

2016 RESEARCH PROGRESS REPORT

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IMPROVING COORDINATED TOURETTE CARE

1ST ANNUAL COMBINED CENTERS OF EXCELLENCE, MEDICAL ADVISORY, AND SCIENTIFIC ADVISORY BOARD MEETING

The TAA's first combined meeting of the Centers of Excellence (CofE), Medical Advisory Board (MAB) and Scientific Advisory Board (SAB) was held April 26-27 at the Sheraton Gateway Atlanta Hotel. The meeting was very well attended, with presentations from the directors/co-directors of all nine CofEs; MAB co-chairs (Dr. Michael Okun, Dr. Douglas Woods) and members; SAB co-chairs (Dr. Jonathan Mink, Dr. Tamara Hershey) and members; as well as members of the TAA staff and Board of Directors.

During the first annual meeting of the TAA Centers of Excellence Program, the directors and co-directors provided progress reports on their efforts to advance the program's mission of providing the highest levels of care, research, education, and advocacy for the TS community. A copy of the TAA Center of Excellence annual report can be viewed by visiting tourette.org/cofe-report. Next year (2017) will mark the final year of the CofE program's three-year initial pilot phase. The CofE Directors, TAA Research & Medical team, independent reviewers and other stakeholders, have begun the process of reviewing the program with the aim of making recommendations for improving it in future years. *For a complete listing of the TAA Centers of Excellence locations, please see back cover.*

The MAB component of the joint meeting provided a comprehensive review of the current status of care and treatments for TS, and began discussions to address priorities and pressing issues in the field. These topics included challenges obtaining insurance coverage for some treatments, such as behavior therapies, and a relative lack of services for adults with TS in certain regions of the country.

As customary, the SAB members and co-chairs met to review this year's cycle of research grant and fellowship proposals. After a detailed and collaborative evaluation process, nine grants were recommended and subsequently approved by the Board of Directors for funding (see page 4).



IMPACTING OUR KNOWLEDGE OF TS GENETICS

TAA INTERNATIONAL CONSORTIUM FOR GENOMICS

Since its inception, the TAA International Consortium for Genomics (TAAICG) has made significant progress in advancing the knowledge of the genetic susceptibility underlying Tourette Syndrome and related disorders.

Through joint TAA/NIH support, the TAAICG has established productive collaborations with TS investigators in the United States and Europe. These collaborations have led to the collection of DNA and phenotypic data on over 4,000 individuals with TS, as well as nearly 2,500 of their relatives.

The Consortium has completed two TS genome-wide association (GWA) studies that have provided key insights into the most common form of TS genetic transmission, its genetic overlap with OCD, and identified a set of genes lying at the threshold of genome-wide significance. In addition, the TAAICG has conducted the largest comprehensive analysis of co-occurring neuropsychiatric conditions in individuals with TS and their relatives. Further, there have been combined analyses of individual tic, OCD and ADHD symptom data to identify novel "cross-disorder" phenotypes that may more directly correlate with the underlying fronto-striatal circuitry that is dysregulated in individuals with TS and related disorders.

The consortium has also completed a genome-wide analysis of large genomic deletions and duplications called copy number variants (CNVs) that has identified recurrent CNVs in two neurodevelopmental genes (NRXN1 and CNTN6) that may confer significant disease risk in 1% of individuals with TS. Results from these and other TAAICG collaborations have resulted in published articles in several high impact scientific journals Such as *JAMA Psychiatry*, *Neurology*, and the *American Journal of Psychiatry*.



THE TAA WELCOMES NEW SCIENTIFIC ADVISORY CO-CHAIRS

Several members of our various advisory boards rotated off after completing their terms, following years of selfless service for which they were appropriately thanked and presented with commendation plaques. These rotations included Dr. Jonathan Mink and Dr. Tamara Hershey who served as co-chairs and regular members of the SAB. They will continue as members for a short period of time as our new SAB co-chairs, Dr. Carol Mathews and Dr. Peggy Nopoulos, take leadership of the group. Dr. Mathews is a Professor of Psychiatry at the University of Florida, and has served as co-chair of the TAA's International Consortium for Genomics and a member of the TAA's MAB. Dr. Peggy Nopoulos is a Professor of Psychiatry, Neurology, and Pediatrics at the University of Iowa Carver College of Medicine, and has been serving as a member of the TAA's SAB for several years.



Dr. Carol Mathews



Dr. Peggy Nopoulos

CDC PARTNERSHIP CONTINUES INTO YEAR 13

The Tourette Association of America and the Centers for Disease Control and Prevention (CDC) are pleased to announce the continuation of their partnership to improve the understanding and awareness of Tourette Syndrome into its 13th year. During the past 12 years of the collaboration, the TAA has received more than \$10 million in grants from the CDC to support the partnership. In the coming year, the team will expand the program's reach and impact by using the latest technology to stream program content online, utilize social media, and develop a robust series of resources to better equip the community with the tools necessary to navigate the often complex Tourette landscape.



CBIT INNOVATION

TAA BTI PROGRAM EXPANDS CBIT's REACH



Comprehensive Behavioral Intervention for Tics (CBIT) is a safe and effective treatment for Tourette Syndrome and Tic Disorders. Proper administration of CBIT requires specialized training; however the challenge is that there are not enough trained providers. The TAA's Behavioral Training Institute (BTI) was established to help increase the availability of this innovative treatment by certifying providers around the country. In the past year, the TAA has held six BTIs in the United States and Canada, resulting in 100 new CBIT practitioners who will be available to the TS community. The TAA maintains a CBIT provider list at tourette.org and remains committed to the widespread dissemination of CBIT training through the BTI Program. We will look to expand the program further in the coming year.

BRAIN IMAGING RESEARCH... FASTER AND BETTER!

The overall purpose of the TAA neuroimaging consortium is to conduct brain imaging research faster and better; faster, by involving scientists in locations around the country, and better, because larger studies have clearer implications. The TAA neuroimaging consortium is happy to announce that its first report has been accepted for publication in the prestigious journal *Molecular Psychiatry*. The study compared the gray and white matter all across the brain between 103 children with TS, ages 7-17, and 103 children without tics matched carefully for age, sex and handedness. The results suggest additional brain regions that can be examined with complementary methods. The Consortium will be meeting in 2017 to plan future collaborative efforts.





FELLOWSHIP AWARDED IN PRESTIGIOUS PARTNERSHIP

In 2016, the TAA partnered with the American Academy of Neurology (AAN) and the American Brain Foundation (ABF) to sponsor a two-year fellowship for clinical research and training in Tourette. We would like to congratulate Dr. Matthew Capriotti from San Jose State University as the first recipient of this fellowship. His project, titled *Incorporating TeleCBIT into a Hospital-based Tic Clinic*, will examine alternative ways of disseminating CBIT treatment.

The response received and quality of applications was so impressive that the TAA, AAN, and ABF will be partnering again to sponsor two Tourette fellowships in 2017. Fellowship awardees will be announced at the 69th annual AAN meeting held in Boston, MA April 2017.



Dr. Matthew Capriotti

THE TOURETTE ASSOCIATION OF AMERICA FUNDS 9 NEW GRANTS TO STUDY TOURETTE SYNDROME

Cannabidiol for the Treatment of Tourette Syndrome in Adults

Meagan O'Brien Bailey, M.D.

Rush University Medical Center, Chicago, IL

\$39,056

There have been reports that marijuana can be effective in decreasing the amount of tics in Tourette Syndrome (TS). Marijuana would be difficult for most people to use on a daily basis because its main active compound, THC, causes the high associated with the drug and affects the ability to work or go to school. Another common compound found in marijuana called cannabidiol has been isolated, and because it does not cause the high associated with THC it is more easily tolerated and can be taken daily. We plan on studying this drug and whether or not it can decrease tic frequency in adults with TS.



for "stopping." We propose to learn more about and improve this stopping by using transcranial magnetic stimulation and electrical measurements in muscles to compare the brain's stopping system in children with and without TS. We will then use a new training method called "Selective Suppression with Real-Time Feedback" to evaluate how well children can learn to activate their stopping system. Ultimately we aim to find out whether this method can help children gain better control over their unwanted actions.

Investigating the Feasibility, Acceptability and Initial Efficacy of a Comprehensive Transdiagnostic Treatment for Complex Comorbidity in Tourette Disorder

Michael B. Himle, Ph.D. and Adam Lewin, Ph.D.

University of Utah, Salt Lake City, UT

and University of South Florida, Tampa, FL

\$136,500

Children with Tourette Disorder often have additional emotional and behavioral problems which may cause more problems than their tics. Currently, psychological treatments generally take on one disorder at a time that can be time consuming, impractical and expensive. The goal of this project is to develop and test a psychological treatment for children and adolescents to manage the many symptoms that may accompany tics - including problems controlling emotions,



Pilot Study to Evaluate Feasibility of a Novel Voluntary Movement Suppression Paradigm using Real-Time Motor Physiological Feedback in Children with TS

Donald L. Gilbert, M.D., M.S.

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

\$63,275

In children with Tourette Syndrome (TS), tics, impulsive actions, and compulsions may result partly from difficulties in the brain's systems



acting out, reacting without thinking, and trouble making good decisions.

Endogenous and Behavioral Markers of Circadian Rhythmicity in Adults with Persistent Tic Disorders: A Pilot Investigation

Emily J. Ricketts, Ph.D.

University of California, Los Angeles, Los Angeles, CA
\$130,415

Individuals with Persistent Tic Disorders (PTDs) often experience sleep problems, including difficulties falling asleep and staying asleep. Sleep is regulated partly by the circadian system, a near-24-hour biological clock. Prior research suggests the presence of circadian disruption (body temperature, and cortisol dysregulation) in PTDs. Such disruption may impact tic severity and quality of life. Therefore, this study will evaluate circadian rhythms in 20 adults with PTDs and 20 healthy control participants through assessment of endogenous melatonin, circadian phase preference, and 24-hour rest/activity rhythms. Findings may aid our understanding of the nature of tic symptom variability, and help enhance existing treatments.



Frontline Home-based CBIT Treatment Program

Harvey S. Singer, M.D.

Johns Hopkins Hospital, Baltimore, MD
\$136,500

Comprehensive Behavioral Intervention for Tics (CBIT) is a safe, effective treatment for Tourette Syndrome (TS). Unfortunately, there remain insufficient numbers of trained behaviorists to meet the needs of most TS patients. In this study, we will develop a home-based behavioral treatment instructional video and guide. We will then compare reductions in tic severity using this parent-administered therapy to that achieved with traditional face-to-face treatment by an experienced psychologist. Evidence of effectiveness of home-based, parent-directed therapy would enable direct frontline treatment for all individuals affected with tics.



Modeling a Tourette-related Human Development Disorder in Mice with Nerve Growth Factor-related Gene Mutations

Kenneth E. McCarson, Ph.D.

University of Kansas Medical Center; Kansas City, KS
\$136,500

Advances in reading people's genetic code have helped in understanding rare genetic disorders. Our gene sequencing program identified rare gene sequence variations in members of a family with TS across multiple generations. We used this genetic information to engineer mice with identical changes in their normal gene sequence, and will be testing those mice to observe behavioral and anatomic brain changes that might mimic those in the TS affected family. These mice will establish an animal model of TS that could be instrumental in understanding the causes of TS and developing strategies for treating TS.



Basal Ganglia Circuit Mechanisms of Orofacial and Vocal Actions

Lauren E. McElvain, Ph.D.

University of California, San Diego, San Diego, CA
\$40,000

Tourette Syndrome is thought to arise from dysfunction of neural circuits in the basal ganglia, a set of nuclei that control the selection of motor actions. Although prominent symptoms of Tourette Syndrome include aberrant orofacial and vocal actions, how the basal ganglia normally control these actions remains poorly understood. Therefore, we are mapping the basal ganglia circuit pathways that control orofacial and vocal musculature and determining how neurons in these pathways appropriately activate target muscles. Our findings will enable more specific circuit studies of Tourette symptoms with the ultimate goal of identifying more specific therapeutics for orofacial and vocal symptoms.



Incorporating TeleCBIT into a Hospital-based Tic Clinic

Matthew Capriotti, Ph.D.

San Jose State University, San Jose, CA.
\$130,000

We know that several medications can effectively reduce TS symptoms. We also know that a behavioral treatment called Comprehensive Behavioral Intervention for Tics, or CBIT, can work very well; whether it's delivered face-to-face or remotely via video conferencing technology. Most of what we know about these treatments comes from tightly-controlled studies, which are scientifically very sound, but may not reflect how things work in typical clinic settings. So, in this study, we will be comparing these different treatments in a hospital tic clinic under "real-world" conditions. We hope to learn what treatments patients prefer to try, both as first- and second-line treatments. We also hope to begin to learn about how well these treatments work compared to one another in this clinic setting.



Integrating TS Genetics into the Psychiatric Genetics Consortium

Jeremiah Scharf, M.D., Ph.D.
and **Carol Mathews, M.D.**

Massachusetts General Hospital, Boston, MA
and University of Florida, Gainesville, FL
\$90,000

Through collaboration with TS genetics investigators throughout the world, the TAA International Consortium for Genomics (TAAICG) seeks to advance the knowledge of genetic susceptibilities that underlie Tourette Syndrome and related disorders.



Your generous gifts in support of our cutting-edge research programs and dedicated world class scientists are sincerely appreciated. They allow the TAA to meet our mission of making life better for all people affected by TS. tourette.org/research-gift



The TAA has awarded
\$21 Million
to 250 Scientists
over 32 years

IMPACT OF PREVIOUSLY FUNDED GRANTS

Role of 5-Alpha Reductase 2 and Androgens in Tourette Syndrome

Marco Bortolato, M.D., Ph.D.¹

University of Kansas, Lawrence, KS | Funded 2013

The studies funded by this grant led to a number of important results on the role of stress in the course of TS. In particular, we found that: 1) early-life stress interacts with genetic risk factors to increase the severity of tics in TS patients; 2) severe early-life stress strongly predicts impairment in TS patients; 3) our preclinical studies suggest that acute stress may increase tics and other symptoms in TS by promoting the production of the neuroactive steroid, allopregnanolone, which plays a key role in stress response.

Decoding Global Networks Underlying Tourette symptom Subtypes using PET and Electrophysiological Methodologies

Kevin W. McCairn Ph.D.²

Kyoto University, Japan | Funded 2014

The primary goal of our project is to understand how different types of tics, for example vocal and motor tics, are generated in the brain. If it is possible to find which specific regions of the brain generate each specific subtype of tic, it will be possible to develop new and better targeted therapies. In addition to finding out which areas of the brain are involved, it is also important to fully understand how individual and groups of neurons in the affected regions change from normal activity to a state which drives the tics.

My research group uses several investigative techniques to try and answer these questions. By using a technique that measures regional blood flow in the brain, and small changes in electrical signals at the membrane of neurons, we have shown that there are two different circuits respectively for vocal and motor tics. Simple motor tics are generated by a network called the sensorimotor circuit. This region normally controls the body's normal movement. Vocal tics, however, are generated by hyperactivity and increased neuronal synchrony in the network called the limbic system. This region is believed to control emotional and reward responses in the brain.

Measurement of Glutamate and GABA in Motor Pathways: A 1H-MRS at 7 Telsa Study

Harvey Singer, M.D.

The Johns Hopkins Hospital | Funded 2013

The underlying mechanism for tics in Tourette syndrome (TS) likely involves alterations of chemicals (neurotransmitters) that are responsible for transmitting messages between brain cells. Two major brain neurotransmitters are glutamate, which excites, and gamma-aminobutyric acid (GABA), which inhibits. In this study, we used ultra-high field (7T) 1H magnetic resonance spectroscopy (MRS) to quantify glutamate and GABA in children with TS and typically developing controls between ages 5-12 years. Results showed that glutamate was significantly increased in the striatum and pre-motor cortex whereas GABA was elevated in the striatum. These data confirm alterations within the striatum and support hypotheses that suggest tics involve habitual brain behavioral pathways.

Interactions of the Histamine and Dopamine Systems in Tourette Syndrome

Shinjae Chung, Ph.D.

University of California, Berkeley | Funded 2014

Patients with Tourette Syndrome (TS) report significantly more sleep problems. A highly penetrant nonsense mutation in HDC, a gene important for histamine synthesis, was found in patients with TS, suggesting disruption of histamine neurotransmission may contribute to TS. Histamine neurons are involved in brain state control. I used state-of-the-art techniques, such as optogenetic manipulation, to precisely manipulate histamine neurons to show that stimulation of histamine neurons changes brain states. Furthermore, I used rabies virus-mediated circuit mapping tools to identify monosynaptic inputs to histamine neurons. This study advances our understanding of the biology of TS with an ultimate goal that may enable the development of novel therapies for TS.

SELECTED PUBLICATIONS RESULTING FROM TAA FUNDED GRANTS

¹Godar, S. C., Mosher, L. J., Strathman, H. J., Gochi, A. M., Jones, C. M., Fowler, S. C., & Bortolato, M. (2015). The D1CT-7 mouse model of Tourette syndrome displays sensorimotor gating deficits in response to spatial confinement. *British Journal of Pharmacology*, 173(13), 2111-2121.

²Mccairn, K. et al. (2016). A Primary Role for Nucleus Accumbens and Related Limbic Network in Vocal Tics. *Neuron*, 89(2), 300-307.





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