in social activities and organizations, take college classes and pursue an internship or job. They’ll leave at the end of four years with a meaningful credential, prepared for employment success.

The UC Davis MIND Institute and the Office of Diversity, Equity and Inclusion will jointly run the program.
Big brains and white matter: new clues about autism subtypes

MIND Institute researchers tracked brain changes in children over many years using MRI scans

Two groundbreaking studies at the MIND Institute provide clues about possible types of autism linked to brain structure, including size and white matter growth.

The research is based on brain scans taken over many years as part of the Autism Phenome Project and Girls with Autism, Imaging of Neurodevelopment studies.

“There is no other single site data set like ours anywhere,” said Christine Wu Nordahl, associate professor in the Department of Psychiatry and Behavioral Sciences and co-senior author on both papers. “In one of the studies we have over 1,000 MRI scans from 400 kids, which is unheard of. It’s been 15 years of work to get here.”

Big brains: An autism subtype?

In the first study, published in Biological Psychiatry, the researchers used magnetic resonance imaging (MRI) to track brain size (volume) in 294 children with autism and 135 children without autism between the ages of 3 and 12. In children with autism, they found evidence of larger brain size relative to height — or disproportionate megalencephaly — a subtype that has been linked to higher rates of intellectual disability and poorer overall prognosis.

Previous cross-sectional research had found that children with autism have larger brains at early ages, but no evidence of larger brains in later childhood. The widely accepted theory is that these brains “normalized” or shrank as the children grew up.

The MIND Institute study found that wasn’t the case. The children who had bigger brains at age 3 still had bigger brains at age 12. Why? Unlike most research, which studies different individuals at different time points, this research studied the same children longitudinally, or over time.

“Bigger brain size in autism has been linked to lower IQ, and children with intellectual disabilities are harder to scan as they get older.”

— David Amaral, Director of Research, UC Davis MIND Institute

Also, unlike most other studies, this one includes children with significant intellectual disabilities. These were the children who tended to have the “big brain” form of autism.

David Amaral, co-senior author on both studies, suggested that the difference between this and previous research was that children with intellectual disability were left out of previous cross-sectional studies focused on older children.

“Bigger brain size in autism has been linked to lower IQ, and children with intellectual disabilities are harder to scan as they get older,” said Amaral, a distinguished professor of psychiatry and behavioral sciences and MIND Institute faculty member. “It’s a matter of sampling bias and the previous “dogma” appears to be an artefact of who got scanned when,” he explained.
Virtual autism teleconferencing program
for providers now offered in Spanish

Echo Autism, the MIND Institute’s interactive teleconferencing program for providers caring for people with autism, is expanding to offer a Spanish language program: ECHO Autismo.

“There is a huge need for providers to increase expertise in autism, so we are moving knowledge, instead of moving families and children, and we envision improving autism care for children everywhere,” explained Bibiana Restrepo, a developmental-behavioral pediatrician and assistant clinical professor in the Department of Pediatrics.

Restrepo, who’s also a MIND Institute faculty member, has been part of the ECHO Autism team since it launched in 2018. She said the group has participants from the Sacramento region, across the U.S. and around the globe. The goal is to develop a stronger connection with providers in underserved and rural areas who are committed to improving and enhancing autism care. She said the idea to create a program in Spanish came from ECHO participants who log in to the sessions from Latin American countries.

ECHO Autism involves a group of 20 to 25 providers who gather monthly over smartphones, tablets and computers via a teleconferencing platform to connect with the MIND Institute ECHO Autism team. A multidisciplinary team of experts leads the sessions, including developmental and behavioral pediatricians, psychologists, behavioral specialists, and social workers. The core concept is providing evidence-based practices for treating autism and associated conditions.

“After taking part in ECHO for quite a while now, I can tell you that it’s not just the participants who benefit,” Restrepo said. “The team at the MIND Institute learns from every single participant and their unique cases in a safe learning environment. It’s very rewarding!”

White matter: Connecting the clinical dots

The second study, also published in *Biological Psychiatry*, linked changes in the brain’s white matter growth with autism traits in some children. The researchers used a type of MRI scan called diffusion-weighted imaging, which allowed them to look at white matter regions, or tracts, in the brain. White matter provides the structural connections in the brain, allowing different regions to communicate with each other.

The study included 125 children with autism and 69 typically developing children who served as controls, between the ages of 2.5 and 7. The researchers found that the development of the white matter tracts in the brain was linked to changes in autism symptom severity. They observed slower development in children whose symptom severity increased over time, and faster development in those with decreased severity over time.

“From a biological standpoint, this emphasizes the role of white matter development in autism and autism symptoms,” said Derek Sayre Andrews, postdoctoral scholar at the MIND Institute and lead author on the paper. “We hope that in the future, measurements like this can identify children who would benefit from more intensive intervention — and serve as a marker to determine the effectiveness of an intervention for a particular child,” he said.

The studies are unusual not only because they include children with severe intellectual disability, but also because they include a larger number of girls, who tend to be under-represented in autism research.

Biomarkers in mother’s plasma could aid in early autism diagnosis and intervention

Using machine learning, researchers at the UC Davis MIND Institute have identified several patterns of maternal autoantibodies highly associated with the diagnosis and severity of autism. The study, published in Molecular Psychiatry specifically focused on maternal autoantibody-related autism spectrum disorder (MAR ASD), a condition accounting for around 20% of all autism cases.

“The implications from this study are tremendous,” said Judy Van de Water, a professor of rheumatology, allergy and clinical immunology at UC Davis and the lead author of the study. “It’s the first time that machine learning has been used to identify with such accuracy MAR ASD-specific patterns as potential biomarkers of ASD risk.”

Autoantibodies are immune proteins that attack a person’s own tissues. Previously, Van de Water found that a pregnant mother’s autoantibodies can react with her growing fetus’ brain and alter its development.

The research team obtained plasma samples from mothers enrolled in the CHARGE study. They analyzed the samples from 450 mothers of children with autism and 342 mothers of typically developing children, also from CHARGE, to detect reactivity to eight different proteins that are abundant in fetal brain. They then used a machine learning algorithm to determine which autoantibody patterns were specifically associated with a diagnosis of ASD.

The researchers created and validated a test to identify ASD-specific maternal autoantibody patterns of reactivity against eight proteins highly expressed in the developing brain. “The big deal about this particular study is that we created a new, very translatable test for future clinical use,” said Van de Water. This simple maternal blood test uses an ELISA (Enzyme-Linked-Immunosorbent Assay) platform, which is very quick and accurate.

The machine learning program crunched roughly 10,000 patterns and identified three top patterns associated with MAR ASD: CRMP1+GDA, CRMP1+CRMP2 and NSE+STIP1.

“For example, if the mother has autoantibodies to CRMP1 and GDA (the most common pattern), her odds of having a child with autism is 31 times greater than the general population, based on this current dataset. That’s huge,” said Van de Water. “There’s very little out there that is going to give you that type of risk assessment.”

“It’s the first time that machine learning has been used to identify with such accuracy MAR ASD-specific patterns as potential biomarkers of ASD risk.”

— Judy Van de Water, Professor of rheumatology, allergy and clinical immunology

Van de Water noted that with these maternal biomarkers, there are possibilities for very early diagnosis of MAR autism and more effective behavioral intervention. “This study is a big deal in terms of early risk assessment for autism, and we’re hoping that this technology will become something that will be clinically useful in the future.”

UC Davis coauthors include Alexandra Ramirez-Celis, Joseph Schauer and Miriam Nuño.
Gestational age linked to ADHD in children with Down syndrome

A new study by the UC Davis MIND Institute finds a connection between gestational age and later attention deficit/hyperactivity disorder (ADHD) symptoms in children with Down syndrome. The research, published in Scientific Reports, focused on children born at 35 weeks gestation or older. It found that earlier gestational age was linked to increased ADHD symptoms later in childhood. Gestational age is the length of time a fetus has developed since the beginning, or gestation, of a pregnancy.

“Despite growing evidence that gestational age predicts later symptoms of ADHD in the general population, this hasn’t been studied in children with Down syndrome,” said Laura del Hoyo Soriano, neuropsychologist and post-doctoral scholar in the Department of Psychiatry and Behavioral Sciences and lead author on the study. “That makes this study meaningful and an important first step to understanding factors related to ADHD symptoms in this population.”

The study included 49 boys and 56 girls (6–18 years old) born at least 35 weeks gestation with Down syndrome. The children were part of the Down Syndrome Cognition Project. The researchers based their study on the children’s medical records and questionnaires filled out by their mothers, incorporating well-established measures for ADHD symptoms and intelligence. They found that an earlier gestational age was associated with more symptoms of ADHD, even after adjusting for the child’s age and cognitive abilities.

ADHD commonly occurs with Down syndrome. It is generally characterized by inattention, distractibility, poor impulse control and trouble focusing. The study also suggests that ADHD may present in different ways as individuals age. Younger children with Down syndrome generally showed more ADHD symptoms compared to older ones. This is in line with research done in the general population.

“More attention needs to be paid to the care and follow-up of infants born pre-term, even those between 35 and 39 weeks, and perhaps even more so for those with Down syndrome.”

— Laura del Hoyo Soriano, Neuropsychologist

“More attention needs to be paid to the care and follow-up of infants born pre-term, even those between 35 and 39 weeks, and perhaps even more so for those with Down syndrome,” said del Hoyo Soriano. “The implications for early interventions could be significant.”

UC Davis study coauthors include Leonard Abbeduto and Taylor Wood.
International Fragile X Premutation Registry launches

The MIND Institute and the National Fragile X Foundation are working to encourage and accelerate research about the genetic condition with a new registry. The International Fragile X Premutation Registry is welcoming participants worldwide who are interested in taking part in research studies. The goal is to build a contact list containing a large, diverse group of people interested in contributing to research by taking part in clinical trials and other studies.

“This aim is especially important for premutation carriers with the neurodegenerative disease fragile X-associated tremor/ataxia syndrome (FXTAS),” said David Hessl, a psychologist and clinical professor in the UC Davis Department of Psychiatry and Behavioral Sciences who is leading registry efforts for the MIND Institute. “FXTAS, which is characterized by progressive loss of motor function and balance, as well as cognitive changes, currently has no cure or specific treatment.”

What is fragile X syndrome?

Fragile X syndrome (FXS) is a genetic condition. The “X” refers to the X chromosome, where the altered gene that causes it (FMR1) is located. Symptoms vary, but males are more severely affected, and are more likely to have intellectual disabilities and autism symptoms and distinguishing physical characteristics like long faces, larger ears, unusually flexible fingers and flat feet. People with FXS also tend to be very social and friendly and have strong visual or long term memory.

FXS affects approximately 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females. The UC Davis MIND Institute’s Fragile X Research and Treatment Center is a world leader in the field.

What is a premutation carrier?

A premutation carrier also has an altered form of the FMR1 gene, through the mutation is smaller than in those with fragile X syndrome. Carriers may pass on an expanded mutation to a child or grandchild, causing fragile X syndrome. Some carriers also develop fragile X-associated disorders. Those include primary ovarian insufficiency, which affects fertility (FXPOI) and FXTAS, affecting mostly males over age 50. FXTAS was discovered at the MIND Institute in 2001.

In contrast to the relative rarity of fragile X syndrome, an estimated 1 in 151 females and 1 in 468 men are premutation carriers.

How will the registry work?

Anyone 18 or older who is a premutation carrier, anywhere in the world, is encouraged to sign up for the registry. Family members of those affected by fragile X, but who are not premutation carriers themselves are also encouraged to sign up, to serve as research control participants. The registry enrollment link is on the National Fragile X Foundation website, and the database will be managed by UC Davis, where it will be protected in compliance with U.S. and European patient privacy regulations.

Researchers interested in recruiting participants from the registry will notify the registry team and advisory committee, which includes experts and fragile X family representatives, and submit a formal application for review. If approved, the registry team will notify registry participants about the research. There is no obligation to take part in any studies. Researchers will not be given registrants’ information.
The necessary protective gear, which also includes face shields and gowns, can be scary for kids. That makes it tough for pediatric providers to connect with their patients. “Even as an adult I can understand how it looks very intimidating,” said Veronica Tuss, a child life specialist at the MIND Institute. “I noticed that a lot of our patients, even if they had met us previously, would walk in and they were immediately taken aback.”

Tuss decided to do something about that. She ordered a photo printer and supplies and began creating a colorful button featuring a large photo of each MIND Institute provider. They pin their own picture-buttons on their clothing or white coat as a way of sharing a smile when introducing themselves. And it’s working. “As soon as we started wearing them, you’d still have the initial hesitancy, but when I point to the button and say, ‘Hi, this is me, I’m Veronica, this is what I do,’ it just brought back that personal aspect to our care. It’s made a huge difference.”

Most MIND Institute providers now wear their buttons whenever they’re interacting with patients, Tuss said. “The buttons have been so helpful to put kids at ease and to reassure them that there is a person under the PPE (personal protective equipment),” said Mary Jacena Leigh, a developmental-behavioral pediatrician at the MIND Institute. “Even for patients whom I have seen before, the buttons can help them recognize me to decrease any stranger anxiety. They are a wonderful tool to show our patients and families a friendly face as they can’t see that I’m smiling under the mask,” she said.

Before long, providers in other departments were asking Tuss if they, too, could have a photo button. She has now created more than 200 of them, mainly for the MIND Institute and the Department of Pediatrics. She creates, edits, prints, and cuts out each one herself. “Our role in child life is to be that connective piece between providers and patients and to provide comfort to the child to help support and empower them through procedures, and with our PPE, they were afraid of us,” she said. Now we’ve been able to remove this barrier that is physically on our face and reestablish these connections.”

Photo buttons help ease kids’ fears of providers in COVID-19 protective gear

Face masks are a regular part of medical visits now at UC Davis Health, and they are critical for protecting ourselves and those around us from COVID-19. But they also hide our smiles.
Excess folic acid during pregnancy harms brain development of mice

Researchers found too much folic acid was just as detrimental as too little

A UC Davis MIND Institute study of pregnant mice found that high amounts of folic acid during pregnancy harmed the brain development of embryos. Researchers say the findings indicate that more investigation is needed about the best recommended dosage for pregnant women.

“We believe there’s a Goldilocks effect with folic acid. Too little is not good, too much is not good; you have to get it just right,” said Ralph Green, UC Davis distinguished professor of pathology and medicine and a corresponding author of the study.

“We believe there’s a Goldilocks effect with folic acid. Too little is not good, too much is not good; you have to get it just right.”

— Ralph Green, Professor of pathology and medicine

The research, published in Cerebral Cortex, involved pregnant mice who were given either a normal amount of folic acid, 10 times the recommended amount, or none. The offspring of the mice that received the largest amount showed significant brain changes.

“It’s not subtle. It’s substantial,” said Konstantinos Zarbalis, associate professor in the Department of Pathology and Laboratory Medicine and a corresponding author of the research. “It makes a marked difference in brain structure if you take very high amounts of folic acid.”

Paradoxically, changes in the brain due to too much folic acid mimicked those associated with a deficiency of folic acid. “This, to me, was an even more important insight,” said Zarbalis, who is also on the UC Davis MIND Institute faculty. He noted that in humans, research shows that impaired folate uptake into the brain can cause cerebral folate deficiency, a syndrome that is often associated with the development of autism.

Folic acid and pregnancy

Folic acid (the synthetic form of vitamin B9, or folate) supplementation is widely recommended for women of child-bearing age. It has been shown to substantially reduce the risk of neural tube defects, such as spina bifida, in children. Research, including studies at the MIND Institute, has also shown that prenatal vitamins that include folic acid have a protective effect against the development of autism and other disorders.

Women who have given birth to a child with neural tube defects or who have certain conditions like epilepsy and take anticonvulsants, have generally been advised to take much higher doses of folic acid.

“In animal models, we have indications that very high amounts of folic acid can be harmful to brain development of the fetus, and the clinical community should take this indication seriously, to support research in this area to reevaluate the amount of folic acid that is optimal for pregnant women,” said Zarbalis.

Zarbalis and Green suspect that the problem lies in the way folic acid is metabolized by the body and have plans to investigate the phenomenon further.

Co-authors on the study included Angelo Harlan De Crescenzo, now at the University of Nevada, Reno; Alexios Panoutsopoulos, Lyvin Tat, Zachary Schaaf and Shailaja Racherla in the UC Davis Department of Pathology and Laboratory Medicine; Lyle Henderson of the Institute for Pediatric Regenerative Medicine at Shriners Hospital for Children and Nicholas Greene and Kit-Yi Leung of the UCL Great Ormond Street Institute of Child Health, University College, London.
MIND Institute showcases research, gives tour during virtual open house

UC Davis MIND Institute researchers and clinical experts offered a unique behind-the-scenes tour of the internationally recognized clinic, research labs and facility on Saturday, April 10. The annual event is typically held in person, but this year it was virtual due to COVID-19.

Faculty members took advantage of the different format to offer tours of areas that aren’t usually open to the public, such as the Biosciences Building, where many researchers have their labs. The change also allowed people from outside the area — including other countries — to view the event.

“The virtual open house enabled us to connect with families and our community, despite the pandemic,” said MIND Institute Director Leonard Abbeduto. “We enjoyed answering questions and sharing updates about our research into neurodevelopmental conditions. Next year, we very much hope to be interacting in person again.”

The presentation also featured information about clinic visits at the MIND Institute, including what a typical blood draw is like for children, and how the Child Life Program team helps to make the experience more comfortable.

The open house included presentations about the following areas:
- Brain imaging methods: MRI, ERP and EEG
- The Child Life Program and Phlebotomy Lab
- The Genomic Medicine Division
- The Telehealth Program

Abbeduto and other faculty members also answered questions from attendees, which ranged from resources available for parents to what educational path to take for those interested in working at the MIND Institute in the future.

The full open house can be viewed on the MIND Institute YouTube channel.
Development update and program spotlight: interventional genetics

Hello Friends of the UC Davis MIND Institute.

Over the last year our Interventional Genetics (IG) Program has made significant progress researching and developing novel stem cell and gene therapies for (rare) genetically linked neurodevelopmental conditions. In response to these breakthroughs, the IG team has been approached by multiple foundations focused on rare genetic disorders looking to collaborate and develop targeted gene therapies. This is an exciting time for this group, and I’d like to share a little more about this impactful program in my Spring update.

The interventional genetics team is led by David Segal, Jill Silverman and Kyle Fink. The team is focused on leveraging institutional expertise to bring curative therapies to individuals and families with rare genetic neurodevelopmental disorders. This interdisciplinary, multi-investigator program is designed to develop novel therapeutics that target underlying genetic problems using cutting-edge DNA and RNA technologies.

Faculty in the program work collaboratively to develop procedures for modifying gene expression and move from cellular models to tests of treatment efficacy using translationally relevant animal models. They also develop and validate cutting-edge behavioral and neurophysiological outcome measures with high clinical validity. The potential for launching human clinical trials is then made possible through the MIND Institute clinical program infrastructure.

The collaborative efforts of the Center for Interventional Genetics have addressed Angelman, Jordan, Rett, SCN1A/Dravet syndrome and CDKL5 deficiency.

The interventional genetics team is composed of MIND Institute Intellectual and Developmental Disabilities Research Center (IDDRC) investigators David Segal, professor in the Department of Biochemistry and Molecular Medicine, Kyle Fink, assistant professor in the Department of Neurology, and Jill Silverman, associate professor in the Department of Psychiatry and Behavioral Sciences. They are focused on leveraging their expertise to bring curative therapies to these rare, genetically linked disorders. The Fink and Segal labs have developed gene editing tools in cell models to fix the genetic deficit. These advances are now being translated into therapeutic platforms evaluated in animal models by the Silverman lab.

To learn more about the interventional genetics team or other fundraising opportunities, please contact me, MIND Institute Director of Development, Marcus Frost, at jmfrost@ucdavis.edu.
A winter wonderland with twinkling lights, inflatable holiday decorations and volunteers and staff dressed as princesses and superheroes brought the spirit of the season to children with cancer and neurodevelopmental disabilities and their families on Dec 5, 2020.

Nearly 1,200 people (about 300 cars) were invited for a unique, drive-through celebration in the MIND Institute parking lot. The COVID-19-safe event was hosted by the MIND Institute and the UC Davis Comprehensive Cancer Center.

The drive-through extravaganza served as the MIND Institute’s 18th annual Thank You Party for the hundreds of people who participate each year in research studies that advance the understanding and treatment of neurodevelopmental disabilities such as autism, ADHD and fragile X syndrome.

“We were thrilled to be able to show our gratitude with an event, despite the challenges of the pandemic,” said Leonard Abbeduto, director of the MIND Institute. “These families dedicate their time and energy to research that helps all people affected by neurodevelopmental challenges. We are inspired by their commitment and generosity,” said Abbeduto, who attended the event to personally thank many families.

Families drove through the winter wonderland display while listening to a custom playlist of holiday music in their cars, accessed via a QR code on their mobile phones. Each family received a bag filled with treats, stuffed animals and board games to continue the fun at home safely.

The MIND Institute offers a variety of events throughout the year, including fun activities for the whole family, lectures from experts on the latest research, and a variety of support groups. To learn more, please visit our website health.ucdavis.edu/mindinstitute/ and click on news and events.
which will be fully integrated into the campus community. It’s funded largely by a $2.1 million grant from the U.S. Department of Education, and the goal is to create a model that could be used by all schools in the UC and CSU systems. Renetta Tull, vice chancellor for diversity, equity, and inclusion, is also a principal investigator on the grant.

“This really is about diversity, equity and inclusion,” said Leonard Abbeduto, director of the MIND Institute. “People with intellectual disability should have the same rights to post-secondary education options as everyone else.”

Redwood SEED scholars will have a support system, including undergraduate students who will serve as peer mentors, helping with academics as well as social activities, health and wellness and oversight of internships. A curriculum that combines regular UC Davis courses with some special courses focused on relevant issues such as independent living, is also planned.

The program gets its name from the T. Elliot Weier Redwood Grove on the UC Davis campus. “Redwoods don’t grow in the Central Valley,” said Foraker. “Our summers are too hot, and our winters not wet enough, yet this grove flourishes thanks to careful tending, a habitat that allows them to thrive and people willing to make the impossible happen. Redwood SEED Scholars will take their cue from these on-campus giants.”

This story first appeared in the spring/summer issue of UC Davis Magazine.