Center for Neurodevelopmental and Imaging Research at Kennedy Krieger Institute

Research Update – 2020

Dear Families,

I hope that you have all been able to sustain good health and spirits under the challenging circumstances of the past several months. We recognize that the impact of the ongoing crisis has been profound for children and their families. These past months have allowed us to reflect on the substantial contributions that you make to our research efforts at the Center for Neurodevelopmental and Imaging Research (CNIR), and how these efforts can best help improve the lives of children and their families.

The CNIR remains dedicated to better understanding the behaviors and brain circuits involved in neurodevelopmental disorders like attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and Tourette syndrome. The goal of this work is to improve how we care for, and intervene to help, children facing these challenges. For instance, in a recently published study, we reported on the benefits of a mindful movement (tai chi) practice for children with ADHD. We greatly appreciate all of your efforts in helping us make progress toward these goals. Without dedicated families like yours, we would not be able to gather the information needed to make progress in our research.

In terms of how the crisis has affected our work at the CNIR, while in-person testing has been halted since the beginning of the crisis in mid-March, we have been able to stay productive. We have dedicated this time to in-depth and detailed analysis of the vast amount of information gathered thus far, and to publishing and otherwise disseminating these findings to the public. We are excited to send out this newsletter so we may update you on our progress. We hope you find the progress and results of our research presented in this newsletter as exciting as we do.

Regarding our plans for resuming in-person testing for our funded research addressing ADHD, ASD and Tourette syndrome, the safety of our child participants and their families is our top priority. With this priority as our central guide, we have modified our research testing in ways that will best ensure the safety of the children, families and all others involved. We currently have five studies recruiting at the CNIR and continue to look for new participants, so please feel free to share this newsletter with your family and friends.

Thank you again for your participation. We hope you find the newsletter helpful and informative.

Sincerely,
Stewart Mostofsky, MD
Director of the Center for Neurodevelopmental and Imaging Research

INSIDE THIS ISSUE:

PARTICIPATE IN RESEARCH

We are actively recruiting for ongoing studies. Email us at **CNIR@KennedyKrieger.org** or visit our website at **KennedyKrieger.org/CNIR** for more information.

Thank you for your participation!

Kennedy Krieger Institute

New in Autism Research

Imitation in Children With Autism

Even as newborns, children love to copy the actions and behaviors of others. As children grow, many skills are learned through imitation. A child's imitation ability can refer to how they copy others' actions with objects, like throwing a ball or brushing teeth with a toothbrush. Imitation can also refer to a child's ability to copy different gestures or movements.

Studies show that children with autism spectrum disorder (ASD) tend to have difficulty with imitation. Some researchers believe this difficulty could affect how children with ASD learn social and physical skills.

At the CNIR, we are interested in investigating motor imitation in children with ASD through a series of different fun dance movements that range in complexity and speed. Using a brief (one-minute), highly engaging "dance imitation" video game, our team at the CNIR created and tested a Computerized Assessment of Motor Imitation (CAMI) using cutting-edge motion-capture technology. This new method automatically measures a child's ability to imitate the actions of a model on a computer screen.

In a study recently published in the journal Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, we applied this technology and discovered that children with ASD have a harder time accurately imitating these dance movements. Furthermore, among children with ASD, CAMI performance is predictive of ASD severity, such that poorer imitation was associated with greater ASD symptom severity.

With this as a foundation, we were recently awarded a grant from the Simons Foundation to investigate the reliability of this fun, brief video game and to identify ASD-associated difficulties with motor imitation. We will be enrolling children with ASD, ages 6–12 years, as well as adults with ASD, ages 18–40 years. We hope to use this greater understanding to help guide better ways of detecting ASD-related difficulties and providing therapy to individuals with ASD.

Children With Autism Process Visual Information Atypically While Performing Motor Tasks

The difficulties children with autism spectrum disorder (ASD) have when imitating others' actions can have profound impact on their ability to learn new skills and to engage in social interaction. That is why it is important to figure out what contributes to imitation difficulties in people with ASD, and then use that knowledge to figure out how to help people with ASD learn new skills.

One promising explanation is that children with ASD may have difficulty perceiving and tracking rapidly-changing visual stimuli that occur with imitation. To figure out if this is the case, we developed a video game-like task that requires the children to squeeze a bar with their hand while tracking a target on a computer screen. The target is either stationary (static) or rapidly moving

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up and down the screen (dynamic). We found that while children with ASD had no difficulty controlling their hand movements to maintain the static target, they had a lot of difficulty controlling the hand movements needed to track the dynamic target moving up and down the screen.

To follow up on this work, we are now recruiting children with and without ASD, ages 6–12 years, with the goal of examining whether slowing down the speed of visual feedback helps children improve their ability to track the moving target. The findings from this work can help to inform new therapeutic approaches, specifically whether slowing the speed of visual information may be an effective way to teach children with ASD new skills, including how they learn through imitation. We look forward to updating you on these findings soon!

Now It's Your Turn: Social Imitation and Storytelling

Most of us have the tendency to automatically copy or mirror other people's actions: We often yawn when we see someone else yawn, or want to scratch an itch when we see someone else scratching. It is possible that this helps us socialize and communicate better with others.

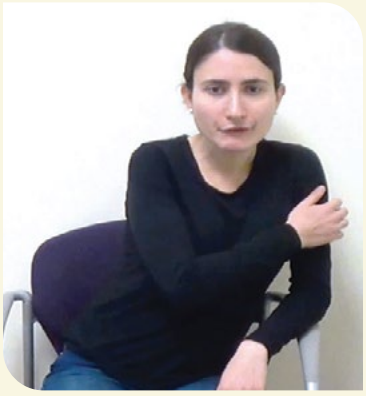
We know that a primary characteristic of autism spectrum disorder (ASD) is a decreased ability to communicate effectively and engage socially with others. This may involve a decreased tendency to copy and imitate others. To explore this further, we investigated how children with and without ASD differ in their tendency to automatically mimic the gestures and movements of a social partner.

For this investigation, we collected data on more than 60 children with and without ASD for this task. Each child watched a video of a narrator who told them an engaging 10-minute story while also doing things such as yawning, scratching an arm and gesturing for emphasis. Each child was then asked to repeat the story to the best of their memory.

We examined whether each child, in retelling the story, was spontaneously imitating the actions and movements they had seen the narrator making. We also analyzed each child's version of the story, looking at, for example, how many details they remembered and how often they used first-person dialogue.

Our next steps include integrating these findings with data from behavioral studies, such as our study of dance imitation, and with neuroimaging data, including data showing differences in the mirror neuron system among study participants. These findings could broaden our understanding of social engagement and communication in children with and without ASD, and could help develop therapies that focus on improving social communication.

Please contact Alyssa DeRonda at **CNIR@KennedyKrieger.org** for more information on how to participate in one of our ASD studies.



Images to the right, from top to bottom: The actor is yawning. The actor is scratching her arm. The actor is explaining "zooming under the bed" with her hand gesture.

New in ADHD Research

Adolescent Outcomes for Girls and Boys With ADHD

Over the past five years, we have invited adolescents 12–17 years old who participated in research at our center when they were 8–12 years old to participate in additional research studies with us. We have also begun recruiting new adolescents who have not previously visited our center to expand our adolescent sample. We have submitted two research papers for publication that compare the development of motor and cognitive control from childhood through adolescence among girls and boys with attention-deficit/hyperactivity disorder (ADHD) to that of typically-developing girls and boys. In addition, we are preparing to submit a third paper reporting on developmental changes in emotional control among girls and boys with and without ADHD. We hope to gain a better understanding of the development course of ADHD by examining the trajectories of neurobehavioral function in relation to ADHD symptom persistence and remittance, as well as the emergence in adolescence of new conditions, such as anxiety, depression and substance use.

The first of the papers we are preparing for publication reports on ADHD-related sex differences in motor function using an exclusively longitudinal sample. We found that girls and boys with ADHD show subtle motor deficits, and that boys with ADHD show greater improvement in motor deficits from childhood to adolescence.

In a second paper, we looked at the ability to inhibit a motor response during a computer task in a large group of 594 children and adolescents with and without ADHD, including longitudinal data from 137 participants. Similar to the motor findings reported above, we found that boys with ADHD show greater improvement in motor response control than do girls with ADHD, compared to same-sex typically-developing peers. Furthermore, greater ability to inhibit a motor response in childhood predicts a greater reduction in ADHD symptoms from childhood to adolescence. This information may help us to understand individual differences in ADHD with regard to outcomes in adolescence and adulthood.

Building off of the evidence of sex differences described above, Dr. Keri Shiels Rosch was recently awarded a two-year grant from the National Institute of Mental Health (NIMH) for a project titled "Examination of developmental trajectories

of cognitive, motor, and emotional control in relation to sex differences in psychopathology." In this project, Dr. Rosch will combine cross-sectional and longitudinal data from multiple studies conducted at Kennedy Krieger Institute involving children with ADHD from preschool age through adolescence. In doing this project, she plans to examine how individual differences in motor, cognitive and emotional control—and in associated brain development—relate to sex differences in internalizing disorders, such as anxiety and depression, and externalizing disorders, such as ADHD, among a sample of children ages 4–17 years.

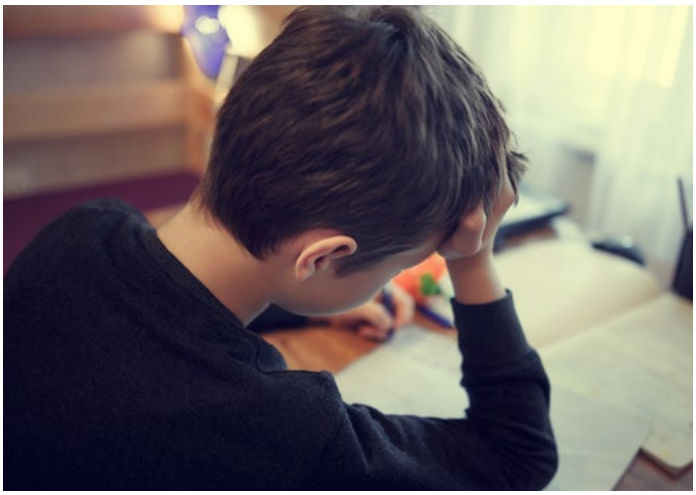
Dr. Rosch was also recently awarded the Goldstein Innovation and Collaboration Grant, a two-year internal grant from Kennedy Krieger, to conduct a study titled "Characterizing heterogeneity in decision-making in adolescents with ADHD: considerations of effort, delay, and risk." In this study, Dr. Rosch plans to expand her extensive research examining delay discounting (a preference for smaller, immediate rewards over larger, delayed rewards) among children and adolescents with ADHD to include new areas of decision-making of great relevance for adolescents with ADHD, including decisions about risk and effort. This important work will also examine whether stimulant medication, an evidence-based treatment for ADHD, alters decision-making in adolescents with ADHD for participants regularly taking prescribed stimulant medications. Finally, decision-making processes will be examined in relation to real-world functioning, including risk-taking behavior and ADHD symptoms and impairment.

Frustration Tolerance in Children With ADHD

One prominent impairment in children with attention-deficit/hyperactivity disorder (ADHD) is emotion dysregulation. Emotion dysregulation has been defined as an individual's inability to modify an emotion state so as to promote adaptive, goal-oriented behaviors. Prior research suggests that as many as half of children with ADHD demonstrate difficulties with dysregulated emotion. In the long term, emotion dysregulation in children with ADHD is associated with increased severity of core ADHD symptoms (i.e., inattention and hyperactivity/impulsivity), elevated rates of comorbid conditions (e.g., anxiety, depression, oppositional defiant behavior, etc.) and greater social impairment.

At the CNIR, we are interested in better understanding the behavioral and neural basis of emotion dysregulation in children with ADHD. In particular, we have focused on two prominent types of emotion dysregulation: frustration and irritability. Our research uses behavioral tasks designed to elicit frustration both in and out of the MRI scanner, as well as questionnaires about children's dysregulation of emotions such as mood and irritability.

Recent findings from our research suggest the importance of sex differences in frustration and irritability in children with ADHD. Using a novel behavioral task developed at the CNIR, we have found that when frustration is added, girls with ADHD show a significant decrease in their ability to inhibit responses compared to typically-developing (TD) girls. In fact, for girls with ADHD, their response inhibition error rate increased by 120% when frustration was added to the task. These results indicate that frustration may not affect all participants equally and may have implications for who is at the greatest risk for negative outcomes due to emotion dysregulation.



Additionally, our research has shown that across adolescence, girls with ADHD show a very different developmental trajectory of irritability than do boys with ADHD or their TD peers. Specifically, while early in development, boys and girls with ADHD show modestly elevated levels of irritability, boys with ADHD show reduced levels of irritability as they progress through adolescence, while girls with ADHD show continued, if not increasing, levels of irritability as they progress through adolescence.

These findings highlight the importance of considering the impact of emotion dysregulation, particularly irritability and frustration tolerance, for children with ADHD. We continue to recruit children with and without ADHD, ages 8–12 years, to participate in this study and plan to continue to examine how emotion dysregulation impacts children, both in the short term and in the long term. As a next step, we plan to examine how interventions could help children with ADHD better respond to frustrating situations.

Motor and Behavioral Control in Children With ADHD

Children with attention-deficit/hyperactivity disorder (ADHD) are at a substantially increased risk for long-term difficulties into adulthood, in their schooling, jobs and relationships with other people. What is not well understood is how to best identify which children might actually be at risk. One promising approach could be to rely on assessment of motor coordination, which can provide highly reliable tools for pinpointing difficulties with controlling responses.

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It has long been recognized that many children with ADHD show difficulties with controlling motor responses that parallel their difficulties with controlling behavioral responses. Recognizing this, over the past several years, we have worked on identifying highly-reliable motor measures that could be used to help better guide ADHD diagnosis and treatment. Our efforts, which were published last year in the journal Neurology, have led to the discovery of two brain-based measures that are abnormal in children with ADHD and, importantly, also predict the severity of ADHD behaviors.

We recently received funding from the National Institutes of Health (NIH) to build on these findings, taking the crucial next steps to determine whether these two measures, performed with brief and safe transcranial magnetic stimulation (TMS), are reliable and meaningful enough to be used to help improve the precision of individually-targeted and effective ADHD treatments. We are planning to initiate this study in the coming months and will be looking to enroll children 8–12 years old with ADHD, as well as typically-developing children (without ADHD) 8–12 years old.

Mindful Movement in Children With ADHD

In a recent study published in the Journal of Developmental & Behavioral Pediatrics, our team at the Center for Neurodevelopmental and Imaging Research found that, for children with attention-deficit/hyperactivity disorder (ADHD), an eight-week tai chi mindful movement intervention was associated with significant improvements in behavior, including inattentive and hyperactive/impulsive behaviors that are core features of ADHD, as well as oppositional defiant behavior and disorganization. We also found that the tai chi intervention was associated with significant improvements in motor control and coordination. Finally, we found a significant association between these two findings: The children who showed the most substantial improvements in motor control also showed the most substantial improvements in ADHD behavior.

It is no secret that mindfulness and embodied practices such as yoga and tai chi have enjoyed a steady stream of successes, both in research and in popular media. Many of these embodied practices cultivate sustained attention and the inhibition of distractions and task-irrelevant behaviors—factors that are definitional to the diagnosis of ADHD. Given this, a few years ago, we began a trial of eight weeks of mindful movement training for children with ADHD (two classes per week, for a total of 16 classes). The mindful movement training is focused on tai chi but also incorporates exercises from other embodied practices such as yoga, walking and seated meditations.

Our findings, revealing that mindful movement intervention is associated with improvements in ADHD behavior, provide support for a promising new avenue of behavioral intervention for children with ADHD and related difficulties. Crucially, the findings also suggest that mindful movement intervention contributes to parallel improvements in motor control, and that motor examination might serve as a valuable tool for monitoring response to this promising intervention.

We are continuing to enroll children with ADHD, ages 8–12 years, for this study and are building toward important next steps, including conducting a follow-up study with a control condition to ensure that the positive impact is specific to the mindful movement intervention, as well as conducting studies beyond eight weeks to see if a longer duration of intervention can contribute to both more immediate and sustained improvements in children's ability to better regulate their attention and behavior.

Please contact Alyssa DeRonda at **CNIR@KennedyKrieger.org** for more information on how to participate in one of our ADHD studies.

New in Autism and ADHD Research

Sleep Disturbances in Children With Autism and Children With ADHD

Difficulty with sleep is commonly experienced by children and can have detrimental effects on school performance, mental health and social functioning. Sleep disturbances are particularly prevalent among children with neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Despite accumulating evidence supporting the prevalence of sleep disturbances and their detrimental effects among children with neurodevelopment disorders, there remains a lot that we do not yet understand.

Prior studies that have examined poor sleep in children with ADHD and those with ASD have most often relied on parent ratings of their children's sleep. More recently, researchers have begun to use wearable technology in the form of a simple wristband to get a more accurate, real-time measure of sleep quality and sleep-wake cycles in children. We recently initiated our own study of sleep disturbance in children with ADHD and children with ASD and recently received a grant from the National Institutes of Health (NIH) in support of this effort. We will use both parent ratings and state-of-the-art wearable wristbands to evaluate sleep. Our goal is to better understand how sleep is affected in these children and how it impacts their ability to function academically, behaviorally and socially.

We are also interested in better understanding the relationship between sleep disturbances and brain development in children with ADHD and children with ASD. We are currently enrolling children with ADHD and ASD, ages 8–12 years, for brain imaging (MRI), with the goal of examining associations between measures of brain structure and function and measures of sleep quality, and with measures assessing the core features associated with ADHD and ASD. We hope to gain insight into the nature of sleep quality in children with ADHD and ASD and how sleep is associated with brain development, as well as the impact of these relationships on behavior and academic functioning. Our work could lead to advances in the identification of sleep disturbances and sleep-based interventions, with the potential to reduce the negative impact on children's behavioral and social functioning.

New in Tourette Syndrome Research

Sensory and Sensitivity in Individuals With Tourette Syndrome

It's long been recognized that people with Tourette syndrome (TS) often report that a sensory "urge," such as an itchy throat, contributes to the need to complete a tic, such as throat clearing. Relatedly, children with TS also may often experience more generalized difficulty ignoring faint, repetitive tactile stimuli. An example of this may be a child being bothered by a tag in their shirt or by seams in their socks.

Recognizing this, we initiated a study to evaluate and compare tactile sensitivity in children with TS to that of typically-developing children, to determine whether impaired tactile sensitivity is associated with the severity of tics and sensory urges, and to look into brain mechanisms that contribute to impaired tactile sensitivity and sensory urges in TS.

So far, our findings reveal that, compared to typically-developing children, children with TS do show increased tactile sensitivity, with reduced ability to adapt to a tactile stimulus. Furthermore, those children with TS who exhibit a reduced range of adaptation also have a greater number of tics.

To examine underlying brain mechanisms, we have employed both brain imaging (MRI) and brain stimulation (transcranial magnetic stimulation, or TMS) methods to examine the function of a key inhibitory brain signal called GABA (short for gamma aminobutyric acid). Our preliminary findings suggest that children with TS show reduced GABA-based inhibition in a region of the brain that is important for selecting and guiding motor responses—the supplementary motor area (SMA), and that reduced GABA in the SMA is associated with both increased tic severity and the frequency and intensity of sensory urges.

We are currently recruiting children with TS, ages 8–12 years, with the goal of using brain imaging and brain stimulation to confirm whether GABA-based inhibition is reduced in the SMA of children with TS, and to better identify how this is associated with tic severity. The findings would provide a basis for helping children with TS reduce tics and sensory urges by targeting GABA and related brain signaling.

Please contact Alyssa DeRonda at **CNIR@KennedyKrieger.org** for more information on how to participate in one of our TS studies.

Some of the photographs that appear in these pages are for illustrative purposes only, and any person shown in those photographs is a model.

Interested in participating?

The Center for Neurodevelopmental and Imaging Research (CNIR) is currently enrolling children to participate in several of the studies described in this newsletter. Research participants have the opportunity to complete an IQ assessment and an MRI scan, along with a variety of motor movement games and sensory tasks. Eligible participants will receive monetary compensation for their participation, an IQ report and a picture of their brain! Participation is associated with minimal risks, such as boredom and fatigue.

Please contact Alyssa DeRonda at **CNIR@KennedyKrieger.org** if you are interested in learning more about our research studies.