



Tourette Syndrome Association, Inc.

Medical and Scientific Programs



RESEARCH

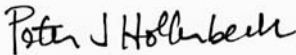
2010 - 2011

*...advancing our understanding of and ability
to treat Tourette syndrome through research,
discovery and development...*

A word from Peter Hollenbeck, Ph.D., Co-Chair, TSA Scientific Advisory Board

In February 2011 I will chair my last meeting of the TSA Scientific Advisory Board. I am stepping down after 7 years in this position, and although my involvement with TSA will continue, it is nonetheless a good time to reflect on what has occurred during my tenure. First, I must tip my hat to my co-chairman, Jonathan Mink. I paraphrase Mark Twain when I say that between the two of us, we understand everything about TS: he knows all that can be known, and I know the rest. Our arrangement of sharing the chair of the SAB between a basic neuroscientist and a clinician-scientist has allowed us to deal confidently with a very wide range of issues in TS science, and we intend that it should continue.

During these 7 years, the TSA's research mission has continued to evolve, with new initiatives and advances in behavioral therapy, neuroimaging, genetics and clinical trials. As always, TSA and its SAB seek new and better ways to leverage our modest research budget into the larger, longer studies that will produce major advances in TS science and treatment. The future holds great promise for better understanding and improved care for TS, and I expect the TSA to continue to identify and enable the best research to lead us there. During these past 7 years, my own research activities and my participation on the NIMH advisory council have exposed me to the workings of many other patient-family based medical organizations. This made it clear to me that none of them affect the lives of their members with as much bang per buck as the TSA. It has been a pleasure to serve this organization, and I wish my successor all the best!



Peter Hollenbeck Ph.D.



Spotlight on TS Research

The national Tourette Syndrome Association, Inc. (TSA)

The TSA was founded in 1972 in Queens, New York. Today, the TSA is the only national, non-profit, member organization of its kind in the USA. The organization is highly regarded internationally and is arguably the most notable supporter of TS research and education in the world. The TSA is governed by a distinguished Board of Directors, and works closely with its Medical and Scientific Advisory Boards whose highly accomplished members guide the organization in the development and implementation of research programs.

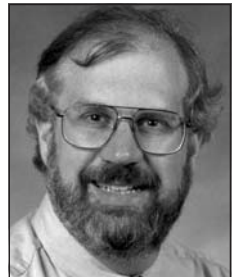
Medical and Scientific Research

The TSA's research mission is to work with and support individuals, groups and institutions to determine the cause(s) and underlying pathogenesis of TS, and develop effective therapies for individuals affected by the disorder. Towards this end, the TSA collaborates extensively with its medical, scientific and other advisors. These internationally renowned clinicians and scientists volunteer their considerable expertise, time and resources to realize the noble objectives of the TSA. These efforts have led to the development and implementation of a wide range of programs which include the following:

- **Research Grants and Fellowships:** These awards fund clinical and scientific researchers conducting studies in all areas of TS, notably in the fields of genetics, neuropathology, neurochemistry, immunology, neuroimaging and animal models development. Importantly, these grants also help to fund drug trials and the development of behavioral therapies for individuals with TS.
- **Scientific Symposia:** These international conferences are held periodically to bring together investigators from across the world to share and discuss new research findings in TS. They also provide a forum to network and thereby foster collaborations among researchers from diverse fields and geographical locations.
- **TSA Consortia:** These are groups of leading experts who collaborate extensively to provide a focused and concerted effort in conducting research in key areas of TS. To date, the TSA has organized and facilitated four consortia (Genetics, Behavioral Sciences, Neuroimaging and Clinical Trials) with a fifth now in the planning stages (Deep Brain Stimulation).
- **Brain Bank Program:** In collaboration with the Harvard Brain Tissue Resource Center (McLean Hospital, Belmont, MA), the TSA supports a valuable collection of brain tissues from individuals who had TS and from unaffected controls. This material is provided to researchers studying the brain for alterations that might play a role in the development of the disorder.



Peter Hollenbeck, Ph.D.
Co-Chair, TSA Scientific
Advisory Board



Jonathan Mink, M.D., Ph.D.
Co-Chair, TSA Scientific
Advisory Board



John Walkup, M.D.
Chair, TSA, Medical
Advisory Board

Spotlight on TS Research

- **Research Recruitment:** The TSA assists medical and scientific professionals to recruit participants for research studies that have the potential to advance our understanding of TS, and which could lead to the development of more effective therapies.
- **Physician Referral List:** The TSA maintains a database of doctors throughout the USA and abroad who state that they have expertise in diagnosing and treating people with TS. This list is made available to individuals with TS and care givers who contact the TSA requesting physician referrals.
- **Educational Material:** The TSA produces and disseminates literature and audio-visual materials to educate professionals, lay people and those affected by TS.
- **Public Policy Positions:** These are designed to educate lawmakers and the public about the impact of legislation, regulatory actions, and government policy on the health and wellbeing of people with TS. For example, issues on health insurance, funding of health research, and prevention of genetic discrimination are addressed.



Judit Ungar, M.S.W.,
President, TSA

Major Accomplishments

The TSA, along with its partners, supporters and funded researchers, has made significant progress in increasing the understanding of TS. Research projects funded by the organization have provided crucial insights into many areas of the disorder. Funding from the TSA has also encouraged many investigators to become and/or remain involved in pursuing TS research. Indeed, support from the organization has helped to train many early career researchers who have gone on to become leading experts in the TS field. While the TSA is proud of its accomplishments since its founding, it recognizes that there remain many unmet needs in TS. Therefore, the organization is now, more than ever, committed to achieving its goals of unraveling the mysteries of TS.

The TSA is particularly proud of the following awards:

- **1984-2010:** Awarded \$17,574,333 in research grants to support more than 200 scientists working in the clinical and pre-clinical fields of TS research.
- **2000-2009:** TSA International Consortium on Genetics awarded a multimillion dollar NIH award to identify the genes implicated in TS.
- **2004-2007:** TSA Behavioral Science Consortium awarded a NIH grant to conduct a clinical trial on Comprehensive Behavioral Intervention for Tics (CBIT) in children.
- **2004-2010:** TSA awarded a CDC grant to train medical and allied medical professionals across the country in the diagnosis and treatment of TS.
- **2009-2011:** TSA International Consortium on Genetics awarded \$1,771,013 from the ARRA stimulus package to conduct research aimed at determining the gene changes that underlie TS.



Kevin McNaught, Ph.D.,
Vice President, TSA Medical
& Scientific Programs

Deficits and Temporal Dynamics of Inhibitory Control over Voluntary and Involuntary Actions in Tourette Syndrome

The spectrum of tic disorders, including chronic Tic Disorder (TD) and Tourette syndrome (TS), has been linked to abnormalities in frontal-basal ganglia circuits. These circuits are critically involved in the activation and inhibition of actions, thus contributing to the brain's network that enables cognitive control over behavior. A disruption in inhibitory control is often proposed as a potential underlying mechanism that is responsible for the unwanted motor and vocal tics, the hallmark features of TS. The objective of the proposed behavioral experiments is to provide new insight into the nature of inhibitory control deficits associated with TS spectrum disorders. A first aim focuses on the effects of tic-spectrum disorder on susceptibility to impulsive reactions and the proficiency of suppressing these action impulses. Because patients can sometimes suppress their motor and vocal tics for short time periods, a second aim considers the impact of tic-spectrum disorders on "proactive control" over impulsive reactions. A third aim considers differences in the ability to suppress impulsive behavior versus suppress deliberately initiated behavior. Finally, a fourth aim considers how inhibitory control over manual and vocal actions may be differentially impacted in tic-spectrum disorder.

In summary, our four aims address novel and complementary issues that further specify the nature and role of inhibitory control dysfunction as a potential mechanism for tic symptoms. A greater understanding of the effects of TD and TS on inhibitory control functions may provide novel measures for future treatment studies and lay the groundwork for future studies that combine behavioral and imaging techniques to further elucidate the neural mechanisms of cognitive control dysfunction in tic spectrum disorders.



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Award: \$52,985

Commentary: This study will investigate the idea that people with Tourette syndrome are unable to suppress impulsive or unwanted actions. In this study individuals diagnosed with Tourette syndrome or a related tic-spectrum disorder will perform a series of tasks that measure the ability to inhibit impulsive actions as well as the ability to stop vocal and manual actions. This work aims to provide new insights on how Tourette syndrome impacts the brain system that is involved in suppressing and controlling actions.

Feedforward Inhibitory Regulation of Basal Ganglia Output and its Relation to Circuit Dysfunction in Tourette Syndrome



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Award: \$29,326

Tics in patients with Tourette syndrome (TS) are thought to reflect hyperactivity of the direct-pathway of the basal ganglia. The activity of direct-pathway Medium Spiny Neurons (MSNs) in the striatum is highly controlled by feedforward inhibition from local fast-spiking (FS) interneurons. To study the role of feedforward inhibition in controlling basal ganglia output, we will selectively decrease activity of FS interneurons in both acute brain slices and in vivo using a compound called philanthotoxin (Phtx). Phtx blocks Ca^{2+} -permeable AMPA receptors which are abundant at excitatory synapses onto FS interneurons but not other classes of striatal neurons. In acute brain slices, Phtx reduces excitatory postsynaptic currents (EPSCs) evoked by intrastriatal stimulation in FS interneurons by 75% but does not affect EPSCs in MSNs. To validate the use of Phtx as a tool to selectively reduce feedforward inhibition in vivo, the firing rates of MSNs in response to cortical stimulation will be recorded in anesthetized mice before and after infusion of Phtx into the striatum through a fluid port mounted to the recording electrode. To test the hypothesis that reduced feedforward inhibition leads to hyperactivation of the direct-pathway and concomitant increases in repetitive motor behavior, we will monitor behavior before and after bilateral infusion of Phtx through cannulas surgically implanted over dorsolateral striatum. Locomotion will be assessed by monitoring the animal's average velocity, number of movement bouts, bout length, and time spent freezing. Other aspects of behavior that will be analyzed are: gnawing, grooming, jumping, circling and taffy pulling, all behaviors that are altered in animal models of Tourette syndrome or the closely related Obsessive Compulsive Disorder (OCD). These experiments will provide insights into the role of FS interneurons in normal striatal function and could establish FS interneurons as important therapeutic targets in TS and other basal ganglia disorders.

Commentary: Tics in patients with Tourette syndrome (TS) arise from dysfunction of the basal ganglia, a brain region critical for motor function. While we know that a part of the basal ganglia called the striatum has fewer fast-spiking nerve cells in people with TS, the functional relevance of this is not understood. Here, we propose experiments to selectively reduce the activity of these fast-spiking nerve cells in the striatum of awake mice so that we can determine what effect this has on motor function. These experiments may yield insights into mechanisms of basal ganglia dysfunction in patients with TS.

Therapeutic Action of 5-alpha-Reductase Inhibitors in Tourette Syndrome

The objective of this research project is to characterize the neurochemical mechanisms involved in the therapeutic effects of 5- α -reductase (5AR) inhibitors in Tourette syndrome (TS). We have shown that the potent 5AR inhibitor finasteride (FIN) reduces tic severity in several male adult TS patients. Moreover, FIN counters the disruption of the prepulse inhibition (PPI) of the startle and the stereotyped behavior induced by the dopamine (DA) receptor agonist apomorphine, two well-validated animal models of TS. Unfortunately, FIN cannot be used in children. Thus, the elucidation of the role of 5AR in TS is critical to develop alternative therapies.

Over the previous funding period, we discovered that, in rat models of TS, FIN's effects are mediated by the nucleus accumbens (nAC) and medial prefrontal cortex (mPFC). These effects appear to be unparalleled by alterations of DA release, suggesting a post-synaptic mechanism of action of FIN. We hypothesize that FIN exerts its therapeutic actions by decreasing 5AR products and increasing 5AR substrates. With this funding we will determine what 5AR substrates and products are responsible for the antipsychotic-like effects of FIN. To this end, we will test the antipsychotic-like effects of FIN in PPI, in combination with systemic and local treatments aimed at reducing the levels of 5AR endogenous steroid precursors or restoring the content of their 5-alpha reduced metabolites.

The identification of the specific role of 5AR substrates and metabolites in the behavioral effects of FIN will provide critical information to understand FIN's mechanism of action in TS. Furthermore, these findings will help elucidate the role of steroids in the pathophysiology of TS, and may help in the development of novel therapeutic strategies with higher specificity and limited side effects.



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Paola Devoto, Ph.D.
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Award: \$72,990 (2nd year)

Commentary: We have shown that finasteride, a medication that blocks the function of male hormones, can lead to a reduction in tic severity and compulsive symptoms in adult males with TS. Unfortunately this medication cannot be used to treat children with TS because it interferes with sexual development. Our long-term goal is to understand how this medication works in the brain so that we can develop novel, effective pharmacological strategies to treat children and adolescents with TS. We anticipate that this work will identify critical targets in the brain that may lead to the development of novel therapies for Tourette syndrome.

Effect of Deep Brain Stimulation in Rats Selectively Bred for Deficient Prepulse Inhibition, An Endophenotype for Tourette Syndrome



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Award: \$60,000

Rats selectively bred for deficient prepulse inhibition (PPI) of the acoustic startle reaction can be used to study the pathophysiological mechanisms and therapeutic strategies for neuropsychiatric disorders with abnormal information processing, such as Tourette syndrome (TS).

We aim to test the effect of deep brain stimulation (DBS) in different regions of the basal ganglia and associated regions in rats selectively bred for high and low PPI, since TS is most likely the result of a dysfunction of information processing within these neuronal circuitries. Specifically, we will compare the effect of chronic DBS in the entopeduncular nucleus (EPN, the equivalent to the human globus pallidus internus), the centromedian-parafascicular complex (CM-Pf), and the nucleus accumbens (NAC) on PPI. Furthermore, we will investigate the possible restorative effect on behavioral flexibility and social behavior of these rats. Since the effect of DBS will likely interact with disturbed neuronal network function, the effect of DBS on single unit activity in the EPN, the CM-Pf, and the NAC will be investigated.

These studies will greatly enhance our knowledge of neuronal systems thought to be involved in the pathophysiology of TS. Rats with PPI deficits may help us to find the optimal location for DBS and the best means of stimulation settings for this disorder. They will give new insight into the plasticity and modulation of the basal ganglia circuitry and their modulation by DBS. Recently our colleagues in the departments of Psychiatry and Neurosurgery started a prospective, controlled, randomized clinical study to evaluate the efficiency of DBS in the CM-Pf and the globus pallidus internus (GPi) for the treatment of severe treatment resistant TS. We envision that the concomitant clinical and experimental study may provide additional insights, in particular with regard to the translational aspects of this experimental therapy.

Commentary: A breakdown of the mechanisms in the brain to suppress irrelevant information can be related to the inability to suppress tics in Tourette syndrome. Rats selectively bred for deficient information processing are often used as a model to study nerve cell changes and therapeutic strategies for TS. In this study we will test whether Deep Brain Stimulation (DBS) in different brain regions can restore the disturbed information processing in these specially bred rats. Nerve cell activity will be measured to evaluate the effect of the treatment in these rats and to determine how DBS may work.

Plasticity and Motor Cortical Excitability in Tourette Syndrome: Response to Therapy and Natural History

The tics of Tourette syndrome (TS) have a surprising variation in clinical history and response to treatment. In many cases, the tics disappear in adolescence and early adulthood. However, in others, the tics persist and although they often respond to treatment with dopamine antagonists; the effect in individual cases is notoriously difficult to predict. The aim of this proposal is to use physiological tools to probe individual differences in brain organization that might be responsible for these effects.

Our current understanding of the neurobiology of TS suggests that tics arise from a combination of two factors: reduced excitability of GABAergic inhibition in striatum coupled with changes in plasticity of corticostriatal synapses. The former leads to release of unwanted movements by reducing inhibitory output of basal ganglia, whereas the latter may promote long term plastic changes in the strength of synapses that impact on the learning processes responsible for development of complex tics and behaviors. Corticostriatal plasticity is heavily influenced by dopaminergic projections, which may account for the clinical effect of dopaminergic antagonists in treating tics.

It is difficult to study directly the corticostriatal system in awake humans. However work suggests that the postulated abnormalities in these deep circuits may also be reflected in organization of cortical circuits that are much more amenable to study. In the present project we will employ a range of newly developed non-invasive electrophysiological tests of synaptic plasticity and inhibition in motor cortex of subgroups of patients who show different characteristics of individual history and response to treatment. We hypothesize that these will provide objective biomarkers to quantify and even predict effects of treatment in individual patients.



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Award: \$74,959

Commentary: Individuals with Tourette syndrome can have a surprising range of clinical characteristics. Some patients have tics in childhood that spontaneously disappear when they reach adolescence or adulthood, whereas other patients may have tics that persist and have to be treated with medications that change levels of chemicals in the brain. Many patients respond well, but in others, treatment is extremely difficult. Our understanding of the mechanisms of how tics are generated has now reached the stage where we think that it will be possible to identify the reasons for differences between individuals. We will use a variety of approaches to record and stimulate important pathways in the brain in order to characterize differences between individual cases. This should enable us to identify the mechanisms that cause tics to disappear and predict which medications may be most effective in treating patients whose tics persist.

Pilot Study: Proportion of Hispanic and non-Hispanic Black Children with Tics in Rochester, New York



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Award: \$75,000

Several investigations have suggested a lower prevalence of Tourette syndrome (TS) diagnosis in black and Hispanic groups compared to non-Hispanic whites. However, these estimates may be biased by ethnic differences in cultural interpretation, medical priorities, tic knowledge, and health care access. Disorders associated with tics can cause significant impairment, even in the setting of cultural interpretation of tics as benign. The prevalence of tics in minority children, rather than a formal TS diagnosis, has not been investigated in detail. Therefore, we propose a pilot study to determine tic occurrence in non-Hispanic black and Hispanic children. Our specific aims are:

- 1) to obtain a preliminary estimate of lifetime tic occurrence in a community-based sample of non-Hispanic black and Hispanic children, and
- 2) to identify high-yield resources for subject recruitment in the Rochester, NY metro area and to assess the feasibility of conducting a community-based study of tics.

Our secondary aims are to explore:

- 1) the phenomenology and severity spectrum of tics (age of onset, tic type and number, severity, frequency),
- 2) the occurrence of disorders commonly associated with tics (ADHD, anxiety, OCD),
- 3) tic knowledge and parent interpretation of tics, and
- 4) access to specialty health care.

If tic occurrence does indeed differ among Hispanic, black and white children, future studies will explore whether this is due to variation in underlying biological or exposure risks. If tic occurrence is comparable between groups, subsequent studies will explore socioeconomic themes underlying differential TS and tic disorder diagnosis rates, despite similarities in tic prevalence.

Commentary: Tics are a type of stereotyped involuntary movement. They are fairly common in childhood and are sometimes associated with other problems such as ADHD or anxiety. It is not known whether tics occur with the same regularity in different racial and ethnic groups. In this study, using interview and observation, we will evaluate how often tics occur in a small group of non-Hispanic black and Hispanic children, in comparison to white children. Results of this study may help more accurately estimate the rate of tics and their impact in a more diverse group of children than has previously been studied.

Uncovering Disparities in Tourette Syndrome Prevalence and Identification between Caucasians and African Americans

Large studies of the prevalence of Tourette syndrome (TS) and Chronic Tic Disorder (CTD) in representative minority populations are rare. This gap may be attributable to two methodological problems. First, large scale epidemiologic studies of the prevalence of TS and CTD require reliable case finding and such case finding is limited by the expense of expert examination. Second, studies of the prevalence of TS and CTD require representative samples so that screenings can be conducted for unbiased detection and treatment. To date, studies have not recruited sufficient minority respondents leading to an unknown prevalence of TS and CTD among minority populations. This proposal will address these problems and will test the use of a Video-Integrated Screening Instrument for Tics and Tourette syndrome (VISIT-TS) and incorporate a strategy for recruiting underrepresented populations in community settings. Specifically, in two phases, we will:

1. Test the feasibility and acceptability of the VISIT-TS 10 minute screening among participants recruited door-to-door in an African-American majority community (Phase 1).
2. Test the demand for the use of the VISIT-TS as a free health screening provided through health fairs in the City of St. Louis and other health screening settings (Phase 2).
3. Estimate the prevalence of TS and CTD in a community ascertained sample (n=200) of 5 – 70 year old people expected to have a high percentage of minority subjects.
4. Prepare a natural study of the prevalence, course and treatment of TS, CTD and their correlates with adequate power to compare prevalence between racial and ethnic groups.



Catherine Woodstock Striley, Ph.D., MSW, MPE
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Kevin Black, M.D.
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Award: \$73,100

Commentary: Studies counting cases of Tourette syndrome (TS) in minority populations have rarely been conducted due to two problems; i) expert medical examination is generally required to reliably determine whether or not the person has TS and ii) such examination on a large scale is expensive. We also lack effective methods to recruit representative minority populations for in-person TS screening. With previous TSA funding we developed a Video-Integrate Screening Instrument for Tics and Tourette syndrome (VISIT-TS). With the current funding, community health workers will test the feasibility of using VISIT-TS at HealthStreet – the community outreach center at Washington University, and at health fairs and other community venues.

Disentangling Neuroanatomic Changes Over Time by a 5-Year Follow-up Neuroimaging Study of a Large Clinical Cohort of Children and Young Adults with TS



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Award: \$66,000 (2nd year)

The aim of the study is to examine the neurobiological changes in the brain of children and young adults with Tourette syndrome (TS) 5 years after the initial examination. Previous imaging studies have suggested long-term activity-dependent plastic changes caused by the lifelong presence of tics in subjects with TS. However, most of these studies in individuals with TS have had the disadvantage of scanning children or adults from clinical cross-sectional samples. Cross-sectional studies give a picture at one point in time, rather than being able to depict a development and are prone to cohort effects. The present study has great potential in that it enables us to differentiate between the anatomical bases of tic behavior and the adaptation of the brain and mechanism to control tics. We thus plan to perform a longitudinal study of neuroanatomical and functional changes in a well-defined clinical cohort of children and young adults with TS using anatomical and functional MR-imaging (fMRI), and diffusion-tensor imaging (DTI). At the initial examination, we examined 39 medication-naïve children (mean age 13.9 years) with TS and 37 healthy controls (mean age 13.8 years). The cohort is well characterized with respect to co-morbidities, severity of tics, and psychosocial and educational consequences of TS. It would be important for the prognosis of TS to confirm the previously described anatomical deviations in a longitudinal study-design. Moreover such knowledge would help to further disentangle the pathophysiology of TS.

This award is funded
by Constantine Scrivanos

Commentary: Previous studies have shown that structures in the brain of individuals with TS might change over time because of the presence of tics. Most of these studies have given a picture at one point in time and have not depicted the development of changes in the brain over time. In previous research, we used Magnetic Resonance Imaging (MRI) to examine the brains of 39 children with TS and 37 healthy children. In this study we will re-scan the brains of the same children, 5 years after the initial scan of the brain. We hope that the results will help in understanding the cause of TS and improve treatment possibilities.

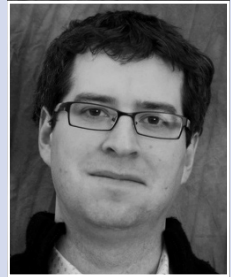
In Vivo Striatal Fast Spiking Interneuron Suppression Using Optogenetic Techniques

The striatal GABAergic microcircuitry likely plays a key role in the pathophysiology of Tourette syndrome (TS). Animal experiments have found that blockade of striatal GABA receptors provokes tic-like movements. Humans with TS have a specific deficiency in GABAergic striatal fast-spiking interneurons (FSIs), which powerfully inhibit striatal projection neurons. These data suggest that FSIs play a critical role in the pathophysiology of TS.

To test this hypothesis, we will use novel optogenetic techniques to selectively silence striatal FSIs in awake, freely behaving mice. NpHR is a light activated chloride pump and neurons expressing this protein rapidly inactivate when illuminated with yellow light. We will infuse an adeno-associated virus containing the double-floxed NpHR gene into the striata of mice expressing Cre recombinase under the parvalbumin (PV, specific to FSIs in the striatum) promoter. This will lead to selective expression of NpHR in FSIs, which can then be inactivated independently of other striatal neurons. Combination fiber-optic/silicon probes will be implanted into the striatum to record electrophysiological activity during periods of FSI inactivation. The electrophysiology and optical FSI inhibition will be synchronized with video recordings to correlate behavioral with electrophysiological changes. We hypothesize that these mice will develop repetitive, stereotyped movements contralateral to the implant during FSI suppression. These experiments will not only investigate a key theory regarding the pathophysiology of TS, but also establish techniques to study the striatal microcircuitry in more detail.



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Award:\$40,000 (fellowship)

Commentary: Recent evidence suggests that abnormalities of a specific type of nerve cell ("Fast Spiking Interneurons" or FSIs) in a region of the brain called the striatum, are important in the development of tic disorders. We will use novel techniques to inactivate these FSI nerve cells in normally behaving mice while recording the activity of other nearby nerve cells. We believe that inactivating the FSIs will cause specific changes in the firing patterns of neighboring nerve cells and also cause tic-like involuntary movements in the mice. If this happens then we will know that the FSI nerve cells play an important role in tic development.

Neuroplasticity in Tourette Syndrome



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Donald L. Gilbert, M.D.
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Award: \$74,837 (fellowship)

Neuroplasticity is the capacity of a neural system to adapt, learn, and remember, which depends in some way on use-dependent and experience-dependent changes. Such changes can be helpful when a new skill or knowledge is learned. However, maladaptive changes may lead to symptoms such as tics. At the level of brain cells, adaptive and maladaptive processes occur at the synapse, through processes such as long-term potentiation (LTP) or long-term depression (LTD).

Transcranial Magnetic Stimulation (TMS) is a technology that enables us to study these processes in the motor cortex in human subjects. A recently developed TMS paradigm called Theta Burst Stimulation (TBS) has been shown to mimic LTP and LTD in the human brain. Prior neuroimaging studies have shown different dorsal prefrontal volumes when comparing Tourette syndrome (TS) patients and controls. Since the frontal lobe is involved in response inhibition, abnormal neuroplasticity may possibly explain the different dorsal prefrontal volumes in Tourette syndrome. Therefore, our hypothesis is that neuroplasticity as measured by TMS-TBS is abnormal in the TS population. Our pilot data with nine TS adults and eleven age-matched controls suggests that the motor cortex LTP in response to intermittent TBS is decreased in TS subjects.

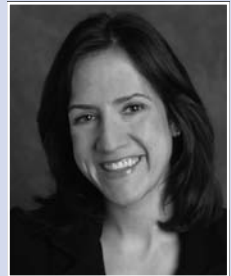
This TSA funding will enable us to study the developmental trajectory for neuroplasticity in TS and to understand whether this relates to the capacity to learn to suppress tics. Our goals are to recruit children with TS/tic disorders and TS adults who have “outgrown” their tics.

Commentary: As the brain matures, it strengthens crucial nerve cell connections that enable us to learn and control movements. Transcranial Magnetic Stimulation is a technology that measures certain brain maturation processes. Our preliminary findings show that adults with TS have a decreased response to TMS when compared to individuals without TS. This generous TSA funding will allow us to further explore brain maturation by studying children with tics and adults who have “outgrown” their tics.

A Virtual Reality-based fMRI Study of Learning Systems in Children with Tourette Syndrome

Neuroimaging studies suggest that the pathophysiology of Tourette syndrome (TS) involves disturbances of the basal ganglia and related Cortical-Striatal-Thalamo-Cortical (CSTC) circuitry, as well as limbic portions of these circuits. Our findings of smaller caudate volumes and impaired habit learning in children and adults with TS suggest that the neostriatal habit learning system is dysfunctional in persons who have this condition. Lesion studies of animals have shown this system to be anatomically and functionally distinct from neural systems that subserve spatial learning. This will be the first study to assess the functioning of multiple learning systems in children with TS. Using a novel, virtual reality-based functional Magnetic Resonance Imaging (fMRI) paradigm, the brain activity of 20 children with TS will be compared to that of 20 control children during their performance of tasks that require habit learning and reward-based spatial learning. These tasks are directly analogous to the behavioral tasks used to study learning and memory systems in rodents. Findings from this translational study will allow us to seek funding to examine the effects of treatments on the functioning of these systems in TS, and to study their functioning in the same children over time to determine whether disturbances in these systems may contribute to the habitual nature and progression of tics into adulthood.

This award is funded by
Karen, Alan and Michael Hart



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Bradley S. Peterson, M.D.
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New York, NY

Award: \$75,000

Commentary: This study will use sophisticated imaging processing (functional Magnetic Resonance Imaging or fMRI) to compare the brain activity in 20 children with TS (ages 6-13) and 20 age-matched children without TS while performing certain learning and memory tasks. Differences between the two groups will indicate how the brains in children with TS functions differently to children without TS, and may lead to future investigations on the nature and progression of tics into adulthood.

Neural Mechanisms of Cognitive Control and Reward-based Learning in Unmedicated Children with Tourette Syndrome



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Award: \$75,000

Widely characterized as a frontostriatal disorder, Tourette syndrome (TS) is believed to involve abnormalities in brain structures that are important for cognitive control: prefrontal cortex (PFC) and the striatum. These behavioral and brain abnormalities are thought to result from abnormal dopaminergic (DA) functioning in TS. Specifically, increased levels of DA lead to an imbalance of DA in frontostriatal pathways that are necessary for the control of thought and action. This study aims to investigate the effects of TS on DA-linked processes, such as response inhibition, reward processing, and feedback-based learning.

In this study, we will compare performance of children with TS to healthy, age-matched controls, ages 7-12, on two variants of a Stop Signal task. During this measure of response inhibition, participants initiate ongoing actions (i.e. pressing a button as fast as possible) in response to a repeated cue, but must inhibit that action (i.e. stop themselves from pressing the button) in response to an occasional stop-signal. By using two variants of this Stop Signal Task, we hope to selectively engage two discrete inhibitory pathways. The proposed hyperdirect pathway from the prefrontal cortex (PFC) to the subthalamic nuclei is believed to remain relatively unaffected by increased DA, while activity in the indirect pathway via the basal ganglia is suppressed by the increase.

In addition to motor control, striatal dopamine is known to play a major role in reward processing and feedback learning. Recent work indicates that fluctuations in dopaminergic activity in TS represent phasic rather than tonic increases. However, it remains unclear whether these TS-related phasic increases interfere with the dopaminergic reward signal. Thus, we will examine the consequences of altered dopaminergic transmission on performance during a reversal learning task that requires updating behavior on the basis of both positive and negative feedback.

This award is funded by
Alisa Yaffa and Ken McElvain

Commentary: Tourette syndrome is thought to be caused by increased levels of dopamine, a brain chemical that is not only critical for movement control but which is also involved in learning and generating a sense of reward. This study examines inhibition and reward sensitivity in children with Tourette syndrome. We will use an imaging technique (functional Magnetic Resonance Imaging or fMRI) to understand how Tourette syndrome and deliberate suppression of tics affects the functioning of brain regions associated with movement control and learning.

Whole Exome Resequencing in Familial Tourette Syndrome

Tourette Syndrome (TS) is a complex neuropsychiatric disorder manifested particularly by motor and vocal tics and often associated with behavioural abnormalities (e.g. Obsessive Compulsive Disorder (OCD), Attention Deficit-Hyperactivity Disorder (ADHD), anxiety disorders, sleep disorders, depression, rage outbursts and oppositional defiant behavior). Various studies have confirmed the genetic basis of TS and concordance rates in twin studies suggest that TS may be caused by a mix of environmental and genetic factors. Parametric/non-parametric linkage studies have largely failed to identify replicable TS susceptibility loci using multi-affected large families. When considering genetic models for complex neuro-developmental diseases, there are only a few possibilities: rare penetrant recessive alleles, rare partly penetrant and more common less penetrant dominant alleles, and interactions between many genes. Genome re-sequencing promises to accelerate the identification of disease-associated mutations but about 98% of the human genome is composed of repeats and intergenic or non-protein-coding sequences. Thus, it is crucial to focus re-sequencing on high-value genomic regions. The protein-coding regions of the genome (the exome) represent such a high-value target. Exon-capture methods (e.g. Agilent Technology, SureSelect Human All Exon ki) coupled to next generation sequencing (e.g. ABI's SOLiD) will allow us to re-sequence approximately 15,000 genes in each DNA sample. This new approach should significantly increase the probability of identifying disease-causing or susceptibility variants.



Guy A. Rouleau, M.D., Ph.D.
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Award: \$75,000

Commentary: Tourette Syndrome (TS) is a complex and poorly treated disorder of the brain. Although genetic factors are known to play a role in TS and despite intensive research efforts, the identification of TS genes has had limited success. We propose to use modern and powerful techniques to examine approximately 15,000 genes in a group of ten individuals from five different TS families. Such a large-scale approach increases the probability of finding a gene associated with the disorder.

Pathophysiological Markers in the “Pre-Tourette” Population



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Award: \$40,000 (fellowship)

As many as 20-30% of all children manifest motor and/or vocal tics at some time in their life. Typically, these new-onset tics disappear within a few months. However, for about 1% of children these tics represent the beginning of a prolonged and often serious disorder: Tourette syndrome (TS) or Chronic Tic Disorder (CTD). Given these epidemiological data, development of TS/CTD could be conceived as a two-step process: first tics appear, then they fail to remit. We propose that this step can be observed prospectively, thereby minimizing the biases inherent in retrospective study designs. Equally important is that studies of tic persistence may identify entirely different causative factors than studies of established TS/CTD, where onset and persistence are confounded. This earliest phase of tic disorders may hold the key to discovering etiology, prevention or treatment.

Our project is the first-ever pathophysiological study of the “pre-Tourette” population (i.e., children with new-onset tics that will either persist or remit with time). With Drs. Kevin Black and Bradley Schlaggar, I will use carefully selected neuroimaging (functional connectivity MRI, task-based fMRI, volumetric structural MRI), neuropsychological, and clinical methods to examine children with recent-onset tics and follow them clinically through the one-year anniversary of tic onset. Those whose tics persist will be compared with those whose tics remit. Thus, we will be able to examine whether putative biomarkers of TS/CTD can be used to predict prognosis of recent-onset tics. Further, this project is meant to demonstrate feasibility of this prospective approach.

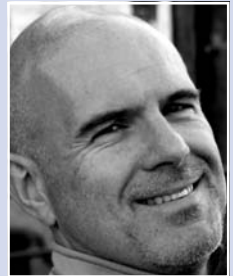
Commentary: In this study we will use advanced brain imaging methods to examine the brains of children who have not yet been diagnosed as having TS. We will do brain scans in a group of children whose tics began within the past few months, and will monitor these children clinically for one year after their first tic. After the year period, many of these children will no longer have tics, but those who do will be diagnosed as having either Tourette syndrome or Chronic Tic Disorder (TS/CTD). Brain scans from these children will be compared with each other. From this work we hope to identify new avenues of research on what causes tics and how to prevent early tics from developing into TS.

Neural Mechanisms of Self-Control

Tourette syndrome is characterized by overwhelming urges to perform simple actions. Self-control can reduce tics – acutely, through conscious effort, and chronically, through cognitive/behavioral therapy and other forms of training. These facts suggest that the brain possesses the ability to control unwanted urges and raise the possibility that self-control could be improved by better therapies, drugs, or deep-brain stimulation. Much evidence suggests that the anterior cingulate cortex (ACC) is a key player in regulation of such impulses. I propose to record responses of single ACC neurons while rhesus monkeys perform a task that demands acute inhibition of the urge to shift gaze. I hypothesize that tonic enhancements in ACC firing rates will predict successful self-control. My first aim is to develop a behavioral paradigm that measures self-control in rhesus monkeys based on Walter Mischel’s self-control paradigm; originally designed for use with young children. My second aim is to characterize the neural correlates of self-control in ACC. While monkeys perform this task, I will record ACC neural responses using extracellular electrodes. I will then analyze these responses to identify patterns of activity that predict upcoming failures and successes at self-control. By focusing on the cognitive processes by which the brain manages to regulate its own impulses, I hope to identify possible treatments for TS that are consonant with these processes.



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Michael L. Platt, Ph.D.
Duke University School of
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Award: \$13,855 (fellowship)

Commentary: Although Tourette syndrome is described as a movement disorder, tics can be reduced using self-control strategies. Despite recent advances, we know very little about what happens in the brain when unwanted urges and tics are controlled. Imaging studies of the brain suggest that a part of the brain called the anterior cingulate cortex may be involved. In this study I propose to examine nerve cell activity in this region of the brain in monkeys performing a self-control task. These studies may contribute to our understanding of the mechanisms by which deliberate effort reduces the symptoms of Tourette syndrome and could identify novel targets for future treatments.

Imaging Cognitive Motor Control in Tourette Syndrome



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Award: \$75,000 (2nd year)

Tourette syndrome (TS) has long been regarded as a disorder of involuntary movement. That is, the “tics” are thought to be the result of a deficit in motor response inhibition. On the other hand, many patients with TS report a premonitory feeling or an “urge” to move prior to the generation of tics. This observation has led to some investigators to liken TS to Obsessive Compulsive Disorder (OCD) and to conceptualize shared neural processes between TS and OCD.

The present study is designed to distinguish between two hypotheses: Is TS a disorder of impaired motor response inhibition or an OC spectrum disorder? By combining functional magnetic resonance imaging (fMRI) and a stop signal task, we propose to investigate the neural processes of cognitive motor control in patients with TS. In previous studies we examined the neural processes of motor response inhibition and error processing during the stop signal task. Deficits of motor response inhibition manifest as diminished activation of a dorsomedial prefrontal cortical region, while error processing engages a distinct circuit of dorsal anterior cingulate and subcortical regions. These results provided a unique platform to distinguish the two hypotheses.

In our preliminary findings, we observed that patients with TS demonstrated decreased error-related activations in the thalamus, similar to that seen in patients with OCD. In this proposal, we will investigate the molecular bases of the altered error-related thalamic activation in TS patients. Specifically, we will use positron emission tomography (PET) imaging to examine whether the altered activation is related to differences in norepinephrine transporter (NET) availability in the thalamus. We will use a PET radioligand (S,S)-[¹¹C]O-methyl reboxetine to compare NET availability in 12 TS patients and 12 demographics matched control participants. We believe that the potential results could provide information instrumental in the development of novel therapeutics for TS.

Commentary: Tourette syndrome is a chronic, debilitating neurological illness. The etiology of Tourette syndrome remains unclear and current treatments are only partially effective. With previous funding we showed that a part of the brain called the thalamus is affected in patients with Obsessive Compulsive Disorder as well as in patients with Tourette syndrome. In this study we will continue to examine the bases of this dysfunction in the thalamus. We anticipate that the results could provide information instrumental in the development of novel therapies for Tourette syndrome.

Genotype and Phenotype Analysis in Large Extended Pedigrees with Tourette Syndrome and/or Tics

This research on Tourette syndrome (TS) and chronic tics will apply the newest genomic technologies to some large extended pedigrees collected in the state of Utah and surrounding areas. This will involve genetic mapping and exome sequencing of several large extended Tourette pedigrees, including ones with 65, 31 and 23 descendants. This research will include extensive phenotypic characterizations of these unique pedigrees with TS and other co-morbid conditions such as attention deficit hyperactivity disorder (ADHD) and Obsessive Compulsive Disorder (OCD). We plan to obtain dense genotyping using the Illumina 610K chip, with genotyping performed by our collaborator at the Children's Hospital of Philadelphia, Hakon Hakonarson. We will perform standard linkage analysis, along with copy number variation (CNV) detection using available algorithms. We also plan to perform exome sequencing on carefully selected members of these pedigrees, giving us the ability to identify exonic mutations shared amongst affected members of the pedigree, and not found in unaffected members of the pedigree. This will likely identify candidate genes worth following up in other members of the pedigree and in unrelated cases. The overall goal will be to identify rare (or even private) mutations that cause TS within these families. This research may shed light on new biological pathways implicated in the disorder.



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Hilary Coon, Ph.D.
University of Utah,
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Award: \$73,818

This award is funded by Ralph Ochsman
and the Ochsman Foundation

Commentary: Tourette syndrome seems to run in families, but finding the gene has been difficult. In recent years, technology has advanced so much that we can now study most of the genes in any particular family. Because family members are more genetically similar than unrelated people, comparing genes from affected family members with unaffected family members is one of the most successful techniques for genetic discovery. However, there are two critical requirements for this type of research: 1) the families must be large enough for the genetic effect to be visible, and 2) the researchers must know how family members are related to each other. These critical components come together in Utah, where we propose to do this research.

Role of the Orbitofrontal Cortex and Midbrain Dopamine Neurons in Associative Learning from Reward Prediction Errors



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Award: \$40,000 (fellowship)

The orbitofrontal cortex (OFC) is central to our understanding of OCD (Obsessive Compulsive Disorder), which is frequently associated with Tourette syndrome (TS). A common feature of OCD and TS is an inability to inhibit unwanted actions that follow premonitory experiences such as thoughts (OCD) and sensations (TS). This similarity indicates a common underlying inability to inhibit inappropriate responses, an ability which has long been linked to the OFC. Consistent with this hypothesis, brain imaging studies have demonstrated changes in OFC function in OCD and TS. For example, patients with OCD show reduced activation of the OFC during reversal learning; a type of associative learning that is exquisitely sensitive to manipulations that disrupt OFC function. However, the precise role that the OFC plays in supporting adaptive behavior in reversal-like settings remains controversial.

Inhibitory interneurons defined by the fast-spiking phenotype and expression of the calcium binding protein parvalbumin (PV) are implicated in TS pathophysiology. For example, a strong imbalance between the numbers of PV neurons and projection neurons in basal ganglia in individuals with TS was recently reported. Considering the possibility of a common defect of PV neuron migration during embryogenesis between basal ganglia and cortex, there may be a similar imbalance in the OFC in TS subjects. In this project we will address the role of PV neurons in the OFC for associative learning induced from reward prediction errors. We will use optogenetic technology which enables us to specifically manipulate activities of PV neurons on millisecond order. We will then monitor activity of midbrain dopamine neurons to examine the impact of PV cells in OFC over the dopaminergic neurons. This study may provide a novel insight into the underlying circuit abnormalities in TS and OCD, and ultimately suggest potential therapeutic approaches for these disorders.

Commentary: In addition to often being co-associated, Tourette syndrome (TS) and Obsessive Compulsive Disorder (OCD) are similar in that a premonitory urge is followed by an inappropriate and unwanted action. This observation has led scientists to propose that a glitch in normal brain function may be responsible for both disorders. In this study, we will focus on a part of the brain that is involved in decision-making and which is thought to be implicated in both TS and OCD. More specifically, we will attempt to determine whether dysfunction in this part of the brain results in abnormal activity of nerve cells that contain dopamine. Abnormal activity of these dopamine containing nerve cells has long been implicated in the generation of tics. Results from this study may help us understand the neurological basis of TS and OCD.

Evaluation of Prenatal and Perinatal Risk Factors for Tourette Syndrome and Chronic Tic Disorders in a Large, Prospective, Population-based Cohort

Although Tourette Syndrome (TS) and chronic tic (CT) disorders are highly heritable, non-genetic factors are also thought to play a role in their development. Previous studies have reported a number of candidate “environmental” TS/CT risk factors, particularly events or exposures arising in the prenatal or perinatal period (during pregnancy and delivery). Unfortunately, these studies have produced conflicting results, possibly because of hidden biases related to their retrospective designs, the limited availability of well-documented environmental exposures or the lack of a comparable unaffected control group. Thus, there is a great need to examine these potential risk factors in individuals where detailed information is identified prior to the onset of any tic symptoms.

In this project, we are evaluating the previously reported candidate prenatal and perinatal TS/CT risk factors in a large, prospective British pre-birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). This unique sample contains data collected from all children born to mothers in a specific geographical area between 1991-1992, and includes questionnaires completed during pregnancy, birth records and serial questionnaires about child development, environmental exposures and health outcomes every 6-12 months to the present day. In Year 1 of this award, we determined the prevalence of TS/CT in ALSPAC children and have promising preliminary data regarding prenatal and perinatal risk factors. For Year 2, we will explore these data further with more sophisticated analytic methods. In addition, we will examine how TS/CT cognitive profiles are modified by common co-morbidities and whether these profiles share common non-genetic risk factors with TS/CT.

We anticipate that this research will contribute toward improved understanding of the underlying causes of TS and CT and will lay the foundation for future gene-by-environment interaction studies that could identify the specific mechanisms through which these non-genetic factors contribute to the development of these conditions.



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University of Bristol, Bristol, UK



Carol Mathews, M.D.
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Award: \$39,683 (2nd year)

Commentary: Although TS is an inherited condition scientists believe that other non-hereditary factors might influence the development of the disorder. In this study, we will obtain a large database from the United Kingdom (UK) that contains information on the lifestyle, environment and health of parents and their children. This study could lead to the identification of environmental factors that are involved in the development of TS and chronic tics.

Journal Publications Resulting from Previous TSA Research Grant Awards*

Following are extensive listings of recent scientific journal publications and professional conference presentations by TSA grant award recipients. The depth, range and outstanding quality of these TSA funded investigators' work attest to the significant influence our Association's funding has had on the entire field of TS research.

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Journal Publications Resulting from Previous TSA Research Grant Awards*

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Journal Publications Resulting from Previous TSA Research Grant Awards*

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**Presentations reported to TSA by grantees. Funded presenters are indicated in bold and research grant year(s) in brackets.*

Tourette Syndrome Research Grants and Fellowships

The Tourette Syndrome Association accepts research grant proposals from M.D. and Ph.D. researchers in basic and clinical studies on all aspects of Tourette Syndrome. The TSA will provide awards of up to \$40,000 for post-doctoral fellowships and up to \$75,000 for research grants. Fields of interest include:

- Pathophysiology
- Genetics
- Animal models
- Neuropathology
- Pharmacology
- Clinical trials
- Behavioral interventions
- Surgical treatments

For more information and submission dates and deadlines visit <http://tsa-usa.org/research.html>

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The national Tourette Syndrome Association, Inc. is committed to the belief that increased knowledge of the basic underpinnings of Tourette Syndrome (TS) will lead to improved medical treatments with fewer side effects. That is why our Scientific Advisory Board has designated those research areas that offer the best promise for improved understanding of what causes TS, and which also capitalize on recently developed, exciting new technologies that are now available to researchers. Always at the forefront of TS research, we continue to proactively encourage internationally recognized scientists to pursue focused studies in both clinical and basic sciences.



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