

Letter from CART Director: “*Reflections on Autism Awareness Month and Progress in Autism Research*”

By: Daniel Geschwind, M.D., Ph.D.

It has been 3 years since we launched our seasonal CART newsletters and I thought it would be worthwhile to take the opportunity provided by Autism Awareness Month in April to communicate some reflections on new developments in our center and more broadly, in the field. The last several years of research has yielded many significant advances, including many new genes identified, improved understanding of how autism arises during brain development, dozens of new cell and animal models for understanding disease mechanisms and new evidenced based treatments. Although we still have a long way to go to effectively translate all of these advances into patients’ lives, the progress is nothing short of remarkable.

Before we delve into the science in more detail, I wanted to introduce several new faces in CART. I first introduce, Monica Belli, who is our new Center Administrator. Monica was born in Santa Monica, CA and graduated from Pitzer College and Seattle University School of Law. She comes to us with several years of experience in healthcare, including previously working with the UCLA Faculty Practice Group’s Ambulatory Operations department with a focus on the patient experience.

We also welcome Amanda Gulsrud, PhD, who trained with Connie Kasari, Director of Treatment Research. Along with Jim McCracken, Dr. Gulsrud has reorganized The Child and Adult Neurodevelopmental (CAN) Clinic, formerly the Autism Evaluation Clinic. Dr. Gulsrud is developing a multi-disciplinary clinic providing evaluation and treatment services for individuals with suspected disorders of social, cognitive, language, and motor development, including Autism Spectrum Disorders (ASD). Our goal is a multi-disciplinary training clinic, while also expanding treatment services and evaluation options. The training clinic includes psychiatrists specializing in medication management, a behavioral child neurologist who specializes in developmental disabilities, and clinical psychologists delivering brief treatment consultations and therapy. Treatment services include an array of empirically supported therapies for individuals of all ages on the spectrum in both individual and group settings and brief treatment-focused evaluations. For more information please visit: www.semel.ucla.edu/autism/clinic or call our clinic coordinator, Maya Lazar, at 310-794-4008.

Epidemiological research has clearly revealed that ASD prevalence is even higher

than previously expected. Several studies, including one in Korea, and monitoring by the Center for Disease Control indicates that an autism spectrum disorder (ASD) is observed in between 1/60 and 1/88 children. This number is shocking and provides clear indication that ASD is not rare, as previously thought even up to 5 years ago. All of the reasons for this increase are not known, but large contributors include changes in diagnostic criteria and the ability of clinicians to recognize ASD. Vaccines have been proven in several studies to not play a role. Other environmental factors, as yet to be determined, do need to be considered. The role of some prenatal or perinatal factors that are known to stress pregnancy, such as birth hypoxia (lack of oxygen to the brain), has been established in the past. There is a need for careful studies of the role of maternal environmental factors on ASD related outcomes.

Recognizing the need for rigorous studies of environmental factors during gestation, CART, in collaboration with the Semel Institute and the UCLA Clinical and Translational Science Institute (CTSI) recently funded a pilot project led by Beate Ritz, M.D., Ph.D., her researcher, Jasveer Virk, MPH, Ph.D., and colleagues in the UCLA School of Public Health. Dr. Ritz's research project assessed the association between dietary folic acid supplementation during pregnancy and diagnosis of ASD in offspring in a longitudinal population of women, the Danish National Birth Cohort (DNBC). The study was unable to corroborate previous reports that suggested reduction in risk for ASD in offspring among women using folic acid supplements preconceptionally and early in pregnancy.

This Pilot project is part of CART's larger efforts to bring new investigators and new areas of scientific inquiry into the field of autism research and capitalizes on the outstanding and extraordinarily diverse research community at UCLA. In collaboration with the UCLA CTSI and the Semel Institute, CART has been able to fund 2 to 3 such new pilot projects per year. Last year's Pilot Grantees also included Hongjing Lu, Ph.D., who conducted a study that looked at the impact of autism on action perception and research by Danny J.J. Wang, Ph.D., whose project was entitled, "Perfusion MRI and functional connectivity in ASD," which involved applying new imaging technologies to investigate organization of the brain in autism. Over the last decade, investment in these Pilot projects has been highly successfully and have resulted in numerous outside grants. In the future, we hope to fund many more Pilots grants, as the UCLA research community has a great deal of talent to bring to autism research.

The last 3 years of genetic research in ASD has also been remarkably productive. Gene sequencing has yielded many dozens of genes and mutations that increase risk for ASD. A series of four major publication used exome sequencing¹ to identify mutations disrupting proteins in patients with ASD in 2012. These studies showed a big effect of paternal age – older fathers contributed more to ASD due to new mutations occurring in sperm. They also predict that mutations in between 500-1000 genes contribute ASD,

¹ Sequencing the portion of the human genome that codes for proteins.

indicating enormous heterogeneity² UCLA investigators have played major roles in these findings. Recently, a study led by M.D. Ph.D. student Neel Parikshak in Dr. Geschwind's laboratory, published in the journal *Cell*, showed how many mutations involved in ASD converge to affect fetal brain development. These findings provide crucial evidence that autism arises during fetal brain development and points to specific biological processes that we hope to target for treatment in the future. Dr. Geschwind's group also leads a newly funded Autism Center of Excellence focused on finding genes in a population that until now has been under-represented in ASD research, the African American Community.³

From a clinical neurogenetics standpoint, CART investigator and child neurologist Dr. Shafali Jeste has designed the first prospective study of infants with Tuberous Sclerosis Complex (TSC), a genetic disorder that confers a high risk for both ASD and intellectual disability. In collaboration with Dr. Charles Nelson at Boston Children's Hospital, this study has followed infants with TSC from age 3 months to 36 months using both electrophysiological and behavioral measures. Their findings, soon to be published in the journal, *Neurology*, demonstrate cognitive predictors of ASD as early as 12 months of age. This work has led to the integration of these high-risk infants into an early intervention that targets social communication function (Dr. Connie Kasari, PI: JASPER) in order to improve their developmental trajectories.⁴ Future work will target a variety of these high-risk genetic syndromes to better understand pathways to and predictors of ASD in order to inform more targeted treatments for these children.

UCLA is one of the few centers in the world using EEG to study minimally verbal and very young children with ASD. Through our electrophysiology core, directed by Dr. Jeste, we have been using EEG to investigate brain function to understand patterns of learning and cognition, all of which will help inform treatment strategies and predictors of outcome. A recently published study by her group found that subgroups of preschoolers with ASD show a distinctive EEG profile in visual pattern learning that relates to their social ability and non-verbal cognitive function⁵. Another study from Dr. Jeste's group found that certain brain oscillations relate to language ability in young children with ASD. These important studies aim to identify early biomarkers that can help with earlier diagnosis and a lead to a better understanding of prognosis.

² See for example Berg and Geschwind 2012 *Genome Biology* or Geschwind 2011 *Trends in Cognitive Neuroscience*, for more detail (www.pubmed.org).

³ NIMH. *A Total of 11 Centers Now Funded for up to Five Years*. N.p., 2 Apr. 2013.

<http://www.nimh.nih.gov/news/science-news/2013/new-nih-funding-for-two-autism-centers-of-excellence.shtml>.

⁴ Jeste SS et al. Early Cognitive and Developmental Trajectories are Associated with ASD in Infants with Tuberous Sclerosis Complex. *Neurology*, 2014.

⁵ Jeste SS et al. Electrophysiological evidence of heterogeneity in visual statistical learning in young children with ASD. *Developmental Science*, 2014.

A new 5-year multi-site project studying ASD in girls has been started in collaboration with Kevin Pelphrey, Ph.D. at Yale University led by Susan Bookheimer, Ph.D. and Daniel Geschwind, M.D., Ph.D. at UCLA. Here, investigators at UCLA, Yale University, University of Washington, and Harvard University will study several hundred girls with ASD to understand the appearance of ASD in girls, and understand brain physiology and structure and how it might differ from boys. This is the first study focused on understanding autism in girls in a comprehensive manner. One of the ideas being studied is the idea of female protective factors that could be responsible for the lower incidence of autism in girls.

We refer you to our website for other updates and details about our ongoing studies by CART investigators, how to participate in research, and how to support CART. Over the last five years, we have integrated our clinical, research, and treatment programs so as to provide a true multidisciplinary approach to autism spectrum conditions, ranging from molecular genetic studies, animal models, and brain imaging, to infant-toddler research and treatment in adolescents, and non-verbal children with autism. We invite you to join us and continue to be our partner, as we cannot achieve our goals without you.

Updates at CART –New Faculty

While the field of Autism Spectrum Disorders (ASD) continues to grow, it still presents numerous challenges to the many families, practitioners, and researchers who deal with this very complex neurodevelopmental disorder. Offering hope, our CART scientists continue to collaborate across disciplines to explore the underlying mechanisms, biological markers, and developmental trajectories of ASD and to develop and test effective interventions.

I am proud to report that we've had exceptional success in several areas, including supporting promising junior faculty and trainees, securing renewed as well as new National Institute of Health (NIH) funding, and making important scientific advances. Some examples are highlighted in this issue. Dr. Amanda Gulsrud, a clinical psychologist working in the Kasari Lab, is featured as a new CART faculty member who focuses on novel interventions for young infants at-risk for developing an ASD.

In the Jeste Lab, Kevin McEvoy, a graduate student pursuing an M.D., Ph.D., has been awarded the Dennis Weatherstone Predoctoral Fellowship through Autism Speaks to study electro-encephalography (EEG) as biomarkers to predict language function in ASD children.

UCLA CART's Dr. Charlotte DiStefanno, was recently awarded a 2014 Mexiner

Postdoctoral Fellowship in Translational Research by Autism Speaks. She will use EEG to understand language and literacy abilities in minimally verbal children with ASD. Dr. DiStefano has worked as a postdoctoral scholar with the UCLA Department of Psychiatry since 2013 under the mentorships of Drs. Connie Kasari and Shafali Jeste.

Both Drs. Connie Kasari and Jeffrey Wood have secured additional grant funding for evidence-based intervention studies for school-aged children with ASD. And in the Geschwind Lab, we have received NIH funding for another 5 years for our ACE Network genetics grant, which involves 6 research sites nationwide, collaborating in a systematic, comprehensive investigation of ASD genetics in order to identify rare mutations, chromosomal abnormalities, and common variation contributing to ASD susceptibility in the underserved African- American population.

In Dr. Mirella Dapretto's group, doctoral candidate, Shulamite Green, MA, gave a talk at the 2014 International Meeting for Autism Research (IMFAR) entitled, "Neutral responsivity to tactile and auditory sensory stimuli in youth with and without ASD." In this study Green, along with senior authors, Drs. Mirella Dapretto and Susan Bookheimer examined how children and adolescents with and without ASD responded to sensory stimuli. In one of the first fMRI studies of tactile stimulation with children with ASD, the study confirmed prior findings that SOR is related to hyperactivation of the limbic system and primary sensory cortices.

Here are some updates from the CART Principal Investigators and their teams:

The CAN Clinic

By: Amanda Gulsrud, Ph.D.

The Child and Adult Neurodevelopmental (CAN) Clinic, formerly the Autism Evaluation Clinic, is a new multi-disciplinary Clinic providing evaluation and treatment services for individuals with suspected disorders of social, cognitive, language, and motor development, including Autism Spectrum Disorders (ASD).

This year the clinic announced several additions including a new clinical director, CART faculty member, Dr. Amanda Gulsrud and a multi-disciplinary training clinic held on Thursday afternoons. The training clinic includes psychiatrists specializing in diagnosing and treating challenging behaviors in children and adults, a behavioral child neurologist who specializes in developmental disabilities, a pediatrician-internist who addresses the general health care needs of our patients of all ages, early childhood specialists for children <24 months of age, a speech and language pathologist, and clinical psychologists delivering brief treatment consultations and targeted therapy.

Please visit our website to learn more about each member of our team at www.semel.ucla.edu/autism/clinic-team.

The Hutman Lab

By: Ted Hutman, Ph.D.

UCLA studies of infants at high risk for ASD seek to identify early warning signs of ASD and to lower the age at which treatment of early symptoms can commence. High-risk infants have an older sibling with ASD. Ted Hutman, PhD, and his colleagues have reported on visual attention, social responsiveness, joint attention, and functional play as behavioral indicators of autism during infancy. Recent work from Hutman's lab indicates that parent-reported temperament profiles from 6 to 36 months distinguish high-risk infants who will be diagnosed with ASD at age 3 from high-risk infants who show no signs of atypical development. Differences in parent-reported temperament were evident when infants were 6 months of age, well before overt behavioral signs of ASD have been documented. Current work in Hutman's lab suggests distinct language learning pathways in the second year of life among children later diagnosed with ASD. Finally, infants subsequently diagnosed with ASD demonstrate distinctive adaptive skill trajectories when compared to high-risk infants with non-autistic developmental delays. These differences were evident even when variability in infants' cognitive and language skills were taken into account.

PEERS Update

By Elizabeth Laugeson, Psy.D.

Bridging off the groundbreaking work underway at CART in developing and disseminating evidence-based treatments for individuals with ASD, CART scientist Dr. Elizabeth Laugeson recently published *The PEERS Curriculum for School-Based Professionals*, an empirically supported social skills program for teens with ASD, and *The Science of Making Friends*, a parent guide for helping teens and young adults with social challenges. Both books are based on the PEERS program, developed at UCLA, and considered one of the only evidence-based treatments for teaching social skills to those with ASD. This program has been translated into at least 6 languages and is offered in over a dozen countries.

With generous funding support from the Organization for Autism Research, the PEERS lab is currently testing the effectiveness of using a "virtual coach" in supporting the teaching of social skills to teens with ASD using a mobile application called

FriendMaker. In a postdoctoral research fellowship conducted by Dr. Mina Park, the PEERS lab is also testing the effectiveness of *PEERS for Preschoolers*, a parent-assisted, evidence-based social skills program for children 4-6 years of age with ASD. For more information about the research and clinical programs offered at the UCLA PEERS Clinic, contact: (310) 26-PEERS (310-267-3377), or visit the website at: www.semel.ucla.edu/peers.

While we're excited about our research, training mission, and scientific advances, the challenge of declining federal and state budgets at a time when there's so much possibility and hope is disappointing. Thus, now more than ever, we are more reliant on philanthropy to get cutting-edge research off the ground. Please visit the CART website for more information: www.semel.ucla.edu/autism

We continue with our plan to issue a CART Newsletter twice in the coming years – in Spring and Fall. We invite you also to visit our website (www.semel.ucla.edu/autism) throughout the year to stay informed about our research projects, clinical programs, our lecture series as well as our annual symposium and other sponsored events. All CART lectures are open to the community. I hope you will come to some of our lectures or events and I look forward to seeing you there. As always, we invite your feedback so that we can best provide you with what we hope will be interesting and useful information and updates about our work.

With best wishes, and many thanks for your support.

Best regards,



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