NRC newsletter

http://med.uth.edu/nrc | News & Featured Research of the Neuroscience Research Center | volume 23, number 2, fall 2017

The Eyes Have It: Orienting in Autism Spectrum Disorders

By Anne B. Sereno, Ph.D. and Cameron Jeter, Ph.D.

Sereno

Jeter

Abstract: Individuals with autism spectrum disorder (ASD) have impaired social interactions. These individuals do not look at the object of attention or eyes of others as often as typically developing controls. Our research shows that whereas children with ASD can reflexively follow social cues, they have trouble doing so voluntarily. Our tablet-based tasks can be developed as training tools for social orienting.

Just as the one with the most votes wins an election, the eyes select or orient to the object that wins our attention. This orienting thus plays a key role in determining what we observe, understand, and respond to in our world. It is vital to understanding and properly engaging in the subtleties of social communications and interactions. In the *Diagnostic and Statistical Manual of Mental Disorders* (5th Ed.; DSM-5; American Psychiatric Association, 2013), a defining criterion of individuals with autism spectrum disorder (ASD) is persistent deficits in social communication and social interaction across multiple contexts. A fundamental aspect of such deficits might not just be an inability to identify social cues, as is commonly thought, but rather a reluctance to orient or attend to them. In this article, we provide an overview of my lab's [Sereno's] recent studies of orienting and social orienting in ASD, with an idea for the development of an intervention.

Research has shown that individuals with ASD have especially

Continued on page 6; Sereno & Jeter

A Developmental and Behavioral Pediatrics Perspective on Autism Spectrum Disorder

By Anson J. Koshy, M.D., M.B.E , and W. Daniel Williamson, M.D.

Koshy

Williamson

Abstract: Autism Spectrum Disorder (ASD) is a biologically based neurodevelopmental disorder with broad phenotypic variability. For families in need of immediate assistance, the diagnostic evaluation remains the cornerstone for accessing supports and care. Here, we provide an overview of the diagnosis and management of clinical care for children with ASD, based on recommendations of the American Academy of Pediatrics. Our aim is to promote increased awareness of ASD and the need for comprehensive, evidence-based clinical care.

The patience of even the most seasoned medical professional navigating the Texas Medical Center during morning rush hour can sometimes run dry. For families coming to a clinic at UTHealth's Children's Learning Institute (CLI), the chaotic traffic is no doubt the least stressful part of the search for an answer to their question, "Does my child have autism?" Clinicians working with this unique patient population must be mindful of the countless stressors affecting a family and their experience with the medical community. Our team at CLI, including developmental pediatricians, psychologists, a nurse practitioner, and a speech and language pathologist, focuses on providing family-centered and evidence-based assessments, recommendations, and guidance in a clear and compassionate manner.

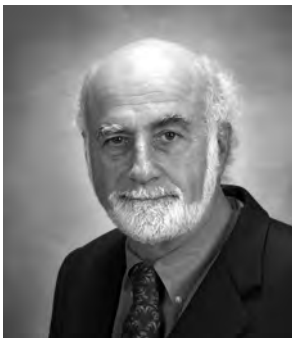
The 2013 revision of the *Diagnostic and Statistical Manual of Mental Disorders* (5th Ed.; DSM-5; American Psychiatric Association)

Continued on page 8; Koshy & Williamson

UTHealth® | Neuroscience Research Center
The University of Texas Health Science Center at Houston

Director's Column

From the Director, John H. Byrne, Ph.D.



This issue of the newsletter focuses on autism spectrum disorder (ASD), which has gained considerable attention in recent years and was in the public eye, front and center, in early 2017. The film, *Life, Animated*, based on a book by Pulitzer Prize-winning journalist Ron Suskind about his child's and family's experience with autism, was nominated for the Academy Award for Best Documentary. TV focused on ASD, too. *Sesame Street* added a character with autism to its regular cast, and *60 Minutes* as well as National Public Radio ran features on it.

The NRC Executive Committee was certainly in time with the public pulse in its choice of autism as the topic for our 2017 Public Forum, held last March. Four faculty members conducted a lively discussion with an audience of the public and professionals in education and support services. (See photo below.)

We maintain the focus on autism in the newsletter's two scientific articles. In one, co-authors Anne Sereno, Ph.D., professor of neurobiology and anatomy at McGovern Medical School, and Cameron Jeter, Ph.D., assistant professor at the UTHealth School of Dentistry, discuss their recent study of eye gaze and social communication in children with ASD. Dr. Sereno's lab has researched attentional dysfunction in such disorders as autism for over 30 years. Our second article provides a clinical perspective. UTHealth co-authors Anson Koshy, M.D., M.B.E., a board-certified developmental and behavioral pediatrician and assistant professor of pediatrics, and W. Daniel Williamson, M.D., a developmental pediatrician and professor of pediatrics, describe and explain the evidence-based, scientifically informed approach to the diagnosis and clinical management of children with ASD that is standard at the Dan L. Duncan Children's Neurodevelopmental Clinic and the Center for Autism and Related Conditions at the UTHealth Children's Learning Institute where they practice.

Another topic claiming the spotlight at UTHealth this year is stroke-related research, treatment, and education. A new, comprehensive, multidisciplinary enterprise, the Institute for Stroke and Cerebrovascular Disease, was inaugurated in early 2017. Spanning across UTHealth's six schools, the new institute promises to be a prominent feature of our virtual neuroscience research landscape in the coming months and years. Under the direction of Sean Savitz, M.D., professor and the Frank M. Yatsu Chair in Neurology, the institute is rooted in the fertile ground of one of the most active research and clinical stroke programs in the U.S. James Grotta, M.D., former chairman of the Department of Neurology at McGovern Medical School and now director of stroke research at the Clinical Institute for Research and Innovation at Memorial Hermann-Texas Medical Center, founded UTHealth's stroke program in the early 1980s. It was shaped in the beginning years through collaborations with faculty in stroke epidemiology, basic science, clinical trial design, and Houston Emergency Medical Services. The program was a lead site in the NINDS tPA stroke studies from 1990-1995 and launched the country's first mobile stroke unit. From 2002-2014, the program served as one of eight centers in the U.S. conducting specialized translational research for the development of novel acute stroke therapies.

The new institute will partner with the Memorial Hermann Health System of hospitals and stroke centers located throughout Houston, in addition to the UTHealth schools and centers and other institutions in the Texas Medical Center. The vision is to develop educational initiatives and multidisciplinary training programs, along with new, interdisciplinary research areas in stroke prevention, stroke recovery, and personalized medicine, such as pharmacogenetics and ethnic and gender disparities. Senior UTHealth scientists who will play key roles in the institute's many initiatives include Jaroslaw Aronowski, M.D., Ph.D., professor, vice-chair, and the Roy M. and Phyllis Gough Huffington Chair in Neurology, and Louise D. McCullough, M.D., Ph.D., professor, chair of the Department of Neurology, and the Roy M. and Phyllis Gough Huffington Distinguished Chair of Neurology. As mentioned in the NRC Newsletter's spring issue, Dr. Aronowski received the highly prestigious international Thomas Willis award at the American Heart Association's 2017 International Stroke Conference. He also recently published in *Nature Communications* the encouraging results of his NINDS-funded research on intracerebral hemorrhage. His findings suggest that certain immune cells, neutrophils, may help heal the brain after intracerebral hemorrhage and could form the basis for the first medicine to treat this type of stroke, for which there are currently no treatments and is often fatal.

Just announced in February, the stroke institute will be a hub of activity, encompassing a bio-core, data core, imaging core,

Continued on page 3; Byrne

Continued from page 2; Byrne

and clinical trial core, as well as a think tank to assist with grant submissions on new clinical trials in stroke and cerebrovascular disease. Investigations will span the effectiveness of care along the continuum from a mobile stroke unit using telemedicine en route to the emergency room to rehabilitation and recovery. New areas of focus include the complications of stroke—cognitive impairment, depression, anxiety, effects on memory, and sleep changes, to name a few. Keep your eye on the new UTHealth Institute for Stroke and Cerebrovascular Disease. It will also have synergistic impact on training and education for trainees at all levels and in various disciplines from nursing students to medical students to post-doctoral fellows.

Education at all levels is an NRC priority and a compelling commitment of my own, even in young children. The excitement in childhood of exploring and understanding aspects of the world around us and ourselves is often what propels people into a scientific career path. One of the NRC's most important programs and a favorite of mine is our annual Brain Night for Kids, held last March at the John P. McGovern Museum of Health & Medical Science. This year's event attracted over 1,350 children, family members, and friends to dozens of fun, hands-on neuroscience activities, coordinated by NRC faculty members, UTHealth graduate and medical students, postdoctoral fellows, and students from Rice University and Texas Woman's University. See the newsletter's "In the Spotlight" section for photos of the event.

Educating the general public through programs like Brain Night and our annual Public Forum, mentioned above, is fundamental not only to the NRC's mission, but to the scientific community overall. Clearly, when people understand and appreciate the role that scientific discovery plays in their everyday lives and in society as a whole—their support for science grows. Along those lines, I was pleased to follow media reports of the phenomenal "March for Science" event on April 22nd, at first a national—and then a global—celebration of science and its role in upholding the common good. Organized as a call for the support of scientific research and the enactment of evidence-based policies, the event comprised a collection of rallies and marches in Washington, D.C. and an estimated 500 cities around the world, including Houston, where one of the key speakers was neuroscientist Huda Zoghbi, M.D., Ph.D., Director of the Jan and Dan Duncan Neurological Research Institute at Baylor College of Medicine and Texas Children's Hospital. The March for Science—with such major partners as the American Association for the Advancement of Science and the Society for Neuroscience—has issued a clarion call to scientists to speak out on the value of science in policy-making and to encourage the public to support science and invest in it. I agree, and I hope that more and more of our neuroscience community will be stepping up to speak out in support of science and to help the public understand advances in scientific knowledge of the brain and brain disorders.

Panelists for the NRC Public Forum, "Autism Spectrum Disorders in the Age of DSM-5," were (from far left) Anne B. Sereno, Ph.D., professor of neurobiology and anatomy; Katherine A. Loveland, Ph.D., professor of psychiatry and behavioral sciences; Deborah A. Pearson, Ph.D., professor of psychiatry and behavioral sciences; and moderator, Pauline A. Filipek, M.D., professor of pediatrics.

The invited speaker for the NRC's Distinguished Lecture in the Neurosciences was Stanislas Dehaene, Ph.D. (center), professor and chair of experimental cognitive psychology at the Collège de France in Paris. Joining him and Dr. Byrne is Nitin Tandon, M.D. (far left), professor of neurosurgery at McGovern Medical School, for the lecture, "Language and Mathematics: Investigating the Singularity of the Human Brain," at UTHealth on May 19.

Grants & Awards

John H. Byrne, Ph.D., professor and chair of the Department of Neurobiology and Anatomy at UTHealth McGovern Medical School, received a UT System Board of Regents' Outstanding Teaching Award for 2017, the regents' highest honor for teaching excellence. In addition, *Learning and Memory: A Comprehensive Reference, 2nd Edition*, edited by Dr. Byrne, was published last summer (Elsevier). Comprising four volumes, each edited by a leading neuroscientist, it incorporates the expertise of over 150 outstanding investigators and scholars.

Qilin Cao, M.D., associate professor of neurosurgery at McGovern Medical School, received an NIH/NINDS R01 grant for $1.7 million for research on spinal cord injury (SCI). He will examine whether reprogramming astroglia into neurons can reconnect injured supraspinal pathways to neurons in the caudal spinal cord and promote functional recovery after cervical SCI.

Jasper Chen, a second-year McGovern Medical School student, was selected as a Howard Hughes Medical Institute (HHMI) Fellow to research glioblastoma multiforme (GBM), the most common malignant primary tumor of the brain, in the lab of Ronald DePinho, M.D., professor at the UT MD Anderson Cancer Center. As an HHMI Fellow, he is receiving $43,000 to pursue the research for one year.

Gerard Francisco, M.D., professor and chair of the Department of Physical Medicine and Rehabilitation at McGovern Medical School, has been elected to membership in the National Academy of Medicine. Chief medical officer of TIRR Memorial Hermann, Dr. Francisco specializes in brain injury and stroke rehabilitation. He is the founding director of the NeuroRecovery Research Center at TIRR, where he and his team study the roles of neuromodulation, human-machine interfaces, robots, and exoskeletons in facilitating neurologic and physical recovery.

Claire Hulsebosch, Ph.D., professor of neurobiology and anatomy at McGovern Medical School, was recently awarded the Reeve-Irvine 2016 Research Medal for her contributions to understanding the mechanisms of spinal cord injury, including her discoveries that are now used routinely in treating chronic neuropathic pain. The medal is given by the Reeve-Irvine Research Center at the University of California, Irvine.

Vasanthi Jayaraman, Ph.D., professor of biochemistry and molecular biology at McGovern Medical School, received a $2.6 million five-year NIH Maximizing Investigators' Research Award. Her research team focuses on enhancing learning and memory and paving the way for new treatments for Lou Gehrig's disease and other neurodegenerative conditions. Dr. Jayaraman also received a 2017 UT Regents' Outstanding Teaching Award.

Cameron Jeter, Ph.D., assistant professor of diagnostic and biomedical sciences at UTHealth School of Dentistry, received a Colgate Award for Research Excellence from Colgate-Palmolive Co. She will develop an oral hygiene app with educational, social, and other features to improve oral health in nursing home residents with Parkinson's disease, which makes oral hygiene challenging.

Nicholas J. Justice, Ph.D., assistant professor in the Institute of Molecular Medicine, McGovern Medical School, received a $2.3 million, 5-year grant from NIMH. With a collaborator at the Feinberg School of Medicine, Northwestern University, he is investigating how stress alters activity of the basal ganglia to influence movement in anxiety and depression, as well as in other contexts such as Parkinson's disease.

Balveen Kaur, Ph.D., joined McGovern Medical School as professor and vice chair for research in the Department of Neurosurgery and the school's second holder of a John P. and Kathrine G. McGovern Distinguished Chair. She was also named a UT System STARs Award recipient. Previously at Ohio State University, her focus was to identify novel therapeutic approaches to treat brain tumors. At UTHealth, she will establish a new neuro-oncology program integrating activities across numerous departments and promoting collaborative research.

Jose Felix Moruno Manchon, Ph.D., postdoctoral research fellow in the lab of Andrey Tsvetkov, Ph.D., assistant professor of neurobiology and anatomy at McGovern Medical School, received a 2-year fellowship grant from the Hereditary Disease Foundation. The foundation's mission is to fund innovative research towards curing Huntington's disease and impacting other brain disorders. Dr. Manchon's project is to better understand the role of sphingosine kinase 2 in promoting DNA damage and neurodegeneration in Huntington's.

Rodrigo Morales, Ph.D., assistant professor of neurology at McGovern Medical School, received a 5-year grant from the NIH/NIAID for a project to explore the dynamics of environmental contamination by prions that cause chronic wasting disease. He will focus specifically on natural and man-made environmental components that increase disease transmission.

Ines Moreno-Gonzalez, Ph.D., assistant professor of neurology at McGovern Medical School, received a 3-year Convergence Science Research Award from the U.S. Department of Defense, Peer Reviewed Alzheimer's Research Program. Her project will examine the effects of single-acute and also repetitive-mild traumatic brain injury on

A congressional resolution sponsored by U.S. Rep. Sheila Jackson Lee of the 18th Congressional District was presented to Dr. Byrne at the public forum in March. The community liaison from the congresswoman's Houston office made the presentation in recognition of the NRC's educational programs, community service, and support for neuroscience research.

Ndidi Uzor, a Ph.D. student specializing in neuroscience, received the NRC's 2017 Graduate Student Brain Awareness Outreach award for her dedication to community service and the many educational presentations she has given. Dr. Byrne made the presentation at the Public Forum.

the initiation of Alzheimer's disease and chronic traumatic encephalopathy pathologies. She will also study the properties of misfolded tau aggregates produced after traumatic brain injury.

Sunil Sheth, M.D., a physician-scientist who specializes in brain injury, joined the Department of Neurology at McGovern Medical School as an assistant professor and received a Rising STARs Award from the UT System. His research focuses on using lipids to identify blood biomarkers of brain injury, an approach that could improve the detection and treatment of traumatic brain injury and acute ischemic stroke.

Claudio Soto, Ph.D., professor of neurology and director of the George and Cynthia W. Mitchell Center for Alzheimer's Disease and Other Brain Related Illnesses at McGovern Medical School, received a U.S. Department of Defense Convergence Science Research Award of $770,000. His project is to adapt and utilize protein misfolding cyclic amplification technology for the specific detection of misfolded amyloid-beta and tau oligomers in cerebrospinal fluid and blood after traumatic brain injury. Also, **George Edwards III, M.S.**, a research assistant in Dr. Soto's lab and student in The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, received an NIH/NINDS predoctoral training grant of $71,000 for the project, Effect of Traumatic Brain Injury on Tau Pathology by a Potential Seeding Mechanism.

Farhaan Vahidy, Ph.D., assistant professor of neurology at McGovern Medical School, received a grant from the Lone Star Stroke Research Consortium of Texas to research the factors underlying decisions to treat patients with intracerebral hemorrhage at various levels of care, patients' resource utilization during and after hospitalization, and patients' functional and quality of life outcomes post-discharge.

Consuelo Walss-Bass, Ph.D., associate professor of psychiatry and behavioral sciences at McGovern Medical School, and **Joy M. Schmitz, Ph.D.**, professor of psychiatry and behavioral sciences at McGovern Medical School, have received a $2.6 million award from the NIH/NIDA and Fogarty International Center. In collaboration with an investigator at the Pontificia Universidade Catolica in Rio Grande do Sul, Brazil, they will study the effects of environmental stressors on the development of cocaine use. They will look at two stressors in particular—trauma exposure and HIV infection—in combination with the genetic profile of people who are addicted to cocaine.

Jerry S. Wolinsky, M.D., professor emeritus of neurology at McGovern Medical School, recently received two distinctions for his career-long commitment to multiple sclerosis research, education, and patient care. The Consortium of Multiple Sclerosis Centers awarded him its 2017 Lifetime Achievement Award, and the Society for Clinical Trials awarded him the 10th Annual David Sackett Trial of the Year Award for the Oratorio clinical trial, for which he was the senior investigator.

John J. Kopchick, Ph.D., a 1980 alumnus of The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences and a renowned molecular endocrinologist at Ohio University, together with his wife Charlene, donated $10.5 million to the MD Anderson UTHealth Graduate School. Their gift will establish an endowment for student fellowships, fund a research symposium, and fund competitive research awards to students and their faculty mentors.

Continued from page 1; Sereno & Jeter

strong emotional responses to eyes and often avoid direct eye contact. As reviewed in our journal article (Kirchgessner, Chuang, Patel, and Sereno, 2015, *Front. Neurosci.* 9:453.doi: 10.3389/fnins.2015.00453), investigators have found that when individuals with autism viewed live-action movie clips, they spent less time looking at eyes and more time looking at mouths and objects. Other researchers showed that children with autism exhibit an impaired ability to spontaneously follow another person's changing head and eye movements and orient markedly less than a control group of typically-developing individuals.

Examples of social orienting behaviors that are particularly important for everyday social functioning include attending to the same object as someone else (referred to as joint attention), understanding the intended actions of others, and understanding that others have knowledge and beliefs different from one's own. An example of how one might typically function in the context of ordinary street traffic illustrates these behaviors: Imagine a visitor to your house is departing and you escort her down the sidewalk to the curb. Before crossing the street to her car, you pause, follow her gaze to the oncoming traffic (joint attention), and realize she is preparing to jump out of the way (understanding intent). You simultaneously recognize, unlike your visitor, that the driver of the oncoming car is your neighbor and you tell your visitor the driver will likely turn ("Theory of Mind") into his driveway before reaching you, so there will be no danger in crossing the street. Without first following your visitor's gaze, it would be difficult if not impossible, to determine social intent and to interact appropriately for the context.

The Sereno research group has studied attention and eye movements for over 30 years in various clinical populations. Although the lab traditionally measures eye movements with an infrared eye tracker, for this study in children with ASD, we adapted the social orienting paradigm we had previously designed (Hill, Patel, Gu, Seyedali, Bachevalier, and Sereno, 2010, *Vision Res*., 50, 2080-2092. doi 10.1016/j.visres.2010.07.020) for use on a tablet. In other previous research examining the effects of subconcussive head blows on orienting, we found that tablets were easier to operate and less intimidating for children than eye trackers and most other clinical/experimental testing equipment (Zhang, Red, Lin, Patel, and Sereno, 2013, *PLoS ONE* 8:e57364. doi: 10.1371/journal.pone.0057364). We also found that the tablet was effective for measuring spatial orienting.

Reflexive social orienting, which is automatic and stimulus-driven, occurs when the direction of another person's eye gaze automatically speeds the observer's response to a stimulus in the same direction. In contrast, voluntary social orienting is willful and goal-directed, and thus not automatic. It occurs when additional knowledge (such as contextual information) is willfully taken into account. For example, consider a situation in which a child is crying: A passer-by may automatically orient to the child, and perceiving that he is caught on something, move to help free him. However, in a different situation after automatically orienting, the observer sees, instead, a parent preventing a child from playing with an electrical socket and the child crying in frustration as a result. In that scenario, the observer might voluntarily orient away, thereby ignoring the crying with the goal of reducing the parent's embarrassment. Thus, in the latter example, the voluntary social orienting process imposes cognitive control over the automatic reflexive orienting process.

For our recent study (Kirchgessner et al., 2015) we had two aims: (1) to establish the tablet as a means for measuring the reflexive and voluntary social attentional processes and (2) to test our belief that in children with ASD, reflexive orienting is intact, but the voluntary process is impaired. We designed a set of experiments for a group of high-functioning ASD subjects (with average IQ scores) and a control group of typically-developing subjects. We matched the groups on age. Participants performed the research tasks on the iPad 2 application we had created (https://www.google.com/patents/US20140249447).

Measuring reflexive and voluntary attention is complex, in part because attention is spatially localized and develops and fades across time. (See Kirchgessner et al., 2015 for a detailed explanation of how we controlled, isolated, and measured the two types of orienting across space and time.) Here, we simply summarize the basic task and experiment: Each trial began when the subject touched and held a white circle in the middle of the tablet screen. (For full explanation, see Figure 1.) During practice trials, participants were shown and told that for the given block of trials, the gaze either would not predict the target location or it would fully predict the target location. Our measurements of the time it took to touch the target were in milliseconds.

We found no difference in reflexive social orienting between our sample of children with ASD and the typically-developing control group, with both groups showing faster responses to touch the target when it happened to be on the same side as the gaze direction of the preceding face. In other words, when children with ASD are presented with a face having a potentially valuable social cue (i.e., averted gaze), their attention is automatically driven in the direction of that gaze, just as it is in typically-developing children. In contrast, we found a significant difference between groups in voluntary social orienting. The ASD group showed significantly smaller (or deficient) voluntary social orienting compared to the control group (Kirchgessner et al., 2015). That is, we found that ASD children are not able to use eye gaze as a social cue in a voluntary, goal-directed, or context-dependent way, even when the gaze direction is 100 percent predictive of the upcoming target location.

Interestingly, our prior studies in Tourette syndrome showed that similar orienting measures were able to differentiate levels

Continued on page 10; Sereno & Jeter

In*the*Spotlight

UTHealth graduate student Curtis Neveu represented UTHealth in May as the guest speaker on brain awareness and dementia for a Houston nonprofit, Amazing Place, serving adults with early stage memory loss and their caregiving families. Neveu completed his Ph.D. last summer.

The NRC's 2017 "Brain Night" at the Museum of Health & Medical Science attracted large crowds of excited kids and families over spring break. Left to right: children getting ready for their chance to experience parts of a neurologic exam as they meet Brain Night volunteer, Pedro Mancias, M.D, professor of pediatrics at McGovern Medical School; boy looking at neurons from the hippocampus of a rat's brain; girl preparing to handle a human brain, one of the event's most popular activities.

Continued from page 1; Koshy & Williamson

A young child participates in an assessment with Dr. Koshy at the UTP Center for Autism and Related Conditions. His mother and grandmother look on.

contains updated diagnostic guidelines for what was previously called pervasive developmental disorder (PDD). The broad category of PDD, which had included autistic disorder, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS), was re-worked into a new and more unified nosological category called autism spectrum disorder (ASD). ASDs are defined as neurodevelopmental disorders associated with social-communication difficulties, alongside repetitive and stereotyped behaviors and/or interests, resulting in a functional impairment with symptoms noted in early childhood. Early diagnosis is critical to the initiation of interventions that can lead to a child's optimal development. Families may vigorously resist the diagnosis. For example, during my [Dr. Koshy's] fellowship training at The Children's Hospital of Philadelphia, I encountered the powerful denial of one young patient's father. He struggled so furiously with the news of his son having ASD that I and my team were quite concerned about his physical aggressiveness. Over time, however, as parents gain insight into their child's abilities and impairments, they recognize the value of early identification. A photo of my smiling little patient in Philadelphia is tacked next to my desk today, a fond reminder not only of him but also of his dad, so angry at first and then grateful for the understanding a diagnosis can bring.

A definitive diagnosis is best made, according to the American Academy of Pediatrics (AAP), by a team of child specialists with expertise in ASD. At the UT Physician's (UTP) Center for Autism and Related Conditions at CLI, either a developmental and behavioral pediatrician (whose training includes a three-year fellowship in the subspecialty, in addition to a regular pediatric residency) or a child psychologist, may work with a speech and language pathologist to provide dual assessments at the initial appointment. For children being assessed, a transition into an unfamiliar setting with new people may be quite challenging. Our parents commonly question whether their child will demonstrate the strengths they displayed at home when they are in the clinical setting and likely to be more anxious and easily frustrated. To create a relaxed environment, we start the visit with developmentally feasible, play-based tasks and allow time for a young child to acclimate to his surroundings. Clinicians get on the floor with children in play to help overcome initial fears.

Today's growing list of ASD-specific diagnostic tools helps the clinician conduct a standardized assessment, as called for by the AAP. Measures including the Modified Checklist for Autism in Toddlers Revised take into account parent-reported observations and may be used at routine well-child visits. Screening tools should be combined with clinical history and observations from parents, teachers, and therapists the child knows, along with any neurodevelopmental test results. The combined information helps provide a comprehensive picture and also points to appropriate therapeutic interventions. Such organizations as the American Association of Family Practitioners support the AAP's recommendation to standardize the ASD evaluation. However, compliance with published guidelines, is reported as variable (according to the *Journal of Developmental and Behavioral Pediatrics*). Inconsistencies in evaluations can raise questions regarding diagnostic accuracy and validity, potentially causing problems for families in obtaining insurance coverage.

Since the presenting concern for children with ASD is often a communication or language-based delay, clinicians need to monitor a child's early language development in routine visits. At UTP's Center for Autism and Related Conditions, a speech and language pathologist is a critical member of our team and completes a structured language assessment at the initial visit, if necessary. Some common red flags for ASD include lack of cooing by three months or babbling by 12 months, lack of single words by 12 months or two-word phrases by 24 months, any loss of words or of babbling, lack of pointing to objects to indicate awareness or a request, and trouble expressing needs and wants through typical words or gestures.

Neurodevelopmental disorders in young children often present with overlapping symptoms that must be teased apart to clearly identify, if applicable, a primary diagnosis, along with the most effective and appropriate services as supported by the research. A child with an isolated language delay, for example, may require support services different from those for a child who has a language delay with an accompanying cognitive delay. To differentiate an isolated language delay from a more pervasive social-communication and/or cognitive delay, we also assess

Continued on page 9; Koshy & Williamson

problem-solving abilities in our CLI autism clinics. Our neurodevelopmental testing allows the clinician to estimate a child's current level of functioning (her developmental age). A comparison of the developmental age with the child's chronological age helps delineate the severity of any developmental delays. Discrepancies between the developmental and chronological ages in each domain of development (cognitive, language, motor, adaptive, and social) should be identified, as any one of them may directly affect diagnostic impressions and treatment planning. Other disorders that may co-occur with ASD and confound its diagnosis are attention-deficit/hyperactivity disorder (ADHD), specific learning disorders, and anxiety, to name a few.

Although the association of ASD with known genetic disorders is less than 10 percent, ASDs are associated with a wide variety of neuro-genetic syndromes, including fragile X, Angelman, Rett, tuberous sclerosis, phenylketonuria, and 22q11.2 deletion syndrome (also known as velocardiofacial syndrome). In addition, up to 7 percent of children with Down syndrome meet diagnostic criteria for ASD. Establishing a diagnosis of ASD in a child with a known primary genetic disorder can be a challenge, as ASD symptoms may also be solely attributed to a prior underlying genetic diagnosis. For example, most children with Down syndrome demonstrate better social understanding and behavior than other children who have similar levels of cognitive and communication delay, including those with ASD. Occasionally, parents are not clear as to whether their child with Down syndrome could also have ASD. Parents may view a lack of social-communication skills, repetitive behaviors, and self-injury as reflective of Down syndrome, when in fact these symptoms are classic signs of ASD. Although a child may have a primary and definitive genetic diagnosis, it is critical for clinicians to identify such co-occurring neurodevelopmental issues as ASD, so that supports targeting a child's strengths and functional deficits can be augmented appropriately.

A regression in development is often viewed as a hallmark of ASD. Nearly 30 percent of children with ASD demonstrate a regression of skills, including social skills and gesture use, as well as the verbal skills we previously mentioned. If a clear language regression has occurred or seizures are noted, an EEG should be considered. The AAP further recommends a referral to a pediatric neurologist when a child presents with a regression of language or other developmental milestones, a history of seizures/epilepsy, or abnormal findings on a neurological exam, in which case neuroimaging is also warranted. When dysmorphic features are noted on a child's physical exam, consultation with a clinical geneticist is recommended. Neuroimaging (MRI or CT) and specific genetic testing (for example, DNA for fragile X and either chromosomal microarray or karyotype) are recommended when ASD is accompanied by intellectual disability.

Clinicians at UTP's Center for Autism and Related Conditions meet to discuss their assessments before providing feedback to the family when appropriate. Once a formal diagnosis of ASD is made, families face the challenges of obtaining therapies. Insurance coverage, if available, often depends on detailed documentation of the diagnostic evaluation (and the standardized measures used). In Texas, public services are available through the Early Childhood Intervention program (for children from birth to three years) and through public school special education programs (for children three years and older). However, continuing government cutbacks limit the availability of public services, and waiting lists for both public and private services are often long. Families may also face geographic restrictions in accessing service programs. Because the systems of service providers are complex and difficult to navigate, parents may be overwhelmed and become vulnerable to practitioners advertising alternative treatments that have little scientific data to support their safety or use with children. Connecting parents to local and national support groups is one way clinicians can help families move forward in a realistic way after they receive an ASD diagnosis.

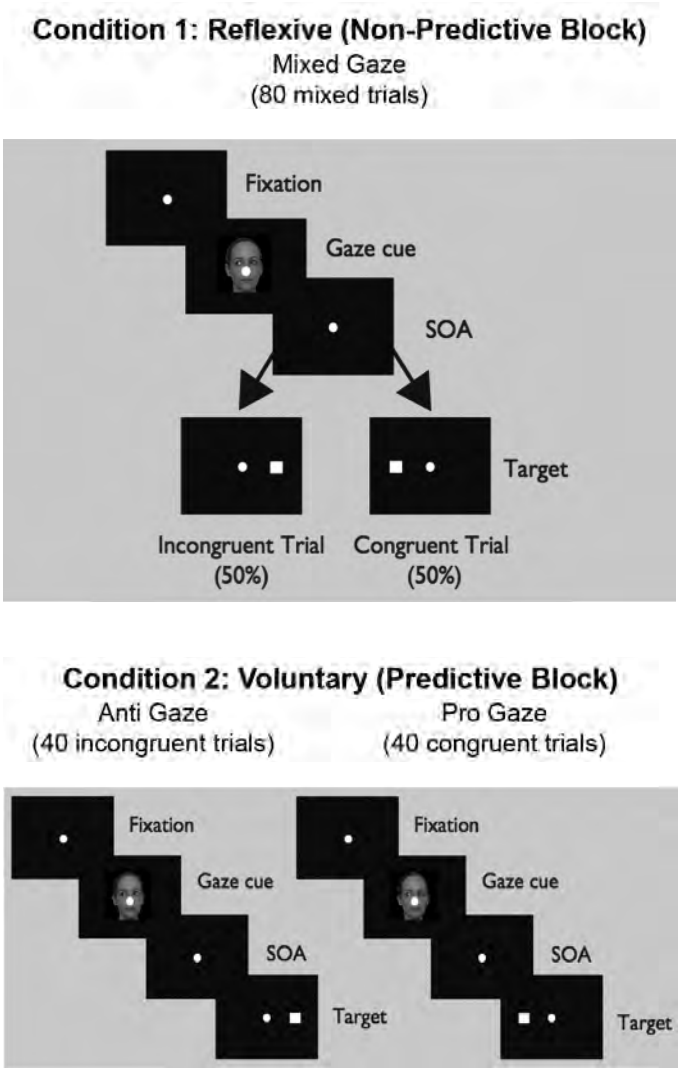
At UTHealth and CLI, the diagnostic assessment is the first step of an evolving collaborative relationship between patients, families, and clinicians. Monitoring a child's progress, identifying therapeutic, educational, and medical interventions, and addressing complex psychosocial and family needs are just a few of the steps that follow an initial diagnostic assessment. Continued research and gains in scientific knowledge of ASD are essential to progress in standardizing the diagnosis of ASD and providing evidence-based and scientifically informed clinical care.

About the Authors

Anson J. Koshy, M.D., M.B.E. is a board-certified developmental and behavioral pediatrician. He is an assistant professor in the Department of Pediatrics and the McGovern Center for Humanities & Ethics at the UTHealth McGovern Medical School. Dr. Koshy is the medical director of the UT Physician's Pediatric Center for Autism and Related Conditions at the Children's Learning Institute. He is also vice president of the Houston Branch of the International Dyslexia Association. His research interests range from the use of culturally appropriate behavioral screening in the primary care setting to ethical issues in pediatric care.

W. Daniel Williamson, M.D., a developmental pediatrician, is a professor of pediatrics at the McGovern Medical School and medical director of the Dan. L. Duncan Children's Neurodevelopmental Clinic in the Children's Learning Institute at UTHealth. He is a member of the Society for Developmental and Behavioral Pediatrics and was elected to the national Society for Pediatric Research for his research in the neurodevelopmental outcomes of children with congenital cytomegalovirus, premature birth, and visual impairment.

Figure 1. Tablet-Based Gaze-Cueing Task



Participants started each trial by touching a central spot ("Fixation") on the screen. Following a time delay, a face appeared with eyes averted right or left ("Gaze cue"). Then, after a variable delay ("Stimulus Onset Asynchrony" or SOA), a solid white square ("Target") appeared, either to the left or right. The task was to touch the target as quickly as possible. We measured participants' response times in 160 trials, completed under two "Conditions." In Condition 1 ("Reflexive Block"), 80 trials were randomly mixed so that sometimes the gaze was in the same direction as the subsequent target ("Congruent" trial) and sometimes it was not ("Incongruent" trial). Hence, the direction of gaze in this condition would not predict the location of the upcoming target. In Condition 2 ("Voluntary Block"), 40 congruent or "ProGaze" trials and 40 incongruent or "AntiGaze" trials were sorted so that gaze would be 100% predictive of target location. For a detailed explanation of how we distinguished and measured reflexive and voluntary orienting, please see Kirchgessner et al., 2015 or contact the authors.

of symptom severity while controlling for comorbid disorders (Jeter, Patel, Morris, Butler, and Sereno, 2015, *J Child Psych and Psychiatry*, 56(2):193-202). Because ASD and Tourette syndrome have the same comorbidities in common (attention-deficit hyperactivity disorder and obsessive-compulsive disorder), it is possible that these orienting measures also will distinguish subtypes or severity on the autism spectrum. Future research in ASD could also examine whether voluntary orienting deficits are specific to social orienting or are more broadly applicable to include non-social situations. Additional questions are whether deficits in voluntary orienting are predictive of, or correlated with other factors such as IQ and verbal fluency.

The brain's ability to change occurs at many different levels, from the synapse to the organization of brain areas themselves. Just as the repeated use of a muscle in the body will strengthen it, activity between brain cells will strengthen the connection, resulting in better communication between brain regions. Recent studies have shown that behavioral training can produce improvements in neural activity and functional connectivity. Further, early intervention is important, because as one ages, some forms of neuroplasticity diminish, and changes are smaller. We believe tablet-based games of social orienting may be an especially promising method of early intervention in children diagnosed with ASD. Tablet-based games that train socially relevant, context-dependent orienting might teach individuals to use social information to orient their attention in a more intentional, goal-directed manner. And since social orienting is important for the development of language and other cognitive abilities, as well as everyday social interactions, a successful, easily available, early intervention could prove widely beneficial for children with ASD.

About the Authors

Anne B. Sereno, Ph.D. is a professor of neuroscience in the Department of Neurobiology and Anatomy at the UTHealth McGovern Medical School. She is also adjunct professor of natural sciences and psychology at Rice University. Her research focuses on the higher cognitive functions of attention and memory, with findings having a direct impact on the diagnosis, treatment, and etiology of various human disorders. She has developed an easy-to-use tablet-based app and recently reported her research team's findings of intact reflexive and deficient voluntary attention in children with autism spectrum disorder. For inquiries, contact her at Anne.B.Sereno@uth.tmc.edu.

Cameron Jeter, Ph.D. is an assistant professor at the UTHealth School of Dentistry and associate member of The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, where she received her doctorate in neuroscience in 2010. Dr. Jeter serves on the Executive Committee of the Neuroscience Research Center. For inquiries, contact her at Cameron.B.Jeter@uth.tmc.edu.

Upcoming Events

24th Annual Baylor / Rice / UTHealth Neuroscience Poster Session

Saturday, December 2, 2017, 9:30 a.m. to Noon

The UTHealth Denton A. Cooley, MD and Ralph C. Cooley, DDS
University Life Center
7440 Cambridge St., Houston, TX 77054

Graduate Student Awards: First, second, and third place prizes

Postdoctoral/Research Fellow Awards: First, second and third place prizes

See the website for details: *https://med.uth.edu/nrc/24th-annual-poster-session/*

For more information contact *NBA-NRC@uth.tmc.edu* or call 713-500-5633.

NRC 2018 Public Forum:

"Parkinson's Disease & Movement Disorders"

Save the Date: Saturday, May 12, 2018

The UTHealth Denton A. Cooley, MD and Ralph C. Cooley, DDS
University Life Center
7440 Cambridge St., Houston, TX 77054

This free, educational event is open to the public. A panel discussion will be moderated by Mya C. Schiess, M.D., professor of neurology and director of movement disorders & neurodegenerative diseases at McGovern Medical School. More details will be available on our website as the date gets closer.

Please check our website (https://med.uth.edu/nrc) for information on additional events. We welcome notices of your neuroscience events (seminars, grand rounds, research colloquia, symposia, and other local or national conferences sponsored by UTHealth, the Texas Medical Center, and Houston area universities and research institutions). Submit the event name, contact information, date, time, and location in an email to nba-nrc@uth.tmc.edu.

UTHealth | Neuroscience Research Center

The University of Texas
Health Science Center at Houston

6431 Fannin St., MSB 7.170
Department of Neurobiology & Anatomy
Houston, TX 77030

NONPROFIT ORG.
U. S. POSTAGE
PAID
HOUSTON, TX
PERMIT NO. 209

ADDRESS SERVICE REQUESTED

Keep in Touch!

Website: https://med.uth.edu/nrc

"Like" UTHealth Neuroscience Research Center at www.facebook.com/UTHealthNRC

@UTHealthNRC; www.Twitter.com/UTHealthNRC

Questions? Comments?

Contact us at 713-500-5538
or E-mail: nba-nrc@uth.tmc.edu

This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the TMC and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC website.

If you prefer to receive a digital copy through email, please contact nba-nrc@uth.tmc.edu with your information.

The Neuroscience Research Center Newsletter
Editor: Anne J. Morris, Ph.D.
Assistant Editor: Paul D. Smolen, Ph.D
Design: Jeremy Buzek, UT Printing & Media Services

The Neuroscience Research Center is a component of The University of Texas Health Science Center at Houston.