

5th International Scientific Symposium on Tourette Syndrome

Prepared by Linda Saslow

Overview:

As part of its mission to identify current research advances, disseminate them among the scientific and medical communities, and establish networks of basic and clinical scientists, the Tourette Syndrome Association, Inc. (TSA) sponsored the 5th International Scientific and Clinical Symposium on Tourette Syndrome, on June 12-13 in New York City. As with the four previous symposia convened by the TSA, the meeting provided a forum for updating current research findings for both basic scientists and clinical researchers, as well as allied medical practitioners.

The symposium brought together 250 delegates and internationally renowned experts in their respective fields, from 17 countries. The target audience for the symposiums included: basic scientists, physicians of general medicine, pediatricians, family practice physicians, neurologists, psychiatrists, internists, psychologists, nurse practitioners, mental health therapists, school psychologists, school nurses, social workers and clinical investigators.

Since the last symposium convened in 2004, significant advances have been made in understanding the basic underpinnings of Tourette Syndrome (TS) as well as in the application of new and refined approaches to clinical care. The biological and medical literature on Tourette syndrome has grown exponentially. Because TS research depends on findings from many research disciplines, information flow and communication across disciplines are vital for the continued efficient and effective study and treatment of this disorder. This symposium served as a highly effective venue for such cross-disciplinary communication. The program included an expert faculty that presented on genetics, neuroimaging, neuropathology, clinical trials (medication and non-medication), epidemiology, neurophysiology, neuroimmunology, and descriptive/diagnostic clinical science. Presenters conveyed their research findings through platform presentations, small group meetings/workshops and poster displays. One of the primary goals of the symposium was to set the agenda for future TS research efforts and improved clinical care.

At the symposium, the TSA's Early Career Research Award was presented to TSA grant recipient Nicole Calakos, M.D., Ph.D., for her work on synaptic and circuit level insights for TS and OCD, using mouse models. Dr. Calakos was also among 57 scientists who presented posters, including six scholarship awardees. The scholarships are part of the TSA's commitment to encouraging young researchers to focus their study on pursuits related to TS.

Summary of Sessions Presented at the Symposium

Session 1: Tourette Syndrome Research: past, present and future

Chair: Mary M. Robertson, MBChB, D.Sc.; Depts. of Psychiatry/Behavioral Science; University College London Medical School; London, UK

1A. TS, The Big Picture, Where Neurobiology Meets Environment

Presented by John T. Walkup, M.D., Division Child/Adolescent Psychiatry; John Hopkins Hospital; Baltimore, MD

Objective: To review the role of treatment advances in the conceptualization of Tourette Syndrome

Discussion: Tourette Syndrome (TS) was first described by scientists studying movement disorders and psychiatric syndromes with physical manifestations (i.e. hysteria). Initial conceptualization of TS was therefore limited by etiological models of the time with TS being treated and conceptualized using psychological models and treatments of the day. This model of TS persisted until the mid-1960s when antipsychotic medications demonstrated efficacy in reducing tic severity. Since that time, TS has been conceptualized as a neurobiological condition with increasing research efforts and scientific advances in our understanding of TS. Our current conceptualization focuses on how TS is a neurological disorder with common psychiatric problems based on family genetic studies in the 80s and 90s, which identified psychiatric disorders as common complications of TS.

New data support the efficacy of behavioral treatments that include habit reversal training in reducing tic severity. Tics can be changed by behavioral changes. Behavioral strategies empower children and families to make a difference. Children are the strongest advocates of behavioral treatment, as they feel more in control. Parents are also supportive as this treatment can mean the avoidance of medications.

We are in the midst of a change in the way of thinking—from intuitive to counterintuitive. The old way of thinking encouraged children and families to ignore tics, reinforced the belief that you can't control tics, that children should not be punished for their tics, they should not try to suppress their tics because suppression can make tics worse or cause new tics to develop. By contrast, the newer way of thinking encourages children to become more aware, to learn to manage their tics. It encourages behavioral management of tics and rewards them for successful management.

Conclusion: A century of treatment, experience and research has changed how we conceptualize TS. The efficacy of behavioral treatments will likely introduce another evolutionary step in our conceptualization of TS. These new treatment paradigms bring excitement and hope to the treatment of TS.

1B. What Will It Take to Hunt Down the TS Genes?

Presented by Nelson E. Freimer, M.D.; University of California, Los Angeles, Center for Neurobehavioral Genetics, Los Angeles, CA

Objective: To analyze the progress made in identifying the specific genetic variants contributing to TS susceptibility

Discussion: Despite the undoubted heritability of TS, identifying the genetic variants contributing to TS susceptibility has proven very difficult. Strategies in the past have focused on linkage analysis of extended pedigrees and affected sibling-pairs. In recent years, interest has grown in using association strategies to find the common variants. Most recently, a Genome Wide Association Study (GWAS) of more than 1,000 TS cases plus ethnically matched controls, genotyped for more than 500,000 single nucleotide polymorphisms (SNPs), is ongoing. The linkage studies have identified several promising TS localizations, most notably a locus attaining genome-wide significance on chromosome 2. While analysis of GWAS is still underway, preliminary results are highly encouraging. The Tourette Syndrome Association International Consortium on Genetics is now engaged in an intensive international effort to identify, phenotypically assess, and obtain DNA samples from a large sample of additional TS affected individuals to attempt to replicate the GWAS finding. The family based and case control study includes 1749 cases and 4410 controls. So far, seven very preliminary strong signals are pointing to genes that were never thought to have had any effect on TS.

Conclusion: Our most crucial task now lies ahead; replication will require collecting samples, genotyping of the replication samples and re-sequencing studies in regions of linkage, association peaks and the whole genome. The future direction in TS GWAS will be a more complete SNP analysis, an analysis of the TS phenotype and a combined analysis with OCD.

1C. Neural Circuits and TS: Integrative Networks Across Basal Ganglia Circuits

Presented by Suzanne N. Haber, Ph.D.; Professor, Department of Pharmacology/Physiology; University of Rochester School of Medicine, Rochester, NY

Objective: To review the basic circuitry that underlies parallel processing and to outline the anatomical basis for integration across different cortico-basal ganglia circuits.

Discussion: TS is a disease of habits. Breaking the habits can be useful to see how the system can be modified to help TS patients. While at its center are motor tics, the tics are temporarily suppressible, and often preceded by premonitory urges, that builds tension over time. Moreover, TS is often associated with OCD. The circuitry most associated with both TS and OCD is the frontal cortico-basal ganglia circuit. We now know that the cortex and basal ganglia play a critical role in the learning process and the development of goal directed behaviors that lead to action plans and habit formation.

The ability to adapt to environmental stimuli and break habits necessitates coordination between limbic, cognitive and motor systems. Growing evidence supports a dual processing system—parallel and integrative processing—and both are needed to modify behaviors.

Growing evidence from both primate and rodent studies have identified anatomical substrates through which transfer of information can occur across functional domains of the basal ganglia. They demonstrate that integration occurs at several stations through the system.

Conclusion: There are integrative mechanisms through each stage of the cortico-basal ganglia circuit. The cortico-striatal connections demonstrate integration across functional domains through convergence of terminal fields at the borders of functional domains, at nodes of convergence within subregions of functional domains, and through a diffuse projection system. The pallidal connections demonstrate integration, through convergence at borders and a diffuse fiber feedback projection system. The striato-nigro-striatal network and the cortico-thalamo-cortical network demonstrate integration through a non-reciprocal, directional specific set of connections.

1D. Twin Studies of Developmental Psychopathology and Wellness: Strategies for the Study of Complex Behaviors (including tics)

Presented by James J. Hudziak, M.D.; Director, Vermont Center for Children/Youth/Families; Thomas M. Achenbach Chair in Developmental Psychopathology; University of Vermont College of Medicine, Burlington, VT

Objective: To explore the relationship between genetic and environmental factors in neuropsychiatric disorders.

Discussion: The complexity of diagnostic criteria for TS presents an obstacle to studying this disorder. Data from a U.S. National Sample and the Netherlands Twin Registry show that growth patterns in the developing human brain vary in identical twins if environmental factors are different. The brain can be changed by environmental factors.

A study of 30,000 children, examining tic and OCD behavior in U.S. singletons and Dutch twins found that the frequency of tic behavior peaks at about age 10, then decreases between 10 and 12 years old.

Conclusion: Behavior appears to be influenced by both genetic and unique environmental factors. Everything is influenced by genes, the environment and their interaction.

Session 2: Circuits in TS

*Chair: Jonathan W. Mink, M.D., Ph.D.; Professor, Neurology/Neurobiology/
Anatomy & Pediatrics, Chief, Child Neurology, University of Rochester Medical
Center, Rochester, NY*

2A. Inhibitory Interneurons in TS Brains

*Presented by Flora M. Vaccarino, M.D.; Child Study Center and Department of
Neurobiology; Yale University, New Haven, CT*

Objective: To assess what might be wrong at the neurobiological level in individuals with TS, and whether the striatal inhibitory network is altered in TS

Discussion: Animal models suggest that GABAergic neurons containing parvalbumin (PV) in the cerebral cortex, hippocampus and basal ganglia modulate motor activity and cognitive functions. These neurons are particularly vulnerable to maldevelopment or death during their extended period of postnatal maturation. A decrease in normal PV neuron number in the mature brain causes an abnormally excitable neural network leading to hyperactivity and even seizures. In the striatum, PV interneurons form a powerful inhibitory network driven by cortical and thalamic inputs, directly or through the mediation of basal ganglia cholinergic interneurons. The PV interneuron network down-regulates the activity of the striatal projection neurons, the medium spiny neurons (MSN).

To assess whether the striatal inhibitory network is altered in TS, the density of different types of striatal interneurons and MSNs were compared between the postmortem brains of TS subjects and normal controls. TS patients demonstrated a 50-60% decrease of both PV+ and choline acetyltransferase (ChAT)+ cholinergic interneurons in the caudate and the putamen, two regions within the basal ganglia.

Conclusion: The selective deficiency in PV and ChAT+ interneurons explains the 5% decrease in caudate nucleus volume, the most consistent structural finding in the brains of patients with TS. A decrease in PV and cholinergic interneurons in TS subjects may result in an impaired cortico/thalamic control of striatal neuron firings in TS.

2B. What Do Striatal Inhibitory Interneurons Do?

Presented by Joshua D. Berke, Ph.D.; Asst. Professor of Psychology & Neuroscience; Department of Psychology; University of Michigan, Ann Arbor, MI

Objective: To study and analyze the physiology of striatal inhibitory interneurons

Discussion: TS is thought to reflect altered physiology of basal ganglia circuitry. Recent postmortem studies have suggested a specific deficit in striatal interneuron populations, particularly the parvalbumin-positive, fast-spiking GABAergic interneurons (FSIs). Although FSIs make up only a small fraction of striatal neurons, *in vitro* studies have suggested that they have a powerful influence over the spiking of striatal medium spiny projection neurons (MSNs). FSIs have been theorized to filter out unwanted actions via a broadly-distributed, feed-forward inhibition of striatal circuitry, but there has been no direct evidence for such a mechanism in awake, behaving brains.

Dr. Berke's group has been conducting some of the first awake *in vivo* electrophysiology analyses of the FSI cell population, using a variety of behavioral tasks and pharmacological manipulations. They found that FSIs show rich temporal sequences of activity during performance of striatum-dependent choice tasks. However, multiple FSIs do not normally act as a coordinated cell population with closely linked firing rates—even with local microregions of striatum. Thus, FSIs are providing a much less uniform signal than other striatal circuitry components, such as the dopamine input and cholinergic interneurons. It was found that FSIs show entrainment to gamma-frequency oscillations, and the researchers are now exploring the relevance of these oscillations to behavioral control and learning mechanisms. Although FSIs normally show idiosyncratic uncoordinated changes in firing rate, there were several important exceptions. In response to drugs that alter dopamine neurotransmission in striatum, FSIs show far more uniform responses than MSNs. The population firing rate of FSIs shows a direct correspondence to psychomotor activity, unlike MSNs. This may be relevant to the current pharmacotherapy of TS, for which D2 antagonists are often given, and to the development of novel therapies.

A coordinated striatal FSI response was also found at one key moment during a decision-making task. When animals have to hold still, and then very rapidly choose one of two highly trained movements, there is a pulse of enhanced FSI activity just as they initiate the chosen movement. This pulse was not seen in conjunction with other, even quite similar, movements performed during the same task, Hypothesis: the critical difference is that for the choice movement there is a need to suppress the alternative action, and the suppression is facilitated by striatal FSIs.

Conclusion: The activity of striatal FSIs can be examined in behaving animals. In behavioral tasks, FSIs show highly idiosyncratic firing patterns. Current studies focused on using new optical and genetic technologies to directly manipulate striatal FSIs in freely moving animals will test the developing hypothesis.

2C. Imaging Evidence for Circuit Dysfunction in TS

Presented by Bradley L. Schlaggar, M.D., Ph.D.; Ernest and Jane G. Stein Associate Professor of Developmental Neurology in Neurology; Associate Professor of Radiology, Anatomy & Neurobiology, & Pediatrics' Director, Pediatric Neurology Residency Training; Washington University School of Medicine & St. Louis Children's Hospital; St. Louis, MO

Objective: To compare the maturation of task control networks in typical development and Tourette Syndrome

Discussion: How does the brain's functional network architecture mature? The network architecture provides a context within which to interpret task induced activation/deactivation. Maturation of network architectures provides insight into both typical and atypical development.

In looking at task-level control: How do people manage to do all the things that people can do—how do they deal with environmental demands, acquiescence to instruction and at their own volition? Systems may be atypical in people with TS.

Two issues in top-down control: People can flexibly configure the specific processes necessary to perform many different tasks and this is done on a massively parallel, interconnected architecture in the brain.

What might task control signals look like in a task with a trial-by-trial structure? A wide range of tasks were included in analyses and 39 regions of the brain, distributed across the cerebrum and cerebellum, showed some combination of task control signals across a majority of tasks; 22 of those regions do not seem related to sensory or motor processing. Many of the regions are in locations that people have previously related to attention and executive processes. Most significant: the regions are not limited to the prefrontal cortex.

Resting state functional connectivity (fMRI): A mapping method allows activities of the brain at rest. A single "seed" produces a map showing that there are large differences in correlation among different brain regions. Correlations in spontaneous fMRI signal fluctuations reflect functional relatedness of regions in a Hebbian sense. These correlations potentially reflect a long history of "firing together."

A dual-network architecture: two networks are characterized by different signal properties. There are at least two relatively separate control systems: frontal-parietal and cingulo-opercular. The distinct control networks appear to mature via mechanisms of segregation and integration. Integration and segregation of the control networks appears to be accomplished, at least in part, by pruning short range and elaborating long range functional connections.

What happens in TS? In a direct comparison of 33 TS participants and 42 unaffected participants, with similar ages (10-15), all males, similar IQs (105-108), TS networks

appeared more immature (more like 7-9 year olds). On average, functional connections in TS were roughly 3 years younger than typical children. In addition, a number of atypical functional connections, not seen in typical adults or children, were observed to predominate in the frontal-parietal network.

Conclusion: The frontal-parietal network is characterized by set initiation signals and error-related signals. The network supports control inhibition and adaptive trial-related adjustments. Adolescents with TS appear to have delayed maturation of the functional connectivity of task control networks in general and atypical configuration of the frontal-parietal network specifically. This work leads to the hypothesis that in TS, there may be alterations in response to error feedback, set initiation and atypical initiation or interruption of signals. This hypothesis is being addressed in present experiments.

2D. Treatments Aimed at Circuits: DBS

Presented by: Veerle Visser-Vanderwalle, M.D., Ph.D; Professor of Functional Neurosurgery; Maastricht Institute for Neuromodulative Development; University Medical Centre; Maastricht, The Netherlands

Objective: To present deep brain stimulation surgery (DBS) as a viable option for treatment of last resort for patients suffering from TS refractory to any behavioral and medical treatment.

Discussion: Deep brain stimulation was first introduced as a new surgical technique for the treatment of intractable TS in 1999. After the initiation of DBS targeted at the medial part of the thalamus, several other targets have also been used. To date, five sites have been targeted for DBS in TS patients: the medial thalamus, posteroventral globus pallidus internus, anteromedial and Internal Capsule/Nucleus Accumbens. .

Different rationale have been presented for targeting each of the sites. Positive effects and tic reduction have been reported in most studies, but there were varying side effects.

The pathology of TS remains poorly understood, but it is widely believed that abnormalities in dopamine neurotransmission play a fundamental role in the pathogenesis of TS. Within the brain, there are anatomically segregated, parallel circuits representing different functions. These basal ganglia circuits traverse the cortex, striatum, globus pallidus, and thalamus. Each circuit includes a direct and indirect pathway. Dopaminergic hyperactivity in TS is hypothesized to inhibit the indirect pathway, leading to an overactivity of thalamocortical drive. The excitatory feedback loops from the centromedian-parafascicular complex of the thalamus to the motor region of the striatum and the midline thalamic nuclei to the limbic part of the striatum are implicated in the pathophysiology of TS and explain the efficacy of DBS in this location.

Conclusion: DBS is a promising therapy for TS patients with very severe cases who have received careful trials of standard therapies without adequate benefit.

Session 3: Public Health

Chair: Lawrence Scahill, M.S.N., Ph.D.; Professor Nursing/Child Psychiatry; Yale University School of Nursing, New Haven, CT

3A. Report on Epidemiologic Findings from CDC

Presented by Rebecca H. Bitsko, Ph.D.; Child Development Studies Team; Center for Disease Control and Prevention; Atlanta, GA

Objective: To determine the prevalence of TS in the United States

Discussion: A report on the prevalence of diagnosed TS cases ages 6-17 in the United States, as of 2007, was published in June in the *Morbidity and Mortality Weekly Report*. A question about TS was included in the National Survey of Children's Health, with the objective of determining the prevalence of children diagnosed with TS, using a nationally representative sample. From April, 2007 until July, 2008, there were 91,642 phone interviews conducted with parents of children birth to 17. The response rate was 46.7% and the cooperation rate among households who were identified to have children was 66%. Included in the survey were three questions about Tourette Syndrome: Has a doctor or health care provider ever told you that your child has TS? If yes, does your child currently have TS? Would you characterize the TS as mild/moderate/severe? Parents were also asked whether the child had other mental health and neurodevelopmental conditions such as attention-deficit/hyperactivity disorder (ADHD), depression, anxiety, behavioral problems, or developmental delays affecting the child's ability to learn.

Results: Approximately 148,000 children (3/1,000) had been diagnosed with TS. Among those whose parent answered yes, 62% still have it (about 92,000 children). Boys were 3 times more likely to be diagnosed with TS, adolescents more likely to be diagnosed compared to younger children. There were no differences found in prevalence related to parental education or household income. Among regional differences, the highest prevalence was in the Northeast. Among children with TS, 80% had also been diagnosed with co-occurring conditions (64% with ADHD). The majority of cases were described as mild, with 27% as moderate or severe.

Conclusion: This was the largest sample for TS prevalence and provides the baseline for future studies. Future research is needed to determine the number of undiagnosed cases, as well as to better understand the differences by race and ethnicity.

3B. The Prevalence and Service Use of Tourette Syndrome in Private Insurance and Medicaid Populations

Presented by John T. Walkup, M.D.; Division of Child/Adolescent Psychiatry; John Hopkins Hospital; Baltimore, MD

Objective: To investigate how many children get treatment for tic disorders and what their risk is for another psychiatric disorders.

Discussion: Studies were conducted from 2001-2004, using a Medicaid sample from 45 states, limited to fee-for-service plans; Insurance policy holders with pharmacy benefits were also analyzed from 2000-2007, contributed by more than 150 companies. The sample selection was: patients age 4-18, with a clinical diagnosis of TS or tic disorder for one calendar year. The prevalence per 1,000 was found to be: .53 for TS; .08 for chronic tic disorder; .43 for other tic disorder. Male: female ratio was 3-4:1.

Children who have TS are 3-4 times more likely to also have ADHD, 11 times more likely to have OCD. Among children with private insurance, 24% received mental health services, compared to 10% of patients on Medicaid. Of privately insured children, 75% are medicated, compared to 85% on Medicaid. Of privately insured children, 33% receive antipsychotics, compared to 54% on Medicaid.

Conclusion: Children who get treatment for TS are rare. Children diagnosed with TS are likely clinically complex. Many receive mental health and neurological services. The greatest limitation to the research was identifying undiagnosed cases.

3C. Disability Associated with Tics in Community Samples

Presented by Anne-Liis von Knorring, M.D.; Professor, Child/Adolescent Psychiatry; Department of Neuroscience; Uppsala University Hospital; Uppsala, Sweden

Objective: To identify the most pervasive developmental and behavioral disabilities associated with TS

Discussion: A study of 4479 children 7-15 years old found the following results:
The age of onset for TS was found to be earlier than with chronic motor/vocal tics—age 4 compared to 6-7. When parents were asked to rank the symptoms of most importance exhibited by their children, 36% responded that rage was the most significant. Parents sought help less for tics, but more often for problems with conduct, learning and attention.

Among children with TS, 92% had one or more diagnoses; 60% had 2 or more diagnoses; 36% had 3 or more diagnoses. For children with co-morbid diagnoses, ADHD decreases with age, while depression increases.

Conclusion: Almost all children with TS have co-morbid psychiatric disorders and many have learning disabilities.

3D. Priorities as Judged by People with TS

Presented by Douglas W. Woods, Ph.D.; Director Clinical Training, Associate Professor of Psychology; University of Wisconsin; Milwaukee, WI

Objective: To evaluate the impact of TS on patients and families

Discussion: The Tourette Syndrome Impact Project was recently completed, modeled after the Trichotillomania Impact Project, for children and adults. Two surveys were used, one for children and the second for adults. Both were completed anonymously and on-line. Child survey included a parents section (demographics, tic severity and history, functional impact, treatment history, support group utilization, child's anxiety, rage attacks, family impact) and child –10-17 years of age—section (tic severity, premonitory urge for tics scale, functional impact, bullying questions, moods and feelings, anxiety). Among the 741 parents who completed the survey, 87% of the responders were mothers, with the mean age 41. The mean age of their children was 10.6, with 51% reported co-conditions—OCD the most common. The adult survey included many of the same factors. Mean age was 35.5, and 50% had other psychiatric diagnoses—OCD the most common.

Treatment history: The most common treatment for tics was medication (83% for children, 94.7% for adults). Other most common treatment for children: diet alterations, omega-3 supplements, behavioral therapy, psychotherapy. For adults: diet alteration, support groups, meditation, psychotherapy. Most common medications for children: clonidine, guanfacine, risperidone. For adults: haldol, clonidine, klonopin. Most common reasons for not using medication: afraid of side effects, worry about long term effects, or tics not severe enough. Behavior therapy is not commonly received. When it is, for children, relaxation training and stress management are most common, while habit reversal therapy (HRT—the one therapy that has evidence of positive results) was cited 6th out of 7. For adults, relaxation and stress management also listed as top behavior therapies, with HRT as number five out of seven.

Conclusion: Overall quality of care for those with TS is questionable. Care provider's knowledge of TS is limited, and it is vital to educate more providers about TS and options in treatment. Many treatments with no evidence of efficacy are being used.

Access to behavior therapy and behavior therapists trained in Tourette's treatment is limited. Most types of behavior therapy being used in the community have little empirical support for their use. There is a need to increase training of behavioral therapists and to educate the public about how to seek good behavioral therapy (i.e., HRT-based procedures).

Session 4: Neuroimmunology

Chair: Tanya K. Murphy, M.D.; Departments of Pediatrics/Psychiatry; University of South Florida; All Children's Hospital; St. Petersburg, FL

4A. Brief Introduction to the Field

Presented by Tanya K. Murphy, M.D.; Professor, Departments of Pediatrics/Psychiatry; University of South Florida; All Children's Hospital; St. Petersburg

Objective: To address the question: Is there a relationship between the immune system—particularly strep—and TS?

Discussion: In the studies of the relationship between PANDAS and TS,—observations reported are: younger age onset for OCD and tics, association with ADHD, co-morbid symptoms such as mood swings and separation anxiety, and compulsive urination while having strep infections. In an immunology study of 109 children, 41 met the criteria. Questions that arose: is it one strep infection that starts the PANDAS or a series leading to a build-up threshold for a dramatic onset? Do repeat strep infections lead to an increased risk?

In 2007, a large study of 703 children, pre-kindergarten through sixth grade, included monthly throat cultures and observations of behavior and movement. Children with repeated strep infections showed more behavioral symptoms but no evidence of increased tics.

More questions have been raised: Will immune markers, and immune risk factors such as infections and allergies, help distinguish between those children with PANDAS and those without?

Is Group A strep causal or coincidence? Do innate or acquired immune defects exist to predispose to these neuropsychological presentations? What are the boundaries? Do other infections contribute or mimic presentations? How do we diagnose and treat? If we do treat, which antibiotics should be used and what dosage? And finally, if the child improves, why? Are immune therapies valuable?

Conclusion: There are more questions than there are answers.

4B. Immunology of the Nervous System

Presented by Michael Schwartz, Ph.D.; Department of Neurobiology, Weizmann Institute of Science; Rehovot, Israel

Objective: To examine how peripheral immune cells maintain brain plasticity in health and disease, and whether congenital immune deficit can explain late onset of psychological disorders.

Discussion: Over the past decade there has been a new perspective to psychological and degenerative disorders, recognizing that systemic immune cells also control the “state of mind.” This new perspective links CNS pathology and physiology to immune system function and malfunction.

Studies over the last decade have shown that the brain is dependent upon its resident immune cells, assisted by the peripheral immune system, for its maintenance, repair and renewal. Researchers discovered that CD4+ T cells recognizing central nervous system protein antigens are essential for neuronal survival, for controlling neurogenesis and oligodendrogenesis from endogenous stem cells, for coping with mental stress, and for cognitive plasticity. When the immune system gets out of control, the result is autoimmune disease.

This new perception of the role of systemic immune system in CNS plasticity, explains how immune system dysfunction affects onset and progression of neurodegenerative diseases and dementia, late onset of abnormal sensorimotor gating in congenital psychological disorders, and development of depression. Neurogenesis is affected by changes in the immunological condition. Results suggest new approaches to bridge disease-induced or age related gaps between the potential for plasticity and the actual compensatory capacity of the central nervous system.

Conclusion: Local and systemic immune cells are needed for brain maintenance and plasticity. The onset of brain pathology in the absence of predisposition is a reflection of insufficient immunity or overwhelming deviation from balance.

Rejuvenation of the immune system is a way of preventing memory loss. Development of a T cell-based vaccination may improve the function of the aging brain and protect brains threatened by mental stress, acute chemical or mechanical insults, or by degenerative diseases.

4C. Neuroimmunology of TS

Presented by Gavin Giovannoni, M.D., Ph.D.; Centre for Neuroscience & Trauma, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, London, United Kingdom

Objective: To analyze the multi-factorial etiology of TS, including the evidence of abnormal immune activation

Discussion: For individuals with TS, genetic, environmental, immunological and hormonal factors interact to establish vulnerability. A higher exposure prior to disease onset to group A B-hemolytic streptococcal (GABHS) infections in children with tics and obsessive compulsive (OC) symptoms is well documented, although their influence upon the course of disease remains uncertain. Increased activation of immune responses in TS is suggested by changes in gene expression profiles of peripheral immune cells, relative frequency of lymphocyte subpopulations, and synthesis of immune effector molecules. Increased activity of cell-mediated mechanisms is suggested by the increased expression of genes controlling natural killer and cytotoxic T cells, increased plasma levels of some pro-inflammatory cytokines which correlate with disease severity, and increased synthesis of anti-neuronal antibodies.

Conclusion: The era of smaller studies has not provided sufficient information, and larger studies are needed. Differences in methodology may account for some inconsistency among results of studies addressing autoantibodies in TS. A general predisposition to autoimmune responses in TS patients is indicated by the reduced frequency of regulatory T cells, which maintain tolerance towards self-antigens. Although the pathogenic role of immune activation in TS has not been proven, a pathophysiological model explains the possible effect of immunity upon dopamine transmission regulation and the generation of tics.

4D. Longitudinal Clinical and Immunologic Study of TS and Streptococcal Infection

Presented by Roger M. Kurlan, M.D.; Professor of Neurology; University of Rochester Medical Center, Rochester, NY

Objective: To determine, by intensive clinical and laboratory prospective observations, whether there is a temporal relationship between antecedent GABHS infection and exacerbations of tic disorder or OCD in subjects meeting diagnostic criteria for PANDAS.

Discussion: A recent multi-center study of 80 subjects (40 PANDAS cases and 40 matched controls) was conducted, using NIMH criteria (presence of OCD or a tic disorder, onset between age 3 and the beginning of puberty, abrupt onset of symptoms or a dramatic exacerbation of symptoms, onset or exacerbation temporarily related to infection with GABHS, abnormal results of neurologic examination during exacerbation). Study method included monthly throat cultures and routine clinical assessments (laboratory personnel blinded). Main difference found was that PANDAS cases had more co-morbidity diagnoses. PANDAS had more clinical exacerbations and a higher rate of strep infections. PANDAS cases had increased likelihood of a relationship between strep and a clinical exacerbation, but only a small fraction of exacerbations had any evidence of being associated with a strep infection. Among controls, exacerbations were more commonly associated with non-strep infections.

Conclusion: Study showed that compared to controls, PANDAS cases are more likely to get strep infections and more likely to see a relationship between streptococcal and clinical exacerbation, but this relationship accounts for only a minority of exacerbations. PANDAS cases represent a sub-group of TS/OCD patients who are susceptible to GABHS infection as a precipitant of their symptoms, but streptococcus is not the only or even the most common precipitant for these patients. It is likely that there are other sub-groups with other “preferred” precipitants. It is unknown whether separating out subgroups based on clinical precipitants has clinical or scientific merit.

4E. PANDAS Reconsidered

Presented by James F. Leckman, M.D.; Director of Research, Neison Harris Professor, Child Psychiatry/Pediatrics; Yale University School of Medicine; Child Study Center, New Haven, CT

Objective: to analyze epidemiological data, promising pilot data regarding psychosocial stress, a new model of PANDAS pathogenesis, and future directions

Epidemiological data: Epidemiological data from a national sample of 742 children identified as having their first onset of either obsessive compulsive disorder (OCD) or a chronic tic disorder were found to be significantly more likely than 3,647 matched control children to have had a streptococcal infection in the 12 months before the onset of their condition. These children were also more likely than controls to have had a prior sinusitis infection in the 12 months before onset. This and one earlier epidemiological study are consistent with GABHS infections potentially an etiological role in a subset of patients. This vulnerability may not be limited to GABHS infections; there may be subsets of ADHD patients with a similar vulnerability.

Psychosocial stress: In a separate study of more than 40 children with TS multiple measures all indicated that TS patients experience a higher level of psychosocial stress than do age matched controls. High stress levels indicated a worsening of tic symptoms a month later. Predictive power of stress to predict tic worsening increased by a factor of three following a new a streptococcal infection. Parental ratings of perceived stress were more predictive of future tic severity than the clinician's ratings on long term objective threat. Antecedent GABHS infections had a modest effect in predicting increases in future tic severity in an unselected TS population.

Biomarkers: Some TS patients may have a decreased capacity to inhibit autoreactive lymphocytes through a deficit in regulatory T cells (Tregs). Work from Madeleine Cunningham's laboratory in Oklahoma indicates that cross reactivity antibodies directed against lysogangliosides can induce increased central dopamine production and may contribute to a failure of T regs to control inflammation in the CNS. It is possible that any compromise of the blood-brain barrier could lead to the introduction of D2 specific autoantibodies into the CNS and that these antibodies could also contribute to an increase in tic and/or OC symptoms in combination with an increase in central dopamine production.

Conclusion: The interface between TS, OCD and the immune system remains to be fully explored. There are several preliminary immune findings, that need to be independently replicated, that suggest that a subset of TS may have immune dysfunction. In addition, it will be necessary to refine the diagnostic criteria for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) by placing a greater emphasis on the acute nature of the exacerbations (<48 hrs), and the development of novel rating scales that would allow clinicians to identify accurately patients with an acute autoimmune process. The use of immune biomarkers may also be of some use in this effort.

Session 5: Neurochemistry/Pharmacology

Chair: Harvey S. Singer, M.D.; Director, Child Neurology; Haller Professor; Johns Hopkins Medical School, Baltimore, MD

5A. Evidence-based Overview of Pharmacological Treatment

Presented by Donald L. Gilbert, M.D., M.S.; Director, TS & Movement Disorders Clinics; Associate Professor, Child Neurology; Children's Division of Neurology; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Objective: To survey recent pharmacological studies in TS whose primary outcome is tic suppression

Discussion: If we understand more about how people tic, we can better understand more productive directions for treatment.

History: Studies from the late 1980s and 1990s were mostly small, single site studies, often uncontrolled. These suggested modest efficacy for dopamine receptor blocking agents. Some other agents showed modest effects. Three rigorous studies from 2002-2005, both involving children with TS and ADHD, showed promise for advancement in knowledge about pharmacological treatment of TS. These included: The landmark TACT study (compared clonidine, methylphenidate, both, or placebo and showed all active treatments improved both ADHD and tics) as well as studies of Atomoxetine and Pergolide (now off market).

More recent small clinical trials on Levetiracetam, Donepezil, Aripiprazole, Tetrabenazine, B6, Magnesium and Omega 3 show modest benefit or no benefit for tics.

Future Challenges: proposed NIH studies have not been funded because the most prevalent TS cases are mild and our treatments are not really novel. NIH funds clinical trials for symptoms with more serious impairment. Pharmaceutical companies are reluctant to fund clinical trials because there is little profitability and most TS patients have complex conditions.

Conclusion: Many medications help a little. There is a need for rigorous studies of novel agents which are safe and effective treatments.

5B. What Can We Learn from Animal Models of TS?

Presented by S. Barak Caine, Ph.D.; Associate Professor, Department of Psychiatry, McLean Hospital/ADARC, Harvard Medical School, Boston, MA

Objective: To discuss four principal areas regarding animal models: pathophysiology, behavior, genetics and preclinical evaluation of candidate medications.

Discussion: Research funded over the last two years has focused on pathophysiology: can we make an animal model with TS? Also studies have been done on behavior and reverse and forward genetics.

Prepulse Inhibition of Startle (PPI): We are measuring the startle response in mice and looking at the question of: how well can we inhibit their responses to stimuli? Dopamine receptors can be used to modify a person's ability to inhibit responses; this may spare side effects and is promising for medications.

Forward genetics: we are looking for genes that are different in mice that exhibit a tic of turning their heads to one side.

Conclusion: The utility of animal models for preclinical evaluation and the study of pathophysiology, behavior and genetics are useful avenues towards finding safe and effective medications without side effects.

5C. Effect of Environmental Factors in the Onset of Hair-pulling and Skin-picking in a Mouse Model

Presented by Joseph P. Garner, Ph.D.; Animal Sciences; Purdue University, Purdue, IN

Objective: To outline the similarities between TS and trichotillomania (barbering)/skin-picking, present data on the role of diet and reproductive hormones in triggering and preventing the onset of symptoms in a genetically at-risk mouse model.

Discussion: Research in the lab is focused on the diversity and development of abnormal repetitive behaviors, both within and between disorders. The goal is to understand how environmental factors halt or enable the development of genetic predispositions into fully symptomatic disorders, so that ultimately, strategies can be designed to prevent disorder developing in at-risk populations. Currently, the two disorders under review are trichotillomania and skin-picking, which though different from TS in many ways, share some symptomatology with TS (premonitory sensations, neuropsychological markers, respond well to habit reversal therapy) and appear to involve overlapping cortico-striatal circuitry.

Following the development of a disorder: we can follow the development with neuropsychological and physiological measures; changes in the genes. As disorders develop, measures become less determinant since closely related disorders share biomarkers. Increasing complexity and divergence of measures, symptoms and the disorders are partly due to genes, partly to environmental factors.

What are environmental triggers? How can we design preventative interventions? One study investigated if there are behavioral underpinnings to ulcerative dermatitis (UD). Hypothesis: Excessive scratching precedes the development of ulcerative dermatitis (UD) lesions. A serotonin enhancing diet induces UD by exacerbating scratching behavior. And there is a relationship between barbering behavior and UD. Mice were categorized into three groups: intact (no barbering), slight barbering and severe barbering. All mice were placed on the same diet. Grooming responses to a mist of water were measured at baseline, week 6 and 12, with hair loss scores and the presence of UD scored weekly. Results found that elevated scratching scores at baseline predicted UD development in response to diet. Also, diet increased scratching behavior. Finally, barbering and UD are related.

The second experiment examined potential neuroendocrine pathways involved in barbering in female mice. Hypothesis: reproductive physiology plays a role in the onset and prevalence of barbering in female mice. By manipulating reproductive hormones, we can alter the onset and prevalence of barbering. Results confirmed that estrogen impacted reproductive physiology. Estrogen also provided a protective effect against barbering in female mice.

Conclusion: The first study demonstrated that there is a behavioral component to UD, which precedes lesion onset, and diets can induce UD by exacerbating scratching. The second study suggests a relationship between barbering and changes in reproductive physiology. Estrogen may play a role in regulating the onset or treatment of the disorder.

Session 6: Behavior Therapy

*Chair: Sabine Wilhelm, Ph.D.; Director, OCD & Related Disorders Program;
Associate Professor, Psychology; Harvard Medical School, Boston, MA*

6A. Physiology of Volitional Control

Presented by Adam R. Aron, Ph.D.; Professor, Department of Psychology; University of California at San Diego, La Jolla, CA

Objective: to discuss volitional control as a fundamental function, how pre-frontally generated stopping affects the motor system, how foreknowledge affects the motor system

Discussion: Volitional control is relevant to many neuropsychiatric conditions, including TS. The challenging problem is to understand the neural basis of volitional control as it relates to TS and other disorders.

The Stop signal behavioral paradigm: its strengths are that cross species are translatable and cognitively tractable. In a series of trials, subjects were given the “go” signal and told to respond, while, at the “stop” signal, subjects tried to stop themselves. The Go process activates the “direct” fronto-striatal-pallidal-thalamic-motor pathway. The stop process activates the right inferior frontal gyrus (IFG) as well as the pre-supplementary motor area and the apparent subthalamic nucleus of the basal ganglia. Lesion studies in humans affirm the critical importance of the right IFG for stopping an initiated response. As damage to the region increases, the ability to stop worsens. There is an apparent three-way white matter tract network in the right hemisphere between the right IFG, the pre-supplementary motor area and the subthalamic nucleus. This network may be important for the control of manual movements as well as eyes and voice.

While this network may be important for stopping outright and quickly, there is also a need to be selective—*anatomical specificity*: and also to know what you want to control. How do you get someone to stop selectively? Hypothesis: selective stopping requires foreknowledge. Behavioral studies and those with transcranial magnetic stimulation suggest that foreknowledge does lead to advance control of a particular response representation.

Conclusion: Selective stopping requires foreknowledge of what to stop, is possibly implemented by proactive control of specific effectors, and can be trained. Future work is needed to establish whether training has generalized effects, including clinical benefit, and whether it occurs via plasticity of neural circuits relevant to TS.

6B. Behavioral Model of Tic Expression and Treatment

Presented by Alan L. Peterson, Ph.D., ABPP; Professor, Behavioral Wellness Center for Clinical Trials; Department of Psychiatry; University of Texas Health Sciences Center at San Antonio, San Antonio, TX

Objective: To review behavioral treatments for TS, and the behavioral model of tics and tic expression

Discussion: Behavioral treatment includes: contingency management, massed practice, relaxation training, hypnosis, exposure and response prevention, and habit reversal therapy—which has garnered the most support. Habit reversal therapy (HRT) was originally researched for use with nail biting, thumb sucking, hair pulling and individual motor tics. The five primary components of HRT are: awareness training, contingency management, relaxation training, competing response training, and generalization training.

Competing response training involves finding something that is opposite to or incompatible with the tic movement, that is capable of being maintained for about one minute, that is socially inconspicuous, and that is compatible with normal ongoing activities.

A problem with HRT: TS is not a bad habit, and early results were discounted by the TS community. But over the next 15 years, similar results followed, validating its success, leading to funding for the current project (Tourette Syndrome Association Behavioral Sciences Consortium), conducted at six centers.

Common criticisms of behavior therapy for tics: trying to stop tics make you tic more (rebound effect) and stopping one tic makes others worse or is replaced by new ones (symptom substitution). Studies have shown that neither rebound nor symptom substitution occurs with HRT.

Negative reinforcement hypothesis of tic maintenance: if we can detect the premonitory urge, a competing response can prevent the tic. Strategies can be developed to break the linkage between the urge and the tic.

Conclusion: Behavior therapists believe that: TS is a genetically-based neurological disorder; a person's environment heavily influences, but does not cause tics; behavior therapy for tics is not a cure, but a management strategy that can help people live a better life.

6C. Exposure and Response Prevention for Tics

Presented by Cara W.J. Verdellen, Ph.D.; Department of Psychology; Clinical Psychologist, HSK Group Den Bosch, The Netherlands.

Objective: To discuss the potency of exposure and response prevention (ERP) as an alternative behavioral treatment for tics

Discussion: Tics are often preceded by unpleasant premonitory sensations and urges, and followed by relief following the tic. Exposure and response prevention (ERP), a promising treatment for tics, aims at interrupting the sequence of the premonitory urge and the following tic. ERP consists of prolonged exposure to the sensations and response prevention of the tics, thus providing the opportunity to habituate to the sensations. In a randomized control trial comparing ERP with habit reversal in 43 TS patients, both treatments were found to be effective in reducing tic symptom severity. Indications were found for habituation to the premonitory sensations, both within and between ERP sessions. There were no indications for a rebound effect following ERP tic suppression.

Conclusion: Research supports ERP as an alternative treatment for tic suppression. Future research is recommended to review evidence based psychosocial treatments of tics, and to compare behavior therapy with pharmacotherapy.

6D. CBIT Methods and Findings

Presented by Douglas W. Woods, Ph.D.; Director, Clinical Training, Associate Professor of Psychology; University of Wisconsin, Milwaukee, WI

Objective: To provide the initial findings from a recently completed, NIMH-funded, multi-site child Comprehensive Behavioral Intervention for Tics Study (CBITS); to describe the treatment and study design, summarize the clinical characteristics of the sample, present the acute outcome data, and benchmark the study findings against standard tic treatments with respect to outcome and adverse events.

Discussion: A five year project was started by the Tourette Syndrome Association, which included two studies: children (study summarized below) and adults (just completed, no results yet.)

The Child Study was conducted at three sites, with 126 children (ages 9-17) with TS. Children were randomly assigned to the CBIT or control group, for an 8-session, 10 week program. Subjects were assessed at baseline, mid-point and end-point. CBIT combined elements of habit reversal training with psycho-education and function-based behavioral interventions. Control group received parallel psycho-education and supportive therapy. Children had a primary diagnosis of TS or chronic tic disorder, with moderate severity or greater, and were un-medicated or stable for stable for the past six weeks.

Primary outcome measures: clinical global impression, tics, impairment and parent tic questionnaire. The compliance rate was high.

Conclusion: Comprehensive behavioral intervention for tics (CBIT) is a viable option for children with tics. The therapy is safe, and does not cause an increase in disruptive behavior. More research is needed on long term outcomes with co-occurring OCD and/or ADHD.

6E. Interpretation and Implications of Behavioral Treatment Studies

Presented by John C. Piacentini, Ph.D.; Director, Child OCD, Anxiety and Tic Disorders Program, University of California, Los Angeles, CA

Objective: To examine the implications—clinical, public health and scientific—of Behavioral Treatment (BT) studies

Discussion: There is a need to examine CBIT efficacy in the context of standard treatment approaches. A comparison of CBIT with recent controlled medication studies showed that CBIT participants had a similar clinical presentation, including tic severity, to participants in controlled risperidone and ziprasidone studies. In addition, CBIT was approximately as efficacious as these other treatments, although importantly, without the serious side effects and safety concerns associated with medication use.

There has been a paradigm shift in TS treatment. Old (intuitive) thinking: ignore tics; tics can't be controlled; don't punish; don't try to suppress; tics and premonitory urges get worse when you suppress; suppression leads to development of new tics. New (counterintuitive) thinking: become more aware; learn to manage tics; reward successful management; use behavioral strategies; tics don't get worse with behavioral treatment; premonitory urges will fade away; new tics won't develop when using behavioral strategies.

This new thinking has generated new advice to parents: Advocacy; Challenge; Comfort very carefully; Expose; Mindful; Take time to manage; Understand the ABCs of tics; Stress proof tic management skills; Celebrate successes. This is a new era in giving youngsters tools with which to manage their tics.

There has been limited awareness and many misconceptions about HRT. New data are emerging that concerns about BT are unfounded and that it is a safe and efficacious treatment.

New factors are facilitating the dissemination of information about BT: More availability of behaviorally oriented practitioners and CBIT manuals; Workshops (more than 1,000 practitioners have received some training); The TS Impact Project (TSIP): to educate the public about expanding treatment options.

More studies being done on BT and its use for chronic tic disorders in children. The next steps are to identify predictors of treatment response. In the same way that genetic studies are being used to identify novel biological targets for psychopharmacological intervention, studies of BT can also be used to identify neurocognitive targets that may enhance treatment efficacy.

Round Table Discussions

Developmental Aspects of Cognitive Control

Led by Rachel Marsh, Ph.D.; Assistant Professor Clinical Psychology; Brain Imaging Lab; Division of Child Psychology; Columbia University, New York, NY

Treatment of Behavioral Co-morbidities

Led by Barbara J. Coffey, M.D.; M.S.; New York University School of Medicine and James T. McCracken, M.D.; University of California, Los Angeles, CA

Technology, Telemedicine, and TS Therapy

Led by Michael B. Himle, Ph.D.; Department of Psychology; University of North Dakota, ND

Patients' and Parents' Response to the Concept that Behavior Therapy Can Reduce Tics

Led by John T. Walkup, M.D.; Johns Hopkins Hospital and Lawrence Scahill, M.S.N., Ph.D.; Yale University School of Nursing, New Haven, CT

What Can We Learn About TS from Imaging?

Led by Kevin J. Black, M.D.; Departments of Psychiatry/Neurology/Radiology & Neurobiology; Washington University School of Medicine, St. Louis, MO

Guidelines and Recommendations on DBS & TS

Led by Jorge L. Juncos, M.D.; Associate Professor of Neurology; Emory university School of Medicine, Atlanta, GA

What Would TS Look Like in an Animal Model?

Led by Joseph P. Garner, Ph.D.; Purdue University, Purdue, IN