

Tourette Syndrome Association Research and Medical Programs

Research Progress Report

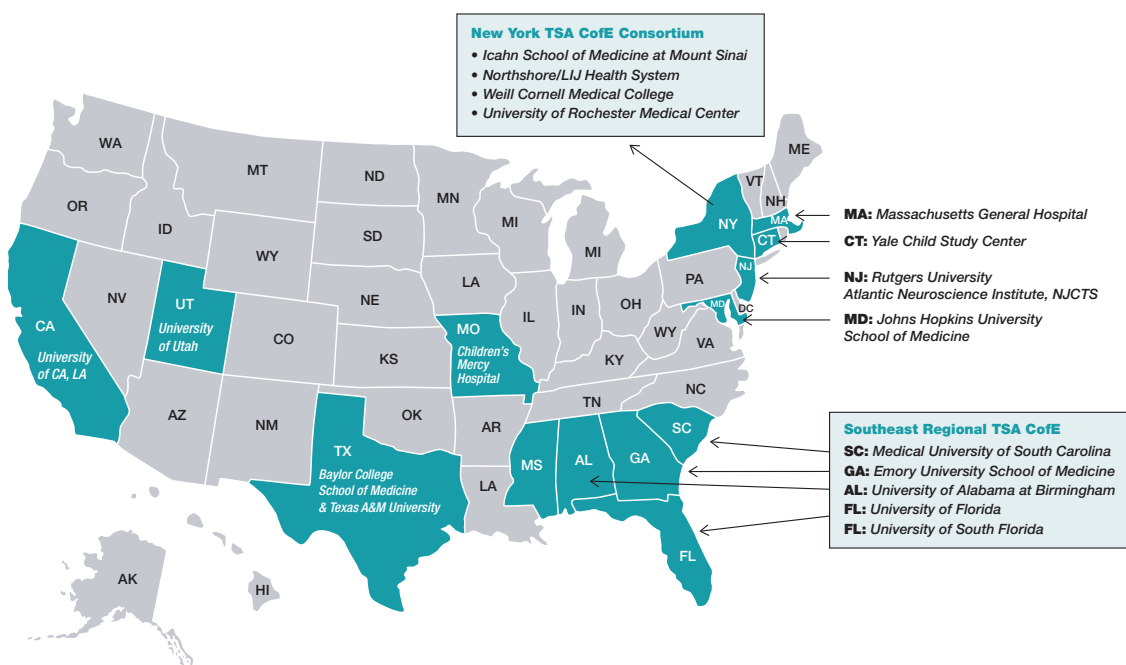
2014-2015

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The TSA designates 10 “CENTERS OF EXCELLENCE” AT U.S. MEDICAL CENTERS AND INSTITUTIONS

The national Tourette Syndrome Association has designated 10 Tourette Syndrome Association Centers of Excellence (CofE) at premier healthcare facilities, research centers and academic institutions located across the United States. Some Centers of Excellence will be awarded up to \$50,000 per year for three years in an effort to improve or build high-level care for individuals living with the disorder. Among the 10 Tourette Syndrome Association Centers of Excellence, are a consortium of individual Centers located within a single state and a network of participating institutions located across several regional states, which will collaborate extensively to meet the many needs of the Tourette Syndrome community.



field. Designated centers will also seek to advance research, improve understanding and build awareness of the conditions among patients, care providers and the general public.

“The designation of Tourette Syndrome Association Centers of Excellence in communities across the country, particularly in underserved areas, is crucial to our mission,” said Annetta Hewko, President of the Tourette Syndrome Association. “Today, there is no standard model of care for Tourette’s or Tic Disorders. Our aim is to partner with the Centers of Excellence to set these standards and increase access to informed, evidence-based treatment, compassionate care and guidance. We are genuinely excited to launch this initiative. It can significantly impact our mission to serve all people affected by Tourette’s and Tic Disorders.”

“The newly designated Centers will be the catalysts for cutting-edge scientific and clinical research aimed at decreasing diagnostic variability, deciphering the cause(s) and improving treatment of both tic and non-tic features. The Centers will also lead the way in training the next generation of experts in TS and Tic Disorders,” said Dr. Kevin St.P. McNaught, the Tourette Syndrome Association’s Vice President for Research and Medical Programs.

For people coping with Tourette Syndrome or other Tic Disorders today, there are inconsistencies in the level of care they receive. The national Tourette Syndrome Association Centers of Excellence (CofE) designation and funding will help to facilitate the development of high-quality, interdisciplinary and multidisciplinary care approaches for the

The CofE program will lead the way for heightened awareness and understanding of Tourette Syndrome and related conditions among community physicians, allied health professionals, patients, families and the general public.

The 1st World Congress on Tourette Syndrome and Tic Disorders will be held June 24-26, 2015, in London, UK

This is the first conference of its kind and its overarching theme is “New Frontiers in Research, Treatment and Global Collaboration.” The Congress aims to bring together clinicians and scientists from academia, industry and non-governmental organizations from across the world to discuss current research and treatments for Tic and related disorders, and set forth an agenda for future research and therapeutic development in these areas. The scientific program will feature a breadth and depth of topics to be covered by leading experts in the areas of genetics, neuroimaging, neuropharmacology, novel treatments, etc. There will be Abstract/Poster presentations of scientific/clinical research, demonstrations and exhibitions, and keynote presentations from renowned speakers.



Members of the TSA International Deep Brain Stimulation Registry featured on CNN



The TSA International Deep Brain Stimulation database has been launched and over 20 institutions worldwide have been engaged in the project. Over 100 cases have been registered, and the collaborative study group has written updated guidelines for Tourette DBS surgery which will appear in the journal *Movement Disorders*. The group met in Sweden in 2014, and will meet again in London in 2015 and there is a planned collaborative worldwide experience paper anticipated by the end of 2015. The project aims to shed light on the most appropriate targets, techniques, and best practices to move the field in a positive direction. This video documentary was featured on CNN's *Vital Signs* hosted by Sanjay Gupta.

The TSA continues to develop and train care providers in the use of CBIT.



In the past year, Dr. Woods' research team has continued to analyze the database that was created as part of the CBIT project. New hypotheses have been formulated, tested, and preparations are being made to submit manuscripts and new study applications based on progress in the past year. There has been particular interest in family functioning of people with TS, the long-term effectiveness of behavior therapy for TS, and considerations of what makes behavior therapy effective. The CBIT project has continued to provide support for the development and dissemination of behavior therapy for TS. The lab has also tested whether or not CBIT can be effectively delivered over Skype, and has begun to develop an online self-help version of CBIT with a company in Houston, TX (PsycTech, LTD) and Dr. Michael Himle at the University of Utah. We anticipate that the website, "TicHelper.com" will be ready for testing in early 2015.

TSA continues to support studies aimed at finding the genes associated with the disorder

Over the past year, the Tourette Syndrome Association International Consortium for Genomics (TSAICG) has published



four genetic analyses: 1) A study in *PLoS Genetics* that provides the first direct genetic evidence that genes contribute about 60% to a person's risk of developing TS,

and shows that, in most people, this genetic susceptibility appears to be spread across many different genes (possibly hundreds), each with a small contribution. 2) A study in *Annals of Neurology* suggesting that a developmental gene, Netrin-4 (NTN4), may be a TS susceptibility gene. 3) A study in *The American Journal of Psychiatry* comparing the whole-genome fingerprint of genetic risk between TS and OCD, suggesting that OCD with TS/tics may have a different genetic structure than OCD without tics. 4) A study in the *Journal of the American Academy of Child and Adolescent Psychiatry* examining large genetic deletions and duplications in TS and OCD which identified a region on chromosome 16 that may be deleted in a small number of individuals with OCD +/- TS and other neurodevelopmental disorders. Lastly, we have a clinical paper in press in *JAMA Psychiatry* examining the range of co-occurring neuropsychiatric conditions in >1300 individuals with TS across the lifespan, which found that over 85% had at least one co-occurring neuropsychiatric disorder (usually OCD or ADHD), and that almost 60% had two or more co-occurring neuropsychiatric disorders. This study also showed that the age of onset for most of these disorders was early in childhood, and provides an important tool that can help guide clinicians who treat individuals with TS in terms of what additional symptoms to screen for and when they are likely to occur.

Neuroimaging project is providing insights into the brain changes associated with TS

The TSA Neuroimaging Consortium has finished its first project, looking at the structure of the brain in 103 children and adolescents with TS, from 7-17 years of age. Each one was paired with a tic-free control subject of the same age and sex, so that we analyzed quality MRI images of the brain from 206 children in all, 162 boys and 44 girls. The MRIs were contributed by 4 different sites: Washington



University in St. Louis, UCLA, NYU, and the Kennedy Krieger Institute. We found less white matter in the TS group in a region previously found to have lower volume in TS. We are preparing a report of this finding for publication. We are also continuing with an analysis of functional images from the same group of children.

TSA funds 9 new grants to study Tourette Syndrome

FAAH Inhibitor Trial for Adults with Tourette Syndrome



Michael H. Bloch, M.D., M.S.
Yale Child Study Center, New Haven, CT
\$74,985

Randomized, controlled studies suggest that marijuana may be effective in reducing tic severity. The use of cannabinoids in TS is limited by their addictive properties, tolerability and strict regulatory control. We propose potentiating endocannabinoid signaling as an alternative to cannabinoid treatment for TS. We propose conducting a double-blind, placebo-controlled crossover feasibility study to examine the safety and tolerability of a Fatty Acid Amide Hydrolase (FAAH) inhibitor in 10 adults with TS. FAAH is the enzyme that is primarily responsible for the breakdown of endocannabinoids in the brain. FAAH inhibitors, in contrast to cannabinoids, do not possess addictive properties.

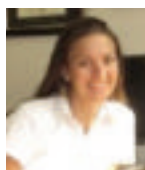
Interactions of the Histamine and Dopamine Systems in Tourette Syndrome



Shinjae Chung, Ph.D.
University of California-Berkeley, Berkeley, CA
\$40,000 (Fellowship)

This proposal aims at understanding how the balance/interaction of dopamine and histamine neurotransmission may be crucial for the symptoms of people with TS. I will use state-of-the-art techniques such as optogenetic manipulation to precisely and specifically manipulate histamine neurons to examine their effect in changing behaviors associated with TS and virus-mediated circuit mapping tools to identify monosynaptic interactions of these two systems. This study will advance our understanding of the biology of TS with an ultimate goal that may enable the development of novel therapies for TS and other neurological conditions.

Fronto-striatal Connectivity in Tourette Syndrome Patients



Colleen A. Hanlon, Ph.D.
Medical University of South Carolina, Charleston, SC
\$39,914 (Fellowship)

While motor tics are the primary behavioral manifestation of Tourette Syndrome (TS), there is a strong limbic component to the disease. Typically, motor and limbic control are modulated by parallel frontal-striatal-thalamic circuits. Our overarching hypothesis is that TS patients have an incomplete functional (Aim 1) segregation between the frontal-striatal circuits that govern limbic and motor control which is related to altered structural connectivity (Aim 2). These hypotheses are based on outcomes of prior {TSA funded} studies and will be tested using interleaved transcranial magnetic stimulation/BOLD imaging (cortex-specific functional connectivity) and diffusion tensor imaging in adolescent TS patients and controls.

Anterior Cingulate Pathways through Core TS DBS Circuitry



Sarah R. Heilbronner, Ph.D.
University of Rochester Medical Center, Rochester, NY
\$40,000 (Fellowship)

Dorsal anterior cingulate cortex (dACC) dysregulation is associated with tic behaviors that are the defining feature of Gilles de la Tourette Syndrome (TS). Importantly, this cortical region lies at the interface of motivational, cognitive and motor functions. The three main targets for deep brain stimulation (DBS), an experimental treatment for TS, are the thalamus, the internal segment of the globus pallidus (GPI) and the internal capsule. The goal of this application is to delineate the dACC pathways through these DBS sites. Results will increase our understanding of the likely circuits involved in TS and DBS treatment.

Molecular Control of Inhibition in D1-MSNs in Tourette Syndrome



Mary K. Lobo, Ph.D.
University of Maryland School of Medicine, Baltimore, MD
\$150,000

Imbalance of the striatal direct-and-indirect-pathways is implicated in Tourette Syndrome (TS). We propose to study the Egr3 transcription factor and its transcriptional regulation of GABA-A receptors in direct-pathway neurons in a mouse line that displays hallmark symptoms of TS including stereotyped movement and tics during juvenile and early adult ages. These mice also display blunted inhibition in direct-pathway neurons, likely through decreased Egr3 regulation of GABA-A subunits. We will therefore rescue the stereotypic movement and tics by overexpressing Egr3 in direct pathway neurons and by enhancing inhibition in these neurons using optogenetics.

Decoding Global Networks Underlying Tourette Symptom Subtypes Using PET and Electrophysiological Methodologies



Kevin W. McCairn, BSc, Ph.D.
Korean Brain Research Institute, Daegu, Korea
\$150,000

Tourette syndrome (TS) is characterized by a number of symptom subtypes, which include simple myoclonic and complex vocal tics. This study will attempt to clarify the role of discrete neural networks which underlie the expression of these two distinct symptom subtypes. The project will use a reversible pharmacological model of TS in nonhuman primates (NHP). This model modulates GABAergic processing in the basal ganglia (BG), which allows monitoring of abnormalities across anatomically segregated networks. We have already established that simple myoclonic tics, caused by targeting the dorsal lateral putamen, induces profound changes across cortico-BG-cerebella networks. We have now extended this methodology to reliably induce complex vocal tics through targeting of the nucleus accumbens. We will use PET imaging and electrophysiological recording to decode the network properties of the central nervous system which drive these behaviors.

Analysis of the Role of Non-coding Sequence Variation in the Aetiology of Tourette Syndrome



Vasily Ramenskiy, Ph.D.
University of California-Los Angeles, Los Angeles, CA
\$150,000

The ultimate goal of this project is to explain the linkage signal observed in TS large families on chromosome 2p by means of accounting for both coding and non-coding variation with potential regulatory function. This includes development of the pipeline for annotation of non-coding sequence variants and prediction of potentially functional regulatory variants. After selection of candidate genes and variants, the discovered top candidate variants will be genotyped in individuals from affected sib pair TS families with subsequent association tests based on potentially functional coding and non-coding variants, including their epistatic interactions.

Finnish Prenatal Study of Tourette Syndrome and Other Tic Disorders (FIPS-TIC)



Andre L. Sourander, M.D., Ph.D.
University of Turku, Turun yliopisto, Finland
\$150,000

We propose to study pre-and-perinatal risk factors for Tourette syndrome and other tic disorders. The study is based on a register-based, nationwide nested, case-control design. It includes 3003 cases and 12,000 controls. The study relies upon linkages between the national registers to identify cases and controls, examine family background, parental factor, maternal health during pregnancy and obstetric complications. In addition to register data, we will utilize Finnish Maternity Cohort to examine the association between Tourette syndrome and maternal CRP-and cotinine levels during the pregnancy in a smaller cohort including 100 cases and 100 controls.

Transcriptome Analysis of the Basal Ganglia in Tourette Syndrome



Flora M. Vaccarino, M.D.
Yale University, New Haven, CT
\$149,301

The basal ganglia and connected regions (cortico-basal ganglia-cortical loops) have previously been implicated in Tourette syndrome (TS). Here we plan to (Aim 1) conduct RNA sequencing of the caudate and putamen (Cd/Pt) and cerebral cortex (Aim 2) in patients with chronic, unremitting TS and matched controls. In Aim 3, we will perform identical analyses in younger patients (<16 years old). We will analyze differential gene expression, differential gene splicing, and perform gene network analyses to understand the neurobiological factors that underlie TS symptomatology. These analyses will provide critical insights into the genetic and neuroanatomical features of TS, guide the design of relevant experimental research models, and aid in the development of new potential treatment strategies.

Tourette Syndrome Research Grant and Fellowship Program

The TSA accepts research grant proposals from M.D. and Ph.D. researchers in basic and clinical studies on all aspects of Tourette Syndrome.

For more information visit www.tsa-usa.org/research.html.

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