James Frederick Leckman

Fenomenologia e história natural da síndrome de Tourette: breve resumo da pesquisa

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Programa de Psiquiatria

Orientador: Prof. Dr. Eurípedes Constantino Miguel Filho

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Phenomenology and natural history of Tourette syndrome: brief summary of research

Thesis presented at *Faculdade de Medicina da Universidade de São Paulo* to obtain the title of Doctor in Science

Program of Psychiatry

Supervisor: Prof. Dr. Eurípedes Constantino Miguel Filho

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There is really no adequate description of the sensations that signal the onset of the actions. The first one seems irresistible, calling for an almost inevitable response ... Intense concentration on the site can, itself precipitate the action … Tourette's syndrome movements are intentional body movements ... The end of the Tourette's syndrome action is the "feel" that is frequently accompanied by a fleeting and incomplete sense of relief.

Joseph Bliss (1980)

I finally apprehend the magnitude of the background noise that I have been experiencing for decades … the people around me do not share my tics because they do not hear the drumbeat. They do not feel the sensations without sources, do not have irresistible urges to pause in mid-sentence … and so on in endless, bewildering variety … Finally and most important, I feel convinced that this complex challenging enigmatic internal world is the obvious core of Tourette.

Peter Hollenbeck (2001)

The human body is the best picture of the human soul.

Ludwig Wittengenstein (1958)

Acknowledgments

I am honored to dedicate this thesis to my friends and colleagues at the Universidade de São Paulo. Among these I am especially grateful to Prof. Dr. Euripedes Constantino Miguel Filho. His friendship, his scholarly pursuits, and his leadership have had a positive impact on my personal life and my academic career for more than two decades.

I also dedicate this thesis to the real experts on Tourette syndrome – the individuals with this disorder and their families. Without their active engagement with our research team, these studies would not have been possible.

I gratefully acknowledge my co-authors on these three studies. Without their dedicated time and effort these studies would not have been possible. I am also most grateful to Dr. Davide Martino who served as my joint editor for our recently published volume entitled *Tourette Syndrome* that was published earlier this year (2013) by Oxford University Press. I need to acknowledge as well that portions of the general discussion (pp. 62-77) have been adapted from the opening chapter of this volume that I co-authored with Drs. Michael H. Bloch, Denis G. Sukhodolsky, Lawrence Scahill, and Robert A. King.

Let me thank my mentors and teachers, in particular Donald J. Cohen for his vision and encouragement for the first two decades of my academic career at Yale University.

In addition, I am enormously grateful to my dedicated colleagues in advocacy organizations across the globe, especially those in Brasil, who continue to seek ways to improve the wellbeing of individuals with Tourette syndrome by reducing stigma and by advancing our scientific understanding of this enigmatic disorder.

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Thanks to my family, especially my dear wife Hannah.

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SUMMARY

Leckman JF. *Phenomenology and natural history of Tourette syndrome: brief summary or research* [Thesis]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2014.

The phenomenology of Tourette syndrome is complex. Although overt motor and vocal tics are the defining features of Tourette syndrome, many individuals report experiencing sensory "urges," which are often difficult to describe. The natural history of this condition is also variable, with some individuals experiencing a marked reduction in tics by the end of the second decade of life while others go on to have a lifelong condition. The aim of this thesis was three-fold: (1) to develop a valid and reliable clinical rating instrument; (2) to investigate the sensory phenomena associated with Tourette syndrome; and (3) to document the course of tic severity over the course of the first two decades of life. Each of these three studies involved groups of patients with Tourette syndrome or a chronic tic disorder and each of these studies has been published in a peer-reviewed journal. The Yale Global Tic Severity Scale (YGTSS) has excellent psychometric properties that have been independently replicated. It has also emerged as the most widely used clinician-rated tic severity scale in randomized clinical trials around the world. Sensory phenomena, particularly premonitory urges, are commonly reported among individuals with Tourette syndrome by the age of 10 years. There is considerable overlap with the sensory phenomena described by individuals with Obsessive-Compulsive Disorder. Tics usually have their onset in the first decade of life. They then follow a waxing and waning course and a changing repertoire of tics. As documented in the third study, for a majority of patients the period of worst tic severity usually falls between the ages of 7 and 15 years of age, after which tic severity gradually declines. This falloff in tic symptoms is consistent with available epidemiological data that indicate a much lower prevalence of Tourette syndrome among adults than children. This decline in tic severity has been confirmed in subsequent studies. In summary, incremental progress is being made in our efforts to characterize the phenomenology and natural history of Tourette syndrome. Revisions to the YGTSS should be considered. Significant advances have been made in measuring the premonitory urges associated with Tourette syndrome. The neurobiological underpinnings of the phenomenology and natural history of Tourette syndrome are currently underway in an effort to identify prognostic indicators.

Descriptors: Tourette syndrome/diagnosis; Tourette syndrome/therapy; Tourette syndrome/complications; Tourette syndrome/psychology; Tourette syndrome/physiopathology; Tic disorders/diagnosis; Tic disorders/therapy; Tic disorders/complications; Tic disorders/physiopathology; Natural history of diseases; Age factors.

Key words: Tourette syndrome, Clinical rating instrument, Motor and phonic tics, Sensory phenomena, Natural history, Growth curve analysis

RESUMO

Leckman JF. *Fenomenologia e história natural da síndrome de Tourette: breve resumo da pesquisa* [Tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2014.

A fenomenologia da síndrome de Tourette (ST) é complexa. Apesar de tiques motores e vocais serem as características definidoras da síndrome, muitas pessoas relatam ter urgências premonitórias (fenômenos sensoriais) de difícil descrição. A história natural da ST também é variável, com alguns indivíduos que experimentam uma redução acentuada nos tiques até o final da segunda década de vida, enquanto outros permanecem com sintomas ao longo de toda a vida adulta. Os objetivos principais desta tese são três: (1) desenvolver um instrumento de avaliação clínica com boa validade e confiabilidade para ST; (2) investigar os fenômenos sensoriais (FS) associados a ST; e (3) documentar o curso da gravidade dos tiques durante as duas primeiras décadas de vida. Para atingir esses objetivos incluíram-se grupos de pacientes clinicamente bem caracterizados e de artigos científicos publicados em periódicos internacionais de alto impacto. A Escala de Gravidade Global de tiques de Yale (YGTSS) apresentou excelentes propriedades psicométricas, o que foi replicado em estudos independentes. Também emergiu como a escala de gravidade mais utilizada em ensaios clínicos randomizados para ST em todo o mundo. Os FS, particularmente urgências premonitórias, são comumente relatados entre os indivíduos com ST com a partir da idade de 10 anos. Há uma sobreposição considerável com os FS descritos por indivíduos com Transtorno Obsessivo-Compulsivo (TOC). Os tiques costumam ter seu início na primeira década de vida e, então, seguem um curso flutuante com mudança do seu repertório. Conforme documentado no terceiro estudo, para a maioria dos pacientes, o período de pior gravidade dos tiques ocorre geralmente entre 7 e 15 anos de idade, após o qual a gravidade declina gradualmente. Esta queda dos sintomas de tiques é consistente com os dados epidemiológicos disponíveis que indicam uma prevalência muito menor de ST entre adultos do que crianças. Em resumo, há um esforço para incremento da caracterização fenomenológica e da história natural da ST. Revisões da YGTSS devem ser consideradas. Avanços significativos foram feitos para caracterizar e mensurar os FS associados a ST. Estudos acerca das bases neurobiológicas, da fenomenologia e da história natural da ST estão em andamento no sentido de identificar os indicadores prognósticos.

Descritores: Síndrome de Tourette/diagnóstico; Síndrome de Tourette/terapia; Síndrome de Tourette/complicações; Síndrome de Tourette/psicologia; Síndrome de Tourette/fisiopatologia; Transtornos de tique/diagnóstico; Transtornos de tique/terapia; Transtornos de tique/complicações; Transtornos de tique/fisiopatologia; História natural das doenças; Fatores etários.

Palavras-chave: Síndrome de Tourette; Instrumento de avaliação clínica; Tiques motores e vocais; Fenômenos sensoriais; História natural; Análise de curva de crescimento; Puberdade.

1. INTRODUCTION

When Gilles de la Tourette (1885) first described the syndrome that bears his name, he used the designation *maladie des tics*. So what are tics? Tics are a bewildering collection of abrupt movements and sounds. Often more easily recognized than precisely defined, tics are sudden, rapid, motor movements or sounds that recur for unpredictable durations. Virtually any movement or sound that the human body is capable of making can become a tic. Indeed, we think of tics as simply fragments of normal behavior that appear without any logical reason. Usually, tics can be easily mimicked, and they can be confused with normal movements or sounds. However, they have a “stereotyped” quality, which simply means that the tic looks or sounds more or less the same each time it occurs. Their sudden unexpected nature can excite surprise. If the observer (a parent, teacher, or a peer) does not know better, he or she may think that tics are being done “on purpose” (Lebowitz; Scahill, 2013; Müller-Vahl, 2013; Pruitt; Packer, 2013).

With few exceptions, clinical descriptions from the nineteenth century onward, including those of Georges Gilles de la Tourette, have largely focused on cataloguing and classifying tics as viewed from the outside. Tics are characterized based on their anatomical location, number, frequency, and duration. Another useful descriptor is the intensity or “forcefulness” of the tic, as some tics call attention to themselves simply by virtue of their exaggerated, forceful character. The variation in intensity ranges from behaviors that are not noticeable (a slight shrug or a hushed guttural noise) to strenuous displays (arm thrusts or loud barking) that are frightening and exhausting. Tics can also be described in terms of their “complexity.” Complexity refers to how simple or involved a movement or sound is, ranging from brief, meaningless, abrupt fragments (simple tics) to ones that are longer, more involved, and seemingly more purposive in character (complex tics) (Leckman et al., 2013).

During the first decade of my work on Tourette syndrome, I was frequently reminded of the need to develop a psychometrically sound clinical rating instrument to characterize and rate the severity of motor and vocal tics.

Within the Yale Tic Disorders Specialty Clinic we worked to develop a psychometrically sound rating instrument for use in evaluating clinical severity of individuals with Tourette syndrome. This effort was based on a wealth of clinical knowledge as well as earlier efforts to develop rating instruments for use in clinical studies including the Tourette Syndrome Global Scale (Harcherik et al., 1984).

However, I was dissatisfied with this instrument and in the mid-1980s I decided to develop a new scale. This was the goal of *Study 1: The Yale Global Tic Severity Scale (YGTSS): Initial Testing of a Clinician-Rated Scale of Tic Severity*. We wanted to enroll a large number of subjects and to evaluate key psychometric properties including inter-rater agreement, test-retest reliability, dimensionality, internal consistency as well as convergent and discriminant validity.

After receiving approval from the Human Investigation Committee at the Yale University School of Medicine and after obtaining consents and assents from the participants, the YGTSS was piloted and refined. The YGTSS allows a multidimensional overview of tic characteristics, as well as the level of functional interference. In order to assess and validate the YGTSS in its final form, individual inventories of motor and vocal tics were collected from a clinic-based sample of 105 well-characterized (and consenting/assenting) individuals with Tourette syndrome (aged 5 to 51 years). The scores on the YGTSS are based on a semi-structured interview of symptoms over the past week, where the clinician is asked to record patients' motor and phonic tics. Subsequently, the tic symptoms are rated separately based on their number, frequency, intensity, complexity, and interference from 0 (no tic symptoms) to 5 (severe) (see Appendix 1). The tic severity sub-score consists of the motor tic severity (0 to 25) and phonic tic severity (0 to 25) scores. These ratings are summed with the impairment score, which rates the severity of functional impairment from 0 to 50, to produce the total score (0–100).

A predetermined set of parametric statistical analyses were chosen to evaluate the YGTSS. The determination of the sample size was based on feasibility and not on any specific power calculations. This article was published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 1989.

The origin of tics may be related to a heightened and selective sensitivity to cues from within the body or from the outside world, possibly as a result of reduced ability to suppress irrelevant information in sensory, motor, and cognitive domains. To a variable degree both motor and vocal tics are preceded by sensory phenomena. First described in detail by Bliss (1980), the premonitory sensory urges associated with Tourette syndrome are commonplace in most individuals with this disorder by the age of 10 years.

In the 1980s, while there was an increasing appreciation of the existence of premonitory urges, there were few empirical studies in the scientific literature. This then became the goal of *Study 2: Premonitory Urges in Tourette Syndrome*. In this study we sought in a cross-sectional study to characterize the antecedent sensory phenomena in a large and diverse group of well characterized clinically referred individuals with Tourette syndrome. We hypothesized that some of the factors that influence the patient's awareness of premonitory urges included the patient's age and the anatomical location of their tics.

After receiving approval from the Human Investigation Committee at the Yale University School of Medicine and after obtaining consents and assents from the participants, a sample of 135 well-characterized individuals with Tourette syndrome (aged 8-71 years) were asked to describe and characterize their premonitory urges using a self-report scale. The YGTSS was used to assess current tic severity. Topics of interest included: (1) the prevalence of premonitory urges in a clinic-based sample stratified on the basis of age, gender, tic severity and anatomical location of the urge; (2) the individual's subjective judgment concerning whether or not their tics were either fully or partially a voluntary response to the premonitory urges; and (3) the prevalence of a "momentary and incomplete sense of relief" following the completion of a tic in a clinic-based sample stratified on the basis of age, gender, tic severity and anatomical location of the antecedent premonitory urge. A predetermined set of parametric statistical analyses were chosen to evaluate the descriptive data collected as part of this cross-sectional study. The method of case finding did not provide an accurate population-based estimate of the prevalence of premonitory urges among individuals with Tourette syndrome. The determination of the sample size was

based on feasibility and not on any specific power calculations. This article was published in the *American Journal of Psychiatry* in 1993.

The natural history of Tourette syndrome is variable, but many individuals with this condition often report that their worst-ever tics occur near the end of the first decade (~10 years of age) and that their tics improve by the end of the second decade of life. However as we were actively involved in seeking to understand the pathogenesis of this disorder, it was clear that a deeper understanding of the natural history of this disorder would be useful to us and to the field in general. This then became the goal of *Study 3: Course of Tic Severity in Tourette Syndrome: The First Two Decades.*

After receiving approval from the Human Investigation Committee at the Yale University School of Medicine and after obtaining consents and assents from the participants, we initiated a birth-year (1975) cohort of 42 individuals with Tourette syndrome who were re-contacted an average of 7.3 years after their initial clinical evaluation at the Yale Tic Disorders Specialty Clinic. The decision to focus on individuals born during the same year was based on wanting to gain a clear age-specific perspective. Data concerning the onset and course of tic severity until age 18 years were available on 36 individuals (Leckman et al., 1998). The method of case finding did not provide an accurate population-based characterization of the natural history of Tourette syndrome. The determination of the sample sizes was based on feasibility and, individual growth curve analyses were used to model aspects of the temporal patterning of tic severity. This article was published in *Pediatrics* in 1998.

2. STUDIES

2.1 Study 1: The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity

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ABSTRACT: Despite the overt nature of most motor and phonic tic phenomena, the development of valid and reliable scales to rate tic severity has been an elusive goal. The Yale Global Tic Severity Scale (YGTSS) is a new clinical rating instrument that was designed for use in studies of Tourette syndrome and other tic disorders. The YGTSS provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms. Data from 105 subjects, aged 5 to 51 years, support the construct, convergent, and discriminant validity of the instrument. These results indicate that the YGTSS is a promising instrument for the assessment of tic severity in children, adolescents and adults.

Key Words: clinical rating instrument, motor and phonic tics, Tourette syndrome.

INTRODUCTION

The signs and symptoms of Tourette syndrome can range from infrequent movements and sounds that are barely discernible or easily camouflaged to dramatic and sustained displays of tic behaviors that are disabling and self-injurious. The frequency of tics can vary markedly over the course of a day. Conscious efforts to "suppress" tics can be successful for minutes or even hours

at a time. Followed over the course of weeks, a bewildering succession of symptoms can appear that defy objective quantification. Despite these intrinsic problems, there have been several attempts to develop rating instruments for use in clinical settings that would permit valid and reliable assessments of tic severity across subjects (Leckman et al., 1988).

One approach has been to base the ratings on tic counting procedures using structured videotape protocols of short duration (Tanner et al., 1982; Shapiro; Shapiro, 1984). This procedure can yield highly reliable tic counts. Meaningful changes in clinical state during clinical trials have been documented using these techniques (Shapiro; Shapiro, 1984). Despite their accuracy, these methods are cumbersome, labor intensive, and vulnerable to sampling bias.

A second approach has been to focus on a longer time interval, typically 1 week, and to form a clinical impression of tic severity based on direct examination and historical data obtained from multiple informants. The Shapiro Tourette Syndrome Severity Scale (TSSS), developed by Shapiro and Shapiro (1984), and the Tourette Syndrome Global Scale (TSGS) (Harcherik et al., 1984) are the most widely used of these instruments. Although both the TSSS and the TSGS have been shown to be reliable and to have convergent validity, they both contain idiosyncratic features. The TSSS contains five ordinal scales that vary in their range and weighting and focus primarily on the social disabilities associated with TS. The TSGS is a multidimensional scale that requires the clinician to rate the frequency and disruption of simple and complex motor and phonic tics as well as a set of frequently associated symptoms (behavioral problems, motor restlessness, and school/work impairment). Weaknesses of the TSGS include its composite character and unusual psychometric properties. The ratings of tic "frequency" proved difficult to apply directly to historical information, and the distinction between simple and complex motor tics was problematic in many cases.

This report presents the development and initial testing of a clinician-rated scale of tic severity, the Yale Global Tic Severity Scale (YGTSS), that is derived in

part from the authors' extensive experience with the TSGS in both clinical and research settings.

Description of the YGTSS

As with the TSGS, the YGTSS is designed for the use of experienced clinicians following the completion of a semistructured interview with multiple informants. The semistructured interview was designed to elicit information concerning the specific character and anatomical distribution of tics observed during the course of a I-week interval before the clinical assessment. This information is recorded on a prepared "Tic Inventory" form (see Appendix 1, pp. 89-97). An interval of 1 week was chosen because it covers a sufficient time period to gain a comprehensive view of current tic severity in multiple contexts. In practice, a week is also a sufficiently brief interval so that accurate recall is generally not a problem.

Following the completion of the semistructured interview and using the Tic Inventory as a guide, clinicians are asked to rate the severity of motor and phonic tics along five separate dimensions: number, frequency, intensity, complexity, and interference. Dimensions were selected based on clinical experience in working with tic disorder patients and their families. Conceptually, the dimensions of frequency and complexity were retained from the earlier TSGS. The dimension of "disruption" contained in the TSGS was broken down into separate dimensions of "intensity" (the forcefulness or volume of the tic symptoms) and "interference" (the degree to which planned actions or speech is interrupted or disrupted by the tic symptoms).

Operationally, a six-point ordinal scale was developed for each of the five dimensions with each point on each ordinal scale fully anchored with descriptive statements and relevant examples. In practice these descriptions have been usefully incorporated into the semistructured clinical interview to elicit the desired information. They were also developed to reflect the descriptions that are offered by families. For example, ratings of tic frequency are based on the duration of tic

free intervals rather than the absolute frequency of observed tic behaviors. The same ordinal scales are used to rate motor and phonic tics.

A separate rating of impairment is also included in the YGTSS. This scale focuses on the impact that the tic disorder per se has had on the individual over the previous week, including self-perception and self-esteem, relationships with close family members, social or peer relationships, and ability to perform in an academic or occupational setting. This rating inevitably reflects the cumulative toll that the tic disorder has had on the individual. Operationally, ratings of impairment are based on a six-point ordinal scale constructed with specific anchors for each point.

The YGTSS was piloted over a 8-month period in the Tic Disorders Clinic of the Child Study Center, during which time refinements were made in the descriptive anchor points. Several co-ratings were also performed to gain an initial sense of the reliability of the scale.

Experience has shown that a high degree of interrater reliability can be quickly achieved among clinicians who are experienced in the care and management of tic disorder patients. An instructional manual describing the YGTSS and its administration is available from the authors.

METHOD

Subjects

Subjects were 105 children and adults seen at the Tic Disorder Clinic at the Yale Child Study Center from January l, 1987 to August 31, 1988. Table 1 presents data concerning the age and gender of the subjects. All subjects completed an extensive neuropsychiatric evaluation (Leckman; Cohen, 1988) and were diagnosed with a tic disorder (Tourette syndrome, *N* = 98; other tic disorders, *N* = 7). Fifty-four subjects received a diagnosis of attention deficit hyperactivity disorder (ADHD) and 23 subjects were diagnosed with obsessive compulsive disorder (OCD).

TABLE 1. ***Age and gender distribution of tic disorder subjects***

Age Group (Years)	Male	Female	TOTAL
5-11	30	6	36
12-17	41	5	46
18-51	17	6	23
TOTAL	88	17	105

Raters

A total of four raters (J.F.L., M.A.R., M.T.H., S.I.0.) trained in the use of the YGTSS contributed to this study. Each of these raters has had substantial experience with management of tic disorder patients and their families, ex- tending over a minimum of 4 years. Two are board-certified child psychiatrists and two are masters-level nurses.

Assessments

All subjects seen in the Tic Disorder Clinic for an initial evaluation were asked to complete the Tourette Syndrome Questionnaire (Jagger et al., 1982) and the Tourette's Syndrome Symptom List (Cohen et al., 1985) during the weeks preceding their scheduled appointment. Letters of referral and copies of available medical records were also requested. For subjects under the age of 18 years, parents were asked to complete the Child Behavior Checklist (Achenbach; Edelbrock, 1983), and the Parent Symptom Questionnaire (Conners, 1970). The child's teacher(s) were also asked to complete the Teacher Questionnaire (Conners, 1969). Academic records were also requested.

Following a review of the available information, subjects were interviewed in the company of other informants (typically parents or spouses) and separately concerning their tic disorder symptoms, associated symptoms, other psychopath- ology and their adjustment at home, with peers and in their academic placement or at their job. The Tic Inventory (past week) of the YGTSS was administered during the interview. Additional information concerning each of the YGTSS an- chor points was also obtained as outlined above. If symptoms of depression or

OCD were present, additional self-ratings were obtained. Following the completion of the interview, the YGTSS was completed on the basis of all available information. The TSSS of Shapiro and Shapiro (1984) was also completed as were a series of Clinical Global Impression (CGI) Scales for TS, ADHD, and OCD (Leckman et al., 1988). The Children's Global Assessment Scale (C-GAS) (Shaffer et al., 1983) or the Global Assessment Scale (GAS) (Endicott et al.,1976) was used to summarize the available information concerning the subject's overall social adjustment and psychopathology. If multiple clinicians participated in the evaluation, consensus ratings were obtained for each of the clinician-rated instruments.

RESULTS

Internal Consistency of the YGTSS

The YGTSS was designed to provide a detailed characterization of motor and phonic tics across a range of dimensions. Each item was designed to contribute equally to a composite subscale score for either motor or phonic tics. In order to examine the internal consistency of the two a priori subscale scores, correlations between item, subscale, and global scores were calculated.

Table 2 presents the Pearson *r* correlations between the YGTSS item scores and the pertinent subscale score and with the overall impairment and global scores. Uniformly, item scores were found to be highly correlated with their respective subscale scores. This was true both when the actual subscale score was correlated with the individual item and when a modified subscale score, excluding the appropriate item from the subscale score, was correlated with the individual item (Table 2). As expected, the item scores were less highly cor- related with the overall impairment score than the subscale score indicating the partial independence of these ratings.

TABLE 2. Correlations between YGTSS item scores and subscale and global scores (N = 105)

YGTSS Items	Subscale score A*	Subscale score M*	Impairment	Global Score
Motor tics				
Number	**0.88**	**0.81**	**0.64**	**0.74**
Frequency	**0.83**	**0.71**	**0.56**	**0.64**
Intensity	**0.82**	**0.73**	**0.58**	**0.64**
Complexity	**0.81**	**0.67**	**0.61**	**0.67**
Interference	**0.79**	**0.67**	**0.63**	**0.67**
Total			**0.78**	**0.83**
Vocal tics				
Number	**0.88**	**0.82**	**0.46**	**0.67**
Frequency	**0.88**	**0.77**	**0.49**	**0.66**
Intensity	**0.90**	**0.85**	**0.47**	**0.65**
Complexity	**0.78**	**0.66**	**0.49**	**0.66**
Interference	**0.89**	**0.84**	**0.57**	**0.73**
Total			**0.87**	**0.77**

Note: All Pearson *r* correlations are at the $p < 0.0001$ level. *A = Actual value for motor or phonic subscale; M = modified subscale score (subscale score - item score = modified subscale score).

Because of the overlapping dimensions (number, frequency, intensity, complexity, and interference) contained in the motor and phonic tic subscales of the YGTSS, a factor analysis of the YGTSS item scores was undertaken to determine whether any of these dimensions would emerge as an underlying factor that would explain the variance in the item scores for this sample. Principal component analyses with varimax rotation were performed on the 10 item scores as well as the rating of overall impairment. Only factors with eigen values of greater than one were retained for analysis. Two factors emerged from these analyses that were readily interpreted. These factors accounted for 8% of the total variance in

the item scores. Factor loadings for each item are presented in Table 3. The factors recombined the items of the YGTSS into categories that are identical to the a priori motor and phonic tic subscales. The overlapping dimensions appear to covary within each of the subscales rather than across them. The overall impairment item was divided between the two factors.

TABLE 3. YGTSS item loadings on two rotated factors (N = 105)

YGTSS Items	Factor 1: Motor Tics	Factor 2: Vocal Tics
Motor tics		
Number	**0.80**	0.28
Frequency	**0.81**	0.11
Intensity	**0.82**	0.12
Complexity	**0.71**	0.36
Interference	**0.80**	0.13
Vocal tics		
Number	0.25	**0.85**
Frequency	0.16	**0.86**
Intensity	0.10	**0.92**
Complexity	0.35	**0.72**
Interference	0.25	**0.86**
Overall Impairment	0.71	0.43

Reliability of the YGTSS

A subset of 20 evaluation interviews was corated by three of the raters (J.F.L., M.A.R., M.T.H.) to assess interrater agreement with the YGTSS. Table 4 presents the intraclass correlation coefficients (ICC) for each of the 11 items on the YGTSS as well as each of the subscale and global scores. The ICC model described by Shrout and Fleiss (1979), which assumes that the three raters represent a random sample of all possible raters, was used for these analyses. In

general, the ICC values indicate good to excellent agreement between raters for the YGTSS. All ICC values were significant ($p < 0.001$). Ratings of motor tic "intensity," however, only achieved a modest level of interrater agreement.

TABLE 4. Summary of interrater agreement with the yale global tic severity scale

YGTSS Items	ICC*
Motor tics	
Number	**0.62**
Frequency	**0.99**
Intensity	**0.52**
Complexity	**0.79**
Interference	**0.62**
Total	**0.78**
Vocal tics	
Number	**0.67**
Frequency	**0.74**
Intensity	**0.71**
Complexity	**0.82**
Interference	**0.74**
Total	**0.91**
Total Tic Scores	
Number	**0.71**
Frequency	**0.75**
Intensity	**0.66**
Complexity	**0.83**
Interference	**0.70**
Total	**0.84**
Overall impairment rating	**0.80**
YGTSS Total Score	**0.85**

*Intraclass Correlation Coefficient (Shrout and Fleiss, 1979) for three raters and 20 subjects. All ICC values were significant ($p < 0.0001$).

Convergent Validity of the YGTSS

In order to test the convergent or criterion validity of the YGTSS, the subscale scores and the global scores were compared with other study assessments that were expected to provide measures of the same or similar dimensions of tic behavior. Table 5 provides a summary of the other clinician rated assessment instruments used in the study. These ratings indicate that the subjects spanned the entire range of tic severity and that the average subject had a "moderate" to "marked" level of severity based on the TS-CGI.

TABLE 5. Summary of clinical assessments

Instrument	N	Mean +/- SD	Range
YGTSS			
Motor tics	105	13.8 ± 4.4	0-23
Vocal tics	105	8.1 ± 5.7	0-21
Total tic score	105	21.9 ± 8.7	0-42
Impairment	105	22.9 ± 10.2	0-45
YGTSS Total Score	105	44.8 ± 17.7	4-87
TSGS			
Motor tics	91	8.3 ± 4.0	0-20
Vocal tics	91	4.2 ± 3.9	0-16
Total tic score	91	12.5 ± 6.7	0-32
Global severity	91	30.8 ± 13.5	2-63
Shapiro TS Severity Scale	64	3.2 ± 1.2	0-6
TS-CGI	90	3.8 ± 0.9	1-6
ADHD CGI	74	3.0 ± 0.9	1-6
OCD CGI	83	2.1 ± 1.4	1-6
GAS	84	63.2 ± 14.8	31-95

Comparing convergent assessments, the YGTSS subscales were found to correlate extremely well with the comparable TSGS scores: YGTSS motor vs. TSGS motor, r = 0.86 (p = 0.0001);YGTSS phonic vs. TSGS phonic, r = 0.91 (p < 0.0001); and YGTSS total tic vs. TSGS total tic, r = 0.90 (p < 0.0001) (Table 6). As expected, the correlation was somewhat lower when comparing the global severity of the two scales because of the additional items on the TSGS that rate nontic behaviors. Good agreement was also observed between the YGTSS and the Shapiro TSSS and the TS-CGI. The close agreement between the YGTSS and the TS-CGI is evident from an examination of Figura 1A, where the YGTSS mean global severity score has been computed for each level of the TS- CGI.

TABLE 6. Comparison of YGTSS scores with convergent clinical rating instruments

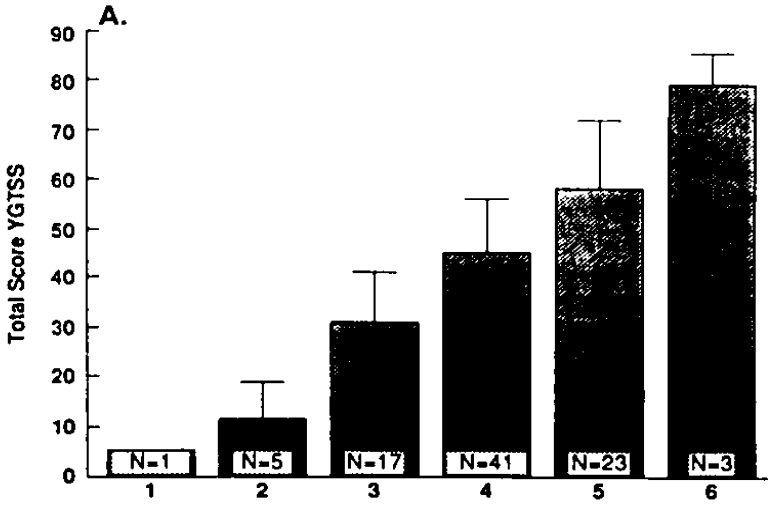
Instrument	**YGTSS**				
TSGS	**Motor**	**Vocal**	**Total Tic**	**Impairment**	**Global**
Motor	0.86	0.48	0.74	0.69	0.76
Vocal	0.46	0.91	0.81	0.51	0.69
Total	0.77	0.81	0.90	0.70	0.85
Global severity	0.54	0.50	0.59	0.59	0.63
Shapiro TSSS	0.76	0.54	0.71	0.67	0.74
TS-CGI	0.81	0.65	0.80	0.74	0.82

Note: Pearson rs for each comparison were significant at the p < 0.0001 level.

Discriminant Validity of the YGTSS Subscale and Total Scores

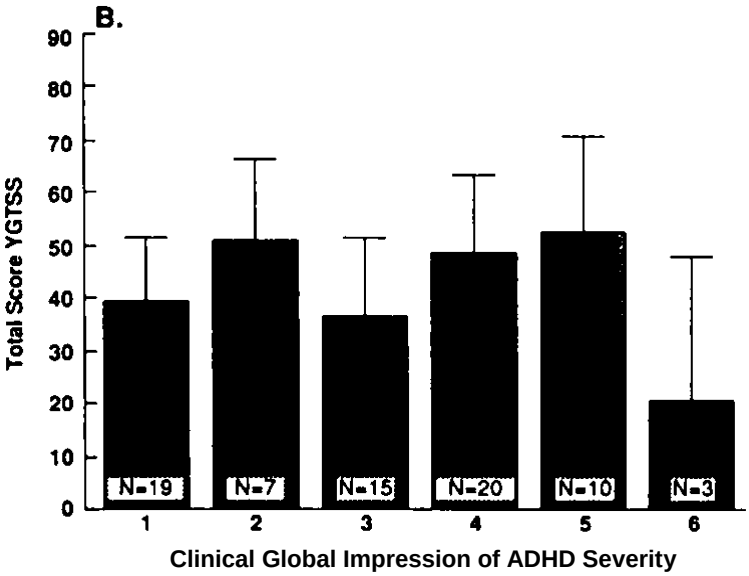
In order to test the discriminant validity of the YGTSS, scores on this instrument were compared with ratings from instruments designed to measure other dimensions of behavior including the severity of ADHD symptoms (ADHD-CGI), the severity of OCD symptoms (OCD-CGI), and the subject's global adjustment. Table 7 presents these data. Complete divergence was observed in the rating of ADHD symptoms in these tic disorder patients (Figure 1B). A modest association between ratings of tic and OCD severity was observed (Figure 1C). As

expected, some colinearity of the GAS ratings was also evident, suggesting that the YGTSS impairment score accounts for as much as 18% of the variance of the GAS score.



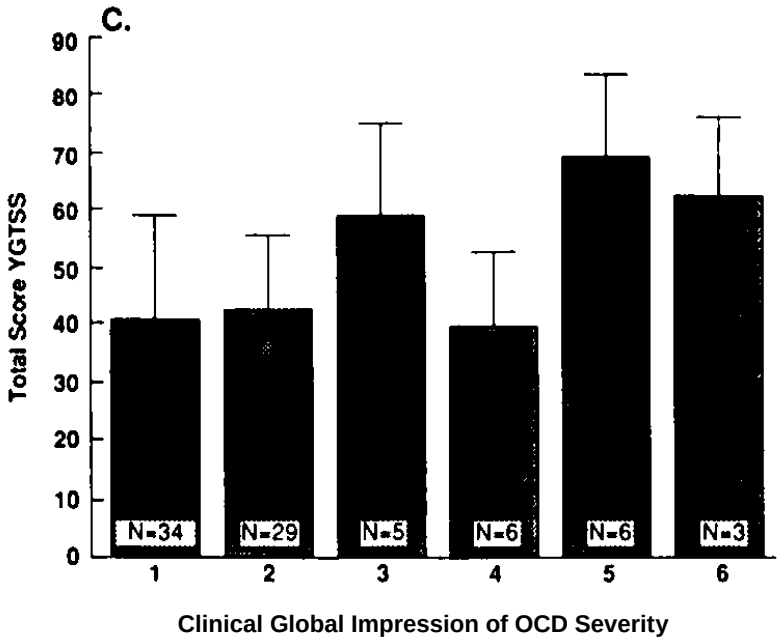
YGTSS vs. Tourette's syndrome CGI, $r = 0.82$, $p < 0.0001$

Figure 1A. Mean total score on the Yale Global Tic Severity Scale (YGTSS) for each point on Clinical Global Impression (CGI) Scale



YGTSS vs. Attention Deficit Hyperactivity Disorder CGI, r = 0.11, N.S

Figure 1B. Total YGTSS vs. clinical global impression of ADHD severity



YGTSS vs. Obsessive-Compulsive Disorder CGI, $r = 0.39$, $p < 0.00$ I .

Figure 1C. Total YGTSS vs. Clinical Global Impression of OCD Severity

TABLE 7. Comparison of YGTSS scores with divergent clinical rating instruments

Instrument	YGTSS				
	Motor	**Vocal**	**Total Tic**	**Impairment**	**Global**
ADHD-CGI	0.08	-0.03	0.01	0.18	0.11
OCD-CGI	0.30**	0.33**	0.36***	0.37***	0.39***
GAS/C-GAS	-0.30**	-0.17	-0.25*	-0.43***	-0.36**

Note: Pearson *r.* * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

DISCUSSION

Validity

The high correlations between the YGTSS items and the subscale scores for motor and phonic tics and the results of the factor analyses that confirmed the a priori structure of subscales both support the construct validity of the instrument. These preliminary data support the use of the motor and phonic subscale scores as well as the total tic score, the rating of overall impairment, and the composite

global severity score. Apart from their inherent descriptive value and their contribution to the subscale scores, the value of the separate ratings for each of the elements (number, frequency, intensity, complexity, and interference) has not been firmly established in this study. Potentially, these ratings may be worthwhile in biological studies. Some dimensions or elements, such as frequency or intensity, may be more physiologically meaningful than other dimensions, such as interference.

Comparisons with the TSGS and other clinical rating instruments support the convergent and discriminant validity of the YGTSS. The lack of association with measures of the severity of ADHD is particularly important given the frequent co-occurrence of these conditions within clinical populations (Comings; Comings, 1987). The modest association with measures of OCD is intriguing and may reflect the etiological connection between Tourette syndrome and some forms of OCD (Pauls; Leckman, 1986).

Reliability

The high ICCs (0.80 to 0.91) for the motor and phonic tic subscale scores, the total tic score, the overall impairment, and the global severity score indicate that these measures can be made with a high degree of accuracy by experienced clinicians working in a busy clinical setting. Some caution is warranted in the use of some of the individual item scores, particularly the rating of the intensity of motor tics, given its modest ICC value.

Comparison with Other Ratings of Tic Severity

The YGTSS is a second generation instrument, based in large on the conceptual framework part of the TSGS. Despite the close agreement between the two scales (Table 6), the YGTSS has much to recommend it in comparison to the TSGS. These features include: greater clarity and ease of administration (the placement of each tic behavior into either "simple" and "complex" tic category is not required by the YGTSS), as well as improved psychometric properties (so that addition rather than multiplication is used to compute the subscale scores).

Another advantage of the YGTSS is its relatively narrow scope. It measures only tic behaviors and their impact rather than attempting to assess a broader range of maladaptive behaviors, such as overall behavioral adjustment, motor restlessness, and academic/vocational performance (all of which were included in the TSGS).

Compared with other available clinical rating instruments, such as the Shapiro TSSS, the YGTSS provides separate ratings for the severity of motor and phonic tic behaviors, which may be an advantage in some settings. The YGTSS also appears to be slightly more reliable as the published ICCs for the Shapiro TSSS total score are in the range of 0.53 to 0.85 (Shapiro et al., 1988). These advantages, however, may be offset by the amount of time required to collect the necessary information (the YGTSS typically requires 15 to 20 minutes to complete compared to 5 to 10 minutes for the Shapiro TSSS).

Clinical Applications of the YGTSS

Based on experience in an active specialty clinic, the authors anticipate that clinicians who are involved in the monitoring and treatment of individuals with tic disorders will find this instrument to be a useful adjunct to their practice. It is a straightforward rating scale and is easy to use and directly elicits information on a variety of clinically relevant topics that would ordinarily be a part of a clinician's systematic review of an individual's status vis a vis Tourette syndrome or another tic disorder. The authors also found that the repeated use of just the impairment subscale provides a good index of an individual patient's long-term course. Alternatively, the TS-CGI, referred to above, is another instrument that could be used to record the clinician's global impression of the individual's progress.

Limitations and Directions for Future Work

Additional work is required to develop and refine the YGTSS. Structurally it may be important to review the anchor points used for the individual items of the YGTSS, as relatively few of the ordinal scales make full use of their potential range. For example, two-thirds of all of the ratings of the frequency of motor tics were 4 or 5, indicating that the tic free intervals of more than an hour were unusual. It

should also be noted, however, that the motor and phonic tic subscale scores are normally distributed, as are the overall impairment rating and the global severity score.

Age and gender-related variations in the distribution of the YGTSS scores may be valuable, as they may provide clinicians with a clearer picture of how an individual subject's symptoms compare with age- and gender-matched samples. Ideally, such studies would focus on nonreferred samples of tic disorder cases so that the effects of referral bias would be eliminated. The large-scale studies of multigenerational families may be one source of nonreferred subjects.

Additional work is needed to document that the YGTSS is a useful instrument to measure change in the course of either clinical trials or studies of the natural history of tic disorders. Such a demonstration should also include comparisons with other instruments and rating techniques in order to assess their relative merits.

The development of valid and reliable clinical rating instruments for specific disorders is prerequisite to scientific progress. For conditions where the underlying pathophysiology is not well understood and informative laboratory studies are not available, clinical rating instruments provide one of the few yardsticks available to make informed estimates of the severity of a condition over time. Preliminary data presented in this report indicate that the YGTSS is a valid and reliable instrument for use with tic disorder patients and their families.

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2.2 Study 2: Premonitory Urges in Tourette Syndrome

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ABSTRACT: Objective. Tourette syndrome traditionally has been viewed as a hyperkinetic movement disorder characterized by involuntary motor and phonic tics. Many patients, however, describe their tics as a voluntary response to premonitory urges. This cross-sectional study evaluated premonitory urges and related phenomena in subjects with tic disorders. **Method.** A total of 135 subjects with tic disorders, aged 8 to 71 years, completed a questionnaire concerning their current and past tic symptoms. Subjects were asked to describe and, if possible, localize their premonitory urges. The Yale Global Tic Severity Scale was used to assess current tic severity. The method of case finding does not provide prevalence data for premonitory urges. **Results.** Ninety-three percent of the subjects reported premonitory urges. Anatomical regions with the greatest density of urges were the palms, shoulders, midline abdomen, and throat. Eighty-four percent of the subjects reported that tics were associated with a feeling of relief. A substantial majority (92%) also indicated that their tics were either fully or partially a voluntary response to the premonitory urges. **Conclusions.** While epidemiological studies of tic disorders have yet to incorporate questions concerning premonitory urges, these results suggest that such urges may be commonplace in adolescent and adult subjects with tic disorders. These results challenge the conventional wisdom that tic behaviors are wholly involunary in character. They also implicate brain regions involved in the processing of sensorimotor information in the pathobiology of tic disorders.

Keywords. Tourette syndrome, premonitory urges, sensory phenomena

INTRODUCTION

Tourette syndrome has been viewed traditionally as a hyperkinetic movement disorder characterized by involuntary motor and phonic tics (Albin et al., 1989). In 1980, Bliss (1980) described his personal experience of the sensory phenomena that precede, accompany, and follow tics and challenged the

conventional wisdom that tics are involuntary in character. Subsequently, Shapiro et al. (1988) introduced the term "sensory tics" to describe some of these phenomena and reported that sensory tics alone or in combination with motor or phonic tics were present in 8.5% of a large series of Tourette syndrome patients. More recently, larger case series have been reported that have focused on either the nature of the sensory phenomena or their voluntary or involuntary character (Kurlan et al., 1989; Lang, 1991). These reports suggest that premonitory sensory urges are frequently encountered in referral samples (Kurlan et al., 1989) and that most individuals do not experience tics as wholly involuntary (Lang, 1991). This paper adds to the growing literature by presenting data from 135 subjects with tic disorder who provided extensive data concerning premonitory urges and related mental phenomena.

METHOD

On the basis of numerous interviews with patients and a review of the available literature, a questionnaire (available on request from the first author) was developed to gather information on the onset, frequency, anatomical location, and character of premonitory sensory and related mental phenomena in tic disorder patients. Subjects responded to such questions as whether they had ever had or currently had premonitory tic sensations, whether these sensations were more mental or more physical in nature, the age at which they first became aware of these sensations, where the sensations were felt on the body, whether they helped to suppress tics, and whether they were affected by medications or certain life situations.

Subjects were instructed to rate the frequency of premonitory urges for eight common motor and phonic tics. Full-page body figures (front and back) were included in the questionnaire so that subjects could mark precisely the location of their premonitory urges. The location of premonitory urges was marked with an x, and the x was circled if relief was felt after the tic. In order to aid in the analysis, the body figures were sub- divided into 87 separate surface regions, front and back, right and left, in accordance with the vernacular descriptions of body parts,

e.g., right palm, left shoulder blade, and anterior right knee (Figure 1). The right side was clearly delineated from the left by a series of midline regions running from the top of the head to the groin. In each of the 87 regions, the circled and uncircled x's were tallied, providing a density for each anatomical region.

Subjects were asked about their perception of their tics. Specificall they were asked whether their tics occurred without any warning and whether they considered the tics to be involuntary, voluntary, or a mixture of both. In addition, subjects were asked to complete the self-report versions of the Yale Global Tic Severity Scale (Leckman et al., 1989) and the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989a;b). On the basis of our pilot data, adolescent and adult patients required 30 to 60 minutes to complete the questionnaire. Prepubertal subjects with parental assistance required somewhat less time.

Once the development of the instrument was complete, 36 questionnaires were distributed to patients at a tic disorder clinic of a university child study center. As in the pilot phase, the questionnaires were subsequently reviewed by clinicians familiar with the patient's case history and medical records for completeness, clarity, and accuracy. If questions arose during the review, the patients were contacted by telephone to obtain clarification and additional information.

With the approval of the Medical Committee of the Tourette Syndrome Association, 327 questionnaires were then mailed to tic disorder subjects in Connecticut, Rhode Island, Massachusetts, New York, New Jersey, Pennsylvania, and Illinois. Subjects were encouraged to contact the center if they encountered any difficulty in completing the questionnaire. A total of 99 questionnaires were returned from this distribution. All questionnaires were reviewed for completeness. Approximately 20% of the subjects who responded by mail were given follow-up telephone calls in order to clarify ambiguous responses or to complete unanswered questions.

No differences were observed between the clinic and nonclinic groups with regard to gender, current age, age at onset of tics, or current severity of either tics (Yale Global Tic Severity Scale) or obsessive-compulsive symptoms (Yale-Brown Obsessive Compulsive Scale) (Table 1). Subsequently, the data from the both

groups were combined to yield a total group of 135 individuals. The age range of the group was 8-71 years.

Statistical comparisons were carried out with Student's t test, Mann-Whitney U test, chi-square analysis, and analysis of variance when appropriate. Class variables included group (clinic versus nonclinic) and gender. Severity of tics (based on the Yale Global Tic Severity Scale score), severity of obsessive-compulsive symptoms (based on the Yale-Brown Obsessive Compulsive Scale), and current age were entered in analyses as continuous variables.

Table 1: Demographic and clinical characteristics of tic disorder subjects

Item	Clinic Subjects (N = 36)	Non-clinic Subjects (N = 99)	Total (N = 135)
Sex			
Men	25	80	105
Women	11	19	30
Age (years)[a]			
Mean ± SD	29.5 ± 9.7	31.6 ± 15.7	31.0 ± 14.3
Range	13-51	8-71	8-71
Age at tic onset (years)[b]			
Mean ± SD	7.3 ± 3.3	6.9 ± 2.6	7.0 ± 2.8
Range	3-16	2-15	2-16
YGTSS, total tic score[c]			
Mean ± SD	27.2 ± 8.1	25.0 ± 8.5	25.6 ± 8.4
Range	8-49	0-47	0-49
Yale-Brown Obsessive Compulsive scale score[d]			
Mean ± SD	12.7 ± 8.5	10.4± 7.1	10.0 ± 7.4
Range	0-30	0-27	0-30

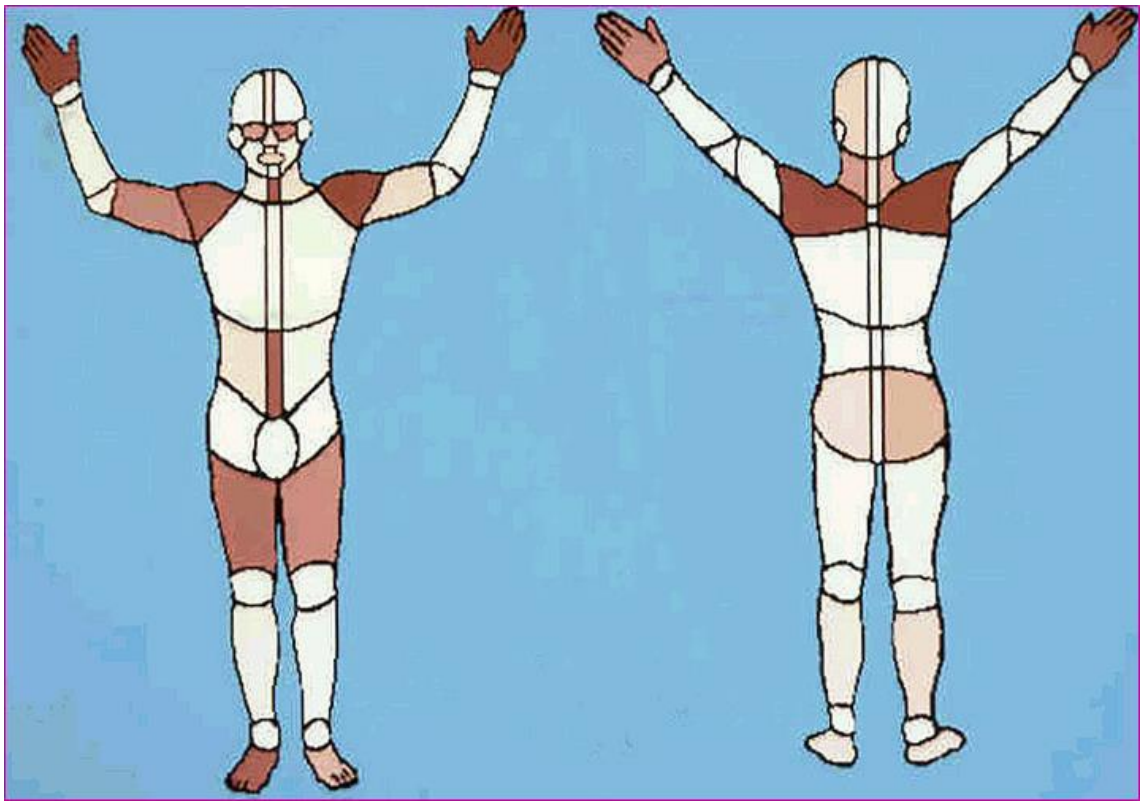
[a]N=98 for nonclinic subjects and 134 for total; [b]N=96 for nonclinic subjects and 132 for total; [c]Sum of motor and phonic tic scores (6). N=90 for nonclinic subjects and 126 for total; and [d]N=33 for clinic subjects, 81 for nonclinic subjects, and 114 for total.

RESULTS

Ninety-three percent of 132 respondents (N=123) identified having a sensation (mental or physical awareness) ("an urge," "a feeling," "an impulse," "a need") to experience a tic during the past week, and 95% of 129 subjects (N= 123) reported ever having had them. Males were more likely to report premonitory urges than females (97%, N=103, versus 83%, N=29; x2=5.0, df= l, p<0.05). The mean age at which respondents first became aware of the premonitory urges was 10.0 years (SD=6.2), which averaged 3.1 years (SD=5.7) after the onset of the tics.

Selected narrative descriptions of the premonitory tic phenomena are presented in Appendix 2. When asked if the sensation or urge was more mental or physical in nature, 109 respondents (89%) said that it was either partly or wholly a physical experience.

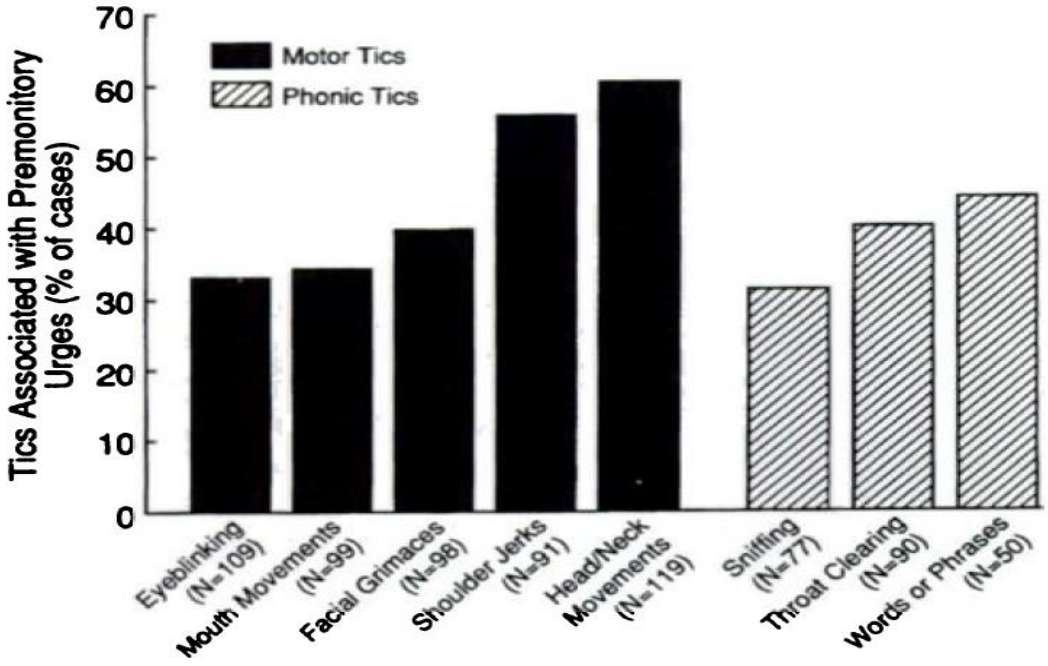
Head, neck, and shoulder tics were reported as being most frequently preceded by premonitory urges (Figure 1). A significant gender difference was found in the frequency of sensations or urges before tics of throat clearing; 67% (N=18) of the female subjects with throat clearing tics had premonitory phenomena, compared with 33% (N=72) of the male subjects (X2=6.67,df=1, p=0.01). According to the body figure data (N= 101), the mean number of anatomically distinct urges experienced during the previous week was 8.7 (S0=9.4, range= 6). The anatomical regions with the highest density of premonitory urges were, in descending order, left palm, right shoulder blade, right palm, left shoulder, left shoulder blade, midline abdomen, throat, right shoulder, back of right hand, front of right thigh, front of right foot, back of left hand, inside of right upper arm/front of left thigh/left eye (last three items equal or in descending order), right eye (Figure 1).



[a]The densities of each anatomical region for the 101 respondents who completed the body figures were tallied, providing total densities for region per person; and the midpoint, 0.20 urges per region per person.

FIGURE 1. Density of current premonitory urges in 101 subjects[a]

Thirty-nine subjects indicated that their urges were completely bilaterally symmetrical in location. Another 29 subjects indicated that half or more of their urges occurred in a bilaterally symmetrical pattern, and four subjects reported some (less than 50%) bilateral symmetry. Of the remaining 29 respondents with asymmetrical patterns, 19 (66%) were entirely unilateral; nine experienced urges only on the right side, and 10 had urges exclusively on the left side.



[a]Subjects indicated whether they almost always, frequently, occasionally, or never experienced a premonitory urge before these commonly occurring tics. Percentages are based on the combined "almost always" and "frequently" responses divided by the total number of subjects reporting those tics.

FIGURE 2. Frequency of premonitory urges before common motor and phonic Tics in 135 subjects with Tic disorders[a]

Most of these urges were judged to be felt in muscle. Forty percent of the respondents reported that the feeling was exclusively felt in the muscle, while another 24% felt it to be located in both muscle and joints. Just 8% felt it exclusively in their joints, and only 3% felt the sensation in their skin.

A total of 121 (92%) of 132 subjects reported that they experienced their tics to be partly or wholly voluntary. This finding was not affected by the severity of tic symptoms. Interestingly, 50% of the female subjects felt that their tics were completely voluntary, compared to only 28% of the male subjects (X^2=5.60, df=l, p< 0.05). When asked if there were certain tics that always occurred without warning, 57 (48%) of 122 respondents reported none.

Medications and certain life situations affect the quality and frequency of pre-tic sensations and urges. According to 63 of 101 respondents, the sensations and urges were altered by medications. Many of these individuals mentioned that

neuroleptics reduced the frequency and intensity of the premonitory urges. Moreover, 92 (77%) of 120 respondents noted that apart from medications, other situations or circumstances also affected their pre-tic urges and sensations; stress and anxiety increased the urge to tic, while relaxation and concentration decreased the urge.

The awareness of the premonitory urges can facilitate tic suppression, according to some of the respondents. Specifically, 24 individuals indicated that this awareness helped them to suppress their tics. The severity of tic symptoms was not a factor in this analysis.

Apart from the few gender differences noted earlier, univariate analyses using current age, tic severity, obsessive-compulsive symptom severity, and clinic versus non- clinic status did not yield statistically significant findings.

DISCUSSION

This cross-sectional survey of 135 subjects with tic disorder confirms Bliss's original observations (Bliss, 1980) that premonitory urges are commonplace among adolescents and adults with tic disorders and that subjects with tic disorders frequently experience their movements as being a voluntary response to these unwanted urges. These findings are consistent with those reported by Kurlan et al. (1989), who found in a telephone survey that 74% of 35 patients with Tourette syndrome reported having a sensation or feeling before tics. The data in the report by Lang (1991), in which only 7% of 60 tic disorder patients experienced all tics as being involuntary, are virtually identical to the 8% figure found in our data. However, given the case finding procedures used in each of these studies, the age-specific prevalence of premonitory urges among tic disorder patients remains to be determined.

The premonitory urges are important clinical phenomena that frequently cause distress in their own right. Indeed, several of the patients in the present study spontaneously reported that the experience of these urges was more troublesome than their tic behaviors. In addition to being a source of constant

distraction, the quasi-volitional nature of the urges was psychologically burdensome to some patients (Cohen, 1991).

The reported lag of 3 years, on average, between the onset of tics and the initial awareness of premonitory urges is also intriguing. Does this reflect a maturational shift in the cognitive processing of sensory information so that these subtle and elusive phenomena can enter the individual's conscious awareness, or is the interval between tic onset and these cognitive/somatosensory phenomena more a function of the location and type of tics involved? The latter possibility is consistent with data concerning the mean age at onset for tics involving those anatomical regions most closely associated with premonitory urges. For example, Shapiro et al. (1988) reported that the mean age at onset for tics involving the hands, shoulders, and abdomen is 11.4, 10.1, and 13.7 years, respectively, whereas the mean age at onset for motor tics in general is 6.7 years. These data also underscore that not all tics are associated with premonitory urges. For example, one patient was largely oblivious to a frequent eye blinking tic but was severely troubled by a shoulder jerk that he experienced as being prompted by a premonitory urge localized in a particular spot over his left scapula.

The frequent coupling of premonitory urges with tic behaviors is heuristically interesting in part because it resembles the coupling of obsessional thoughts or premonitory urges associated with the performance of compulsions or rituals by patients with obsessive-compulsive disorder. The extent to which these phenomena are governed by similar neurobiological mechanisms is un- known. Given the evidence for a common genetic vulnerability underlying both Tourette syndrome and some forms of obsessive-compulsive disorder (Pauls; Leckman, 1986), it may be reasonable to speculate that the repetitive coupling of mental/sensory information and fragmentary behaviors reflects a deeper commonality of these disorders.

The basal ganglia and related cortical and thalamic structures have been implicated in the pathobiology of Tourette syndrome and obsessive-compulsive disorder (Chappell et al., 1990) and may likely play a critical role in the occurrence of premonitory urges. Functionally, the basal ganglia are composed of pathways

that contribute to the multiple parallel cortico-striato-thalamocortical circuits that concurrently subserve a wide variety of sensorimotor, motor, oculomotor, cognitive, and "limbic" processes (Alexander et al., 1986; Goldman-Rakic; Selmon, 1990). It has been hypothesized that Tourette syndrome and etiologically related forms of obsessive-compulsive disorder are associated with a failure to inhibit subsets of the cortico-striato-thalamo cortical minicircuits (Leckman et al., 1991). Specifically, the processing of somatotopically organized sensory information in parallel with adjacent circuits that process information associated with both the planning and performance of motor behaviors may provide the neuroanatomic basis for the premonitory urges of Tourette syndrome and other tic disorders (Jones et al., 1977; Leckman et al., 1992). Although the neurobiological defect that underlies Tourette syndrome and etiologically related conditions remains unknown, a more complete understanding of these disorders will likely illuminate mechanisms that regulate the activity of the multiple parallel cortico-striato-thalamocortical circuits that subserve much of the normal cognitive, behavioral, and emotive repertoire.

Future studies of patients with chronic tic disorder should include measures of the frequency, intensity, and interference associated with premonitory urges. It may also be important to explore the relationship between these sensorimotor phenomena and the perceptually driven need of some individuals with obsessive-compulsive disorder for things to look, feel, or sound "just right."

This cross-sectional survey of 135 subjects with tic disorder confirms Bliss's original observations (Bliss, 1980) that premonitory urges are commonplace among adolescents and adults with tic disorders and that subjects with tic disorders frequently experience their movements as being a voluntary response to these unwanted urges.

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2.3 Study 3: Course of Tic Severity in Tourette Syndrome: The First Two Decades

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ABSTRACT: Objective. Prevalence studies indicate a 10-fold higher rate of Tourette syndrome among children compared with adults. The purpose of this investigation was to examine the course of tic severity during the first 2 decades of life. **Method.** A birth-year cohort of 42 Tourette syndrome patients followed at the Yale Child Study Center was recontacted an average of 7.3 years after their initial clinical evaluation. Data concerning the onset and course of tic severity until 18 years of age were available on 36 Tourette syndrome patients. A variety of statistical techniques were used to model aspects of the temporal patterning of tic severity. **Results.** Mean (SD) tic onset at 5.6 (2.3) years of age was followed by a progressive pattern of tic worsening. On average, the most severe period of tic severity occurred at 10.0 (2.4) years of age. In eight cases (22%), the frequency and forcefulness of the tics reached such a severe level during the worst-ever period that functioning in school was impossible or in serious jeopardy. In almost every case this period was followed by a steady decline in tic severity. By 18 years of age nearly half of the cohort was virtually tic-free. The onset of puberty was not associated with either the timing or severity of tics. **Conclusions.** A majority of patients displayed a consistent time course of tic severity. This consistency can be accurately modeled mathematically and may reflect normal neurobiological processes. Determination of the model parameters that describe each patient's course of tic severity may be of prognostic value and assist in the identification of factors that differentially influence the course of tic severity.

Key Words: Tourette syndrome, natural history, growth curve analysis, puberty

Abbreviations: TS = Tourette syndrome; YCSC = Yale Child Study Center Tic Disorders Clinic; ADHD = attention deficit-hyperactivity disorder; OCD = obsessive-compulsive disorder; CGI = Clinical Global Impression (scale); SES = socioeconomic status; YGTSS = Yale Global Tic Severity Scale; ARRTS = annual rating of relative tic severity; STOBS-R = Schedule for Tourette and Other Behavioral Syndromes, Adult-on-Child Version, Revised; MSRPF = Modified Schedule for Risk and Protective Factors

INTRODUCTION

Epidemiologic studies have indicated a higher prevalence rate of Tourette syndrome (TS) among children compared with adults. In children, prevalence rates as high as 50 per 10,000 have been reported (Comings et al., 1990; Nomoto; Machiyama, 1990). Studies of adolescents and young adults have reported lower rates in the range 0.5 to 4.3 per 10,000 (Apter et al., 1993; Burd et al., 1986a; Robertson et al., 1994). In the one study that ascertained rates for both children and adults, using identical methods, a 10-fold difference was observed (Burd et al., 1986a;b). The reasons underlying this change in prevalence are not well-understood but likely reflect age-related variations in the natural history of the disorder that directly affect case ascertainment (Erenberg et al., 1987; Goetz, et al., 1992).

By early adulthood, follow-up studies have consistently reported improvement in tic severity for a majority of Tourette syndrome patients (Bruun, 1988; Sandor et al., 1990; Torup, 1962). Although a rough time course of tic severity has emerged, age-specific estimates of tic severity have not been reported. Typically, natural history studies of Tourette syndrome have included patients across a broad age range with widely varying follow-up intervals (Kim; Leckman, in press). This cross-sectional, observational approach combined with the failure of most studies to identify key time points in the course of tic severity has made cross-patient comparisons difficult.

Gender and stress-related hormonal factors have been implicated in the pathogenesis of Tourette syndrome(Chappell et al., 1994, 1996; Leckman et al., 1995; Peterson et al., 1992). Although speculation has focused on the role of gonadal androgens during the earliest stages of central nervous system (CNS) development in utero, (Leckman; Peterson, 1993; Peterson et al., 1992) anecdotal case reports and evidence from clinical trials with antiandrogens support the view that alterations in the hormonal milieu during adolescence and adulthood can modulate tic severity (Leckman; Scahill, 1990; Peterson et al., 1994, 1998).

The present study was undertaken to document the time course of tic severity during the first 2 decades of life using data from a single birth-year cohort of Tourette syndrome patients. A birth cohort was selected to maximize our ability to make developmentally uniform cross-patient comparisons. In our analytic approach, we used a variety of statistical procedures to model these data to estimate the age of tic onset, the age when the tics were at their worst, as well as other model parameters. This model was then used to evaluate the a priori hypothesis that pubertal onset is associated with either the timing or degree of worst-ever tic severity.

METHOD

Subjects

Subjects in this study consisted of 36 patients with Tourette syndrome who had been diagnosed and evaluated at the Yale Child Study Center (YCSC) Tic Disorders Clinic. Subjects were selected on the basis of their participation in a case-control study of Tourette syndrome in which extensive data were collected concerning the time course of tic severity. This study identified all Tourette syndrome patients born in 1975 who had ever been evaluated at this YCSC clinic. All patients were initially diagnosed with the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed (DSM-III) or 3rd ed, revised criteria for Tourette syndrome using previously described methods (Leckman et al., 1988). A total of 42 Tourette syndrome cases were ascertained. Of this number, 36 cases (86%) had sufficient information to be included in these analyses (32 males and 4 females).

Procedures and Measures

Demographic and clinical information was collected from four sources: the clinic chart, a preliminary telephone interview with a parent, two in-person interviews with a parent, and an in-person interview of the Tourette syndrome patient.

Chart Review

A clinician with extensive experience with Tourette syndrome families (K.L.) abstracted information from the clinical record using a precoded form. Data recorded included demographic information; diagnostic status with regard to TS, attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and other comorbid conditions; and age of onset and severity at presentation of TS, ADHD, and OCD. Severity ratings were made using eight point ordinal Clinical Global Impression (CGI) scales previously developed at the YCSC for each of these disorders (Leckman et al., 1988). Relevant points on the TS-CGI scale include: mild severity, where the tic symptoms are judged not to interfere and not to be noticeable to most people; moderate severity, where the tics cause some problems in some areas of functioning (self-esteem, home life, peer relations, and/or school performance) and are noticeable to some people outside the family some of the time; marked severity, where the tic symptoms cause clear problems in more than one area of functioning and are frequent and quite noticeable in most situations most of the time; and severe, where the tic symptoms because of their frequency and forcefulness cause significant impairment in one or more area, so that functioning in usual settings is impossible or in serious jeopardy.

One clinic chart could not be located, but the case was clearly identified in the clinic roster permitting the case to be recontacted. In 10 randomly selected cases, another member of the research team (J.F.L.) independently reviewed the same record. Comparisons of age at evaluation, diagnostic status, age of onset, and scores on the respective CGI scales revealed a high level of agreement (Pearson correlations for age of tic onset and age at evaluation were $r = 0.98$ and $r = 0.83$, respectively). The interrater agreement for a diagnosis of Tourette syndrome was perfect, and the κ statistic values for the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV) diagnoses of OCD and ADHD were excellent (0.83 and 0.77, respectively). The Spearman rank order correlations for the CGI scores were also excellent (ranging from $\rho = 0.79$ to $\rho = 1.00$). A comparison of data abstracted from the initial clinic evaluations of the 36 cases included in this analysis and the 6 remaining cases revealed no statistically

significant differences with regard to age at evaluation, sex, socioeconomic status (SES), age of tic onset, or tic severity at initial evaluation.

Initial Follow-up Interview

After an initial letter describing the study and requesting consent, parents were contacted by telephone and inquiries were made concerning current demographic information; the history of the family's contact with the YCSC Tic Disorders Clinic; data concerning their child's tic disorder (age of onset, age when tics were at their most severe, medication history, and a rating of current tic severity using the Yale Global Tic Severity Scale [YGTSS] (Leckman et al., 1989); comparable data concerning ADHD and OCD; and data concerning the onset and duration of puberty). The YGTSS is a standard clinical rating instrument for Tourette syndrome with excellent interrater agreement and other favorable psychometric properties including a high correlation with the TS-CGI scale (Leckman et al., 1989). A slightly modified and expanded form of the YGTSS was used in the telephone interview portion of the study (Leckman et al., 1994). This version has previously been shown to have a high level of agreement with YGTSS ratings independently made by experienced clinicians (Leckman et al., 1994). At the conclusion of the interview, families were invited to participate in a more in-depth in-person interview to take place in the family's home. Interviewers were blinded to the information abstracted from the chart record.

Parent Interviews

After signed informed consent, parents participated in four semistructured in-person interviews. In the first interview, parents again reported on the course of their child's tic disorder (ratings of current and worst-ever tic severity using the YGTSS, annual rating of relative tic severity [ARRTS] using a 6-point ordinal scale [absent, least severe, mild, moderate, severe, and most severe] from which age of tic onset, and age of most severe tic symptoms were transcribed, and a current

medication history). During the second interview, parents reported on comorbid conditions using a semistructured interview, the Schedule for Tourette and Other Behavioral Syndromes, Adult-on-Child Version, Revised (STOBS-R) that has been extensively used in family-genetic studies (Pauls et al., 1991, 1993). The STOBS-R also contains information concerning the onset of puberty. The third interview focused on putative risk factors, a main focus of the formal case control study, and used the Modified Schedule for Risk and Protective Factors (MSRPF) developed by John T. Walkup, J.F.L., and B.S.P. (Leckman et al., 1990). In the final interview, parents were asked about their own tic histories as well as other psychopathology using the STOBS-R, child version. Because of the requirements of the case control study, different interviewers conducted the MSRPF and remained blind to the information concerning tic severity. The results of the case-control aspects of this study will be reported elsewhere.

Patient Interview

The Tourette syndrome patient was interviewed in-person using the STOBS-R. This information was supplemented by current and worst-ever ratings of tic severity based on the YGTSS.

Best Estimate Diagnoses

All available diagnostic information on Tourette syndrome patients and their parents were blindly and independently evaluated by two investigators (J.F.L. and B.S.P.). The resulting DSM-IV diagnostic ratings were compared and discrepancies were resolved using a previously described consensus procedure (Leckman et al., 1982).

Data Analysis

Data analysis was conducted in several stages. An initial aim was to describe the sample and compare ratings across the three time points (clinical evaluation, initial follow-up interview, and in-person interviews with parents and patients). The test-retest reliability of key ratings of tic onset, timing of worst-ever tic severity, current and worst-ever tic severity (using the YGTSS) were then evaluated in an effort to validate the ARRTS.

Examination of the time course of the tic severity curves derived from the ARRTS ratings for individual Tourette syndrome patients led to the development of a mathematical model of tic severity characterized by the identification of an initial point of tic onset, followed by a period of increasing tic severity, followed by an inflection point (corresponding to the period of worst-ever tic severity), after which the tic severity steadily declined. A statistical bootstrapping technique was then used to assess the variability of the estimates for each model parameter (Efron, 1979).

Once this model was established, the hypothesis that the course of tic severity is related to the timing of puberty onset was evaluated by including the main effect of the age of puberty onset and its interaction terms in the model. This computation was carried out in SAS using PROC MIXED (SAS, Cary, NC).

RESULTS

On average, the 36 members of the YCSC 1975 birth cohort were evaluated at age 11.0 years (range: 5.9-16.9; SD: 2.9). The initial telephone follow-up interview occurred when the Tourette syndrome patients were, on average, 17.7 years of age (range: 17-20; SD: 0.7); and the in-person interviews with the parents and the Tourette syndrome patients took place when the patients were, on average, 18.4 years of age (range: 17-20; SD: 1.0). The average interval between the initial YCSC evaluation and the in-person interviews was 7.5 years (range: 1.2-12.1; SD: 2.7). All 36 patients met DSM-IV criteria for Tourette disorder. Of this number, 25 (69%) met lifetime DSM-IV criteria for ADHD (combined type–16

(44%), inattentive type–8 (22%), and hyperactive/impulsive type – 1 (3%)). Another 13 (36%) cases met lifetime DSM-IV criteria for OCD. Most the families were middle-class. The mean SES status of the families was 47.9 (range: 27-64; SD: 10.6).

Current Tic Status

At the time of the in-person interviews, when the Tourette syndrome patients were 18 years of age, tic symptoms for a majority of the 36 cases were minimal or absent. On average, the total tic score of the YGTSS assessed at the time of the in-person interviews with the parents and patients was 7.92 (actual range: 0-30 [possible range: 0–50]; SD: 9.53). Seventeen patients (47.2%) were entirely tic-free during the week before the in-person interviews. Another 4 patients (11.1%) had minimal tic symptoms (YGTSS total tic score of <10). Ten patients (27.7%) had mild symptoms (YGTSS total tic score of ≥10 but <20), and only 4 patients (11.1%) were judged to have a moderate or marked level of tic severity (YGTSS total tic score of ≥20 but <40).

Severity and Timing of Tics During the Worst Period

On average, the worst-ever total tic score on the YGTSS estimated at the time of the in-person interview was 29.8 (range: 4-49; SD: 10.9). Based on the frequency and forcefulness of their tics, 8 patients (22.2%) were judged during their worst period to have severe tics (YGTSS total tic scores ≥40 but <50) that were associated with a significant impairment in their primary social role such that functioning in usual settings was impossible or placed in serious jeopardy. Ten patients (27.8%) were judged during their worst period to have marked tic severity (tics frequent and quite noticeable in most situations most of the time; YGTSS total tic scores ≥30 but <40). Fourteen patients (38.9%) were judged during their worst period to have moderate tic severity (tics cause some problems and are noticeable to some people some of the time; YGTSS total tic scores ≥20 but <30). Only 4 patients (4.0%) were judged to have a mild level of tic severity during their worst period (YGTSS total tic score of <20).

Based on data collected during the initial telephone follow-up and the in-person interviews, the worst tics occurred between the ages of 6 and 15 years (mean: 10.0; SD: 2.4). Figure 1 presents a histogram of these data by year.

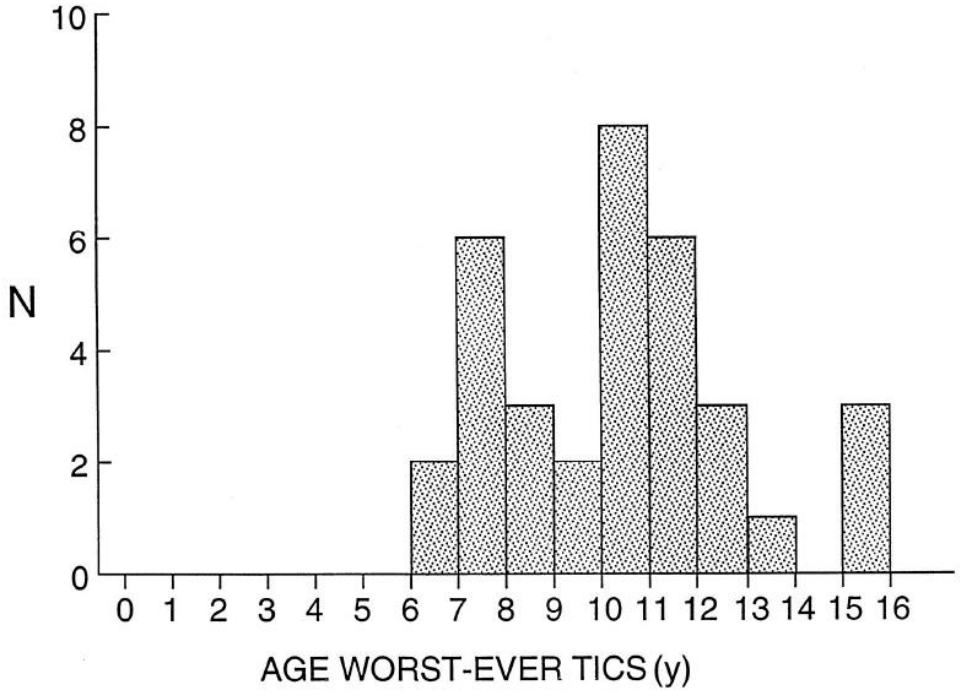

Figure 1. Age distribution of when tic symptoms were at their worst

This histogram presents the age at worst-ever tics as reported by parents during in-person interview.

The level of tic severity during the worst period was positively associated with the patient's age during the worst-ever period (Figure 2: Pearson $r = 0.58$, N = 34, $p < .0001$).

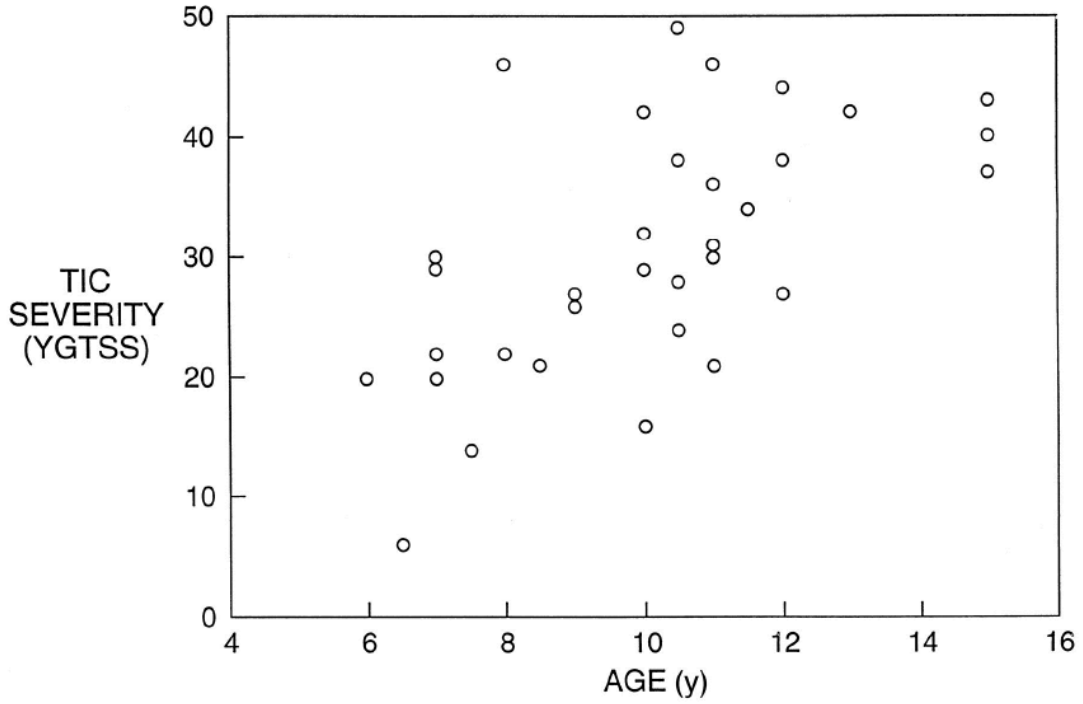

Figure 2. Association of age and level of worst-ever tic severity

This scattergram plots worst-ever tic severity versus age at worst-ever tic severity and suggests a positive association between these variables (Pearson *r*: 0.58, *N* = 34, *p*<.0001).

Predictive Value of Earlier Estimates of Tic Severity

Nine cases were judged to have mild tics during their initial clinic evaluation. Among this group, 3 cases continued to have only mild symptoms during their worst period. In each of these cases, no tics were evident at the time of the in-person interviews. In another 4 of the initially mild cases, their worst-ever tic severity was rated as moderate, and at the time of the in-person interviews tics were either absent (*N* = 2), minimal (*N* = 1), or mild (*N* = 1). Surprisingly, 2 cases judged to have mild tic severity at their YCSC evaluation were judged to have severe tic severity during their worst period, but fortunately in both cases at the

time of the in-person interviews, their tic symptoms were either mild (*N* = 1) or moderate (*N* = 1) in severity.

Sixteen cases were judged to have moderate tic severity at the time of their initial YCSC evaluation. Among this group, 7 cases were judged to have either moderate (*N* = 6) or mild (*N* = 1) tic severity at the time of their worst symptoms. At the time of the in-person interviews, 5 of these cases were tic-free, 1 case had mild symptoms, and only 1 case continued with a moderate level of tic severity.

Of the 9 initially moderate cases remaining, 6 were judged to have marked tic severity during their worst period and 3 were judged to have severe tics. In this subgroup at the time of the in-person interviews, 1 case showed no tic symptoms, 3 had minimal symptoms, 4 had mild, and only 1 case continued with a moderate level of tic severity.

Ten cases presented at the time of their initial YCSC evaluation with a marked level of tics. Seven of these cases were judged to have either moderate (*N* = 3) or marked (*N* = 4) tic severity at the time of their worst symptoms. In this subgroup, three cases were tic-free at the time of the in-person interviews, three cases were rated as having mild tic severity, and in only 1 case did the tic severity remain at a marked level. The three remaining cases with marked severity at the time of their initial evaluation all had severe tic symptoms during their worst period. Remarkably, two of these cases showed no tic symptoms during their in-person interviews, and the remaining case had a mild level of tic severity at follow-up.

Tic severity at initial YCSC evaluation was not related to worst or current tic severity (worst: $F = 2.66$, $df = 2$, *NS*; current: $F = 0.05$, $df = 2$, *NS*). However, current tic severity was significantly correlated with both tic severity at the time of the initial telephone follow-up interview (Pearson $r = 0.66$, $p < .0001$) and with worst tic severity (Pearson $r = 0.37$, N = 36, $p < .03$).

Time Course of Tic Severity Ratings

A majority of Tourette syndrome patients displayed a consistent time course of tic severity. This consistency can be accurately modeled mathematically and may reflect normal biological processes that occur during the course of brain development. Using the ARRTS data collected at the time of the in-person interviews, individual growth curves of tic severity were generated. Figure 3 presents the mean and SDs of these curves.

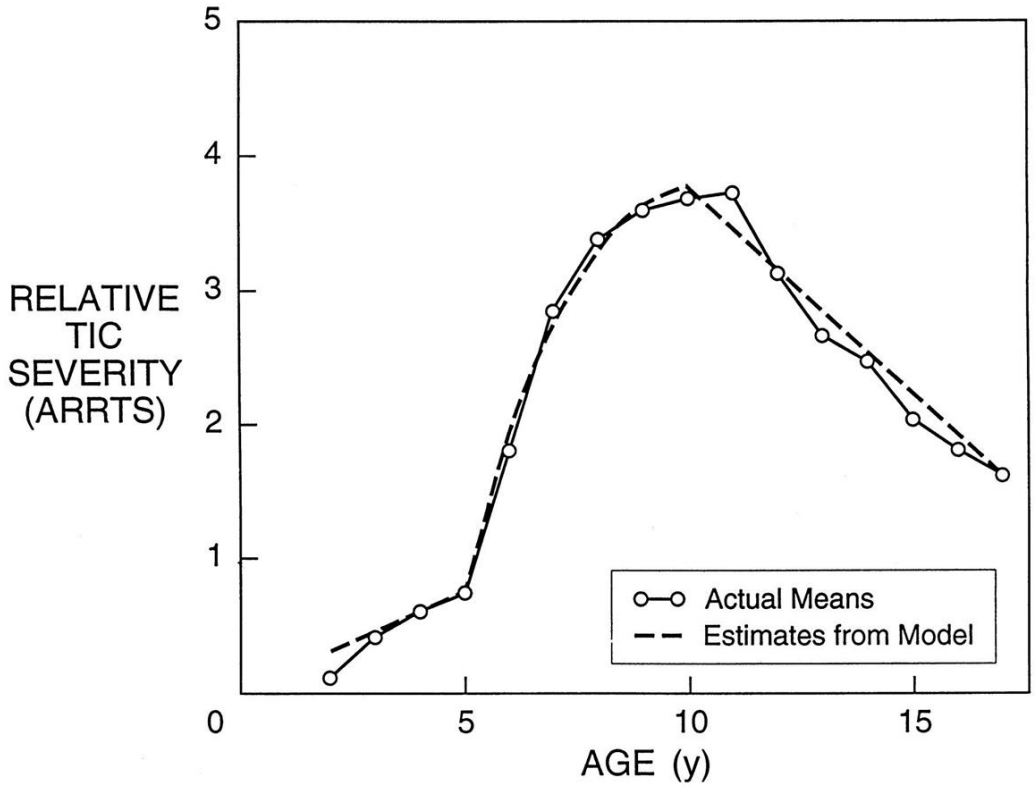

Figure 3. Plot of mean tic severity, ages 2 to 18 years**.** The solid line connecting the small circles plots the means of the annual rating of relative tic severity scores (ARRTS) recorded by the parents. The dashed line was generated using the modeling equations (Table 1) and the mean values for each of the coefficients and intercepts as determined by a statistical bootstrapping technique. Two inflection points are evident that correspond to the age of tic onset and the age at worst-ever tic severity, respectively

In an effort to validate key points along this composite curve, test-retest comparisons were made between the age of onset estimates made at the time of the initial YCSC evaluation, at the initial telephone follow-up interview, and the onset point derived from the ARRTS curves. The mean values for each of these estimates showed a high level of agreement (mean [SD] age of tic onset: estimated

from the chart review: 5.8 years (1.7); from the initial telephone follow-up interview: 5.8 years (2.8); and from the ARRTS curves: 6.0 (2.7)). The test-retest reliability of these estimates was reasonably good (ARRTS estimate vs initial telephone follow-up: Pearson r = 0.67, N = 31, P < .0001; and ARRTS estimate vs chart review data: Pearson r = 0. 58,N = 32, P < .0001). Fewer estimates were available to judge the test-retest reliability of the age of worst tic symptoms. The mean values for each of these estimates showed a good level of agreement (mean [SD] age of worst tic severity estimated from the initial telephone follow-up interview: 10.0 years (2.4); and from the ARRTS curves: 10.8 (3.1)). However, the test-retest reliability of these estimates, was only fair (ARRTS estimate vs initial telephone follow-up: Pearson r = 0.48, N = 31, P < .007).

Descriptively in 2 of the Tourette syndrome cases, the ARRTS curves had 2 points of maximal severity (relative tic severity = 5) separated by a period of 1 year or longer when the symptoms were not as severe. In both cases, rather than taking a mean value of these 2 points (and by doing so identifying a point in time when their tics were not as bad as either of the worst-ever points) a convention was established so that a worst-ever time point was selected on the basis of which period was of the longer duration. In another 5 cases, parents identified relative maximums in tic severity (relative tic severity <5) indicating a fluctuating course.

Mathematical Model of the Time Course of Tic Severity

Given the consistent time course of tic severity across patients, we formulated a mathematical model to describe precisely this pattern. This process is akin to comparing a patient's growth curve for height or weight to a composite curve for a larger number of patients. Based on an examination of the individual and composite ARRTS plots, the ARRTS data were partitioned into three segments. Let t denote age in years. The tic time course, $f(t)$ is characterized by:

$$f(t) = \begin{cases} \alpha t & \text{if } t \leq \tau_1 \\ \beta_0 + \beta_1 t + \beta_2 t^2 & \text{if } \tau_1 < t \leq \tau_2 \\ \gamma_0 + \gamma_1 t & \text{if } t > \tau_2 \end{cases} \qquad (1)$$

Equation 1 where τ_1 refers to the age-at-onset and τ_2 is closely related, but not necessarily equal, to the age at which their tics were at their worst. Table1 displays the parameter distributions of the tic time course function obtained from the bootstrap procedure (Efron, 1979). A plot of this function is included in Figure 3. Individual growth curves were also generated. Mean values for each of the parameters obtained from individual curves were in close agreement with estimates obtained by bootstrap methods.

Table 1. Parameters for the Time Course of Tic Severity Function

Parameters	**Mean (SD)**
Age at onset (τ_1)	4.8 (0.50)
Age when tics were at their worst (τ_2)	9.9 (0.85)
Onset slope (α)	0.15 (0.05)
Intercept for quadratic function (β_0)	-11.9 (8.6)
Ascending slope (β_1)	3.5 (2.4)
Ascending quadratic coefficient (β_2)	-0.19 (0.16)
Intercept for linear decline (γ_0)	6.5 (1.1)
Slope for linear decline (γ_1)	0.29 (0.07)

Timing of the Onset of Puberty and the Course of Tic Severity

The present study was undertaken, in part, to evaluate the a priori hypothesis that pubertal onset is associated with the period of worst-ever tic severity. This hypothesis was not supported in this group of patients. Age at pubertal onset was not associated with the age when the tics were at their worst (r = 0.02, *NS*) or degree of worst-ever tic severity (r = 0.08, *NS*). Similarly, when the timing of puberty onset was included in the time course model (Figure 3), neither its main effect nor its interactions with any of the other parameters were significant.

In an effort to validate the age of pubertal onset, test-retest comparisons were made between the age of pubertal onset estimates made at the time of the initial telephone follow-up interview and during the in-person parental interview. The mean values for each of these estimates showed a high level of agreement (mean [SD] age of puberty onset: estimated from the initial telephone follow-up interview: 13.0 years (1.3); and the direct parental interview: 13.7 (1.7)). The test-retest reliability of these estimates was also reasonably good (direct parental interview estimate vs initial telephone follow-up: Pearson r = 0.67, N = 31, $P < .0001$).

DISCUSSION

The natural history of Tourette syndrome and other chronic tic disorders is not well-understood. In this report we present an explicit model of the time course of tic severity over the first 2 decades of life. This model extends the findings of previous follow-up studies by offering age-specific tic severity estimates and by defining a period of maximal tic severity that usually occurs between the ages of 8 and 12 (Bruun, 1988; Erenberg et al., 1987; Goetz et al., 1992; Sandor et al., 1990; Torup, 1962). If confirmed, this pattern of ascending severity followed by a near linear decline may also clarify the differences in Tourette syndrome prevalence that are found when adult versus child populations are studied using similar methods (Burd et al., 1986a; Burd et al., 186b). By early adulthood, tic severity may have declined sufficiently that a Tourette syndrome diagnosis may no longer be warranted.

Before discussing the clinical implications of this study and its potential value, we should take note of its limitations. Recall bias may have influenced the parents' and the patients' reporting. Our use of test-retest procedures to determine the reliability of key informants and the use of blind interviews of multiple informants (parents versus patients) support the accuracy of our findings. The documented decline in the YGTSS ratings from the initial telephone follow-up to the time of the in-person interviews directly supports the validity of the ARRTS

ratings. Likewise, the consistency of the parental reports (in only 3 cases was there an inconsistency between the level of tic severity observed at evaluation and the family's estimate of tic severity during the worst period) lends support to validity of the time course of tic severity that emerges from this report.

A limitation concerning the mathematical modeling approach is that in a small number of cases (*N* = 2) more than one worst-ever time point was reported. In 5 other cases, relative maximums in tic severity were reported. Rather than seeing these as exceptional cases, it is probably better to consider the unimodal distributions of relative tic severity (seen in all the remaining cases) as being composed of multiple relative maximums in tic severity that are undetectable at this level of temporal scaling. This view is supported by the well-known waxing and waning pattern of tics that occur over weeks to months. This discussion raises the potentially important point that the temporal occurrence of tics may be determined by nonlinear dynamical processes (Peterson; Leckman, 1998). One of the characteristic features of these nonlinear, chaotic, systems is that they are fractal in nature that regardless of the temporal scaling (seconds, hours, weeks, months, years) a similar bursting intermittency is evident (Selz; Mandell, 1992). The tics occur in bouts, the bouts of tics occur in larger superbouts, and so forth. Viewed from this perspective, the unimodal tic severity curves seen in this study may be a reflection of the same processes that underlie both the occurrence of tics in bouts (temporal scaling at the level of seconds and milliseconds) and their waxing and waning pattern (temporal scaling at the level of weeks to months).

The processes that underlie tic onset and the usual time course of tic severity are largely unknown. Hormonal and neurochemical factors active early in CNS development have been the subject of speculation (Peterson et al., 1992; Leckman; Peterson, 1993; Leckman et al., 1997). For example, exposure of the developing CNS to gonadal steroids has been implicated (Leckman; Peterson, 1993; Leckman; Scahill, 1993; Peterson et al., 1994). Although indirect evidence from this study may argue against increasing levels of gonadal androgens during male pubescence as a major risk factor for tic exacerbation, the complexity of hormonally mediated events in the brain surrounding adrenarche and puberty urge

caution (Lephart, 1996) The consistency of the pattern observed across patients strongly suggests the presence of an underlying process. It is intriguing to speculate that this time course may reflect neurobiological events that normally occur during the course of brain development and that are overtly expressed only because of the patient's Tourette syndrome vulnerability.

Caution is warranted in the interpretation of the data concerning puberty onset because these data were not ascertained directly by physical examination or Tanner staging. If confirmed in subsequent studies, the data presented in this report may influence clinical practice. In our experience, families find comfort in the realization that tic severity will likely decline through adolescence. Such knowledge is likely to help families and pediatricians live with the tics and to delay the decision to begin psychotropic medications. Ages 8 through 12 are likely to be critical. If medications can be avoided through this period, the patient may have a good chance of never needing them. Although anti-tic medications are available, none are ideal. Over the longer term, starting medications may do more harm than good, given their potential adverse effects and the difficulties associated with medication withdrawal. This is particularly true of the standard neuroleptic agents such as haloperidol and pimozide (Chappell et al., 1997).

As discussed by Goetz et al. (1992), it is important to be mindful that tic severity early on is not necessarily a good predictor of later tic severity. For example, 20% of the mild cases at clinic evaluation, went on to have severe tics. More importantly, 90% of the patients with marked tic severity at evaluation had mild or no tics by 18 years of age. The finding of an association between age of the patient when their tics were at their worst and the level of tic severity during that same period may have limited predictive value except when older adolescents present with severe tic symptoms-heralding a relatively poor prognosis.

The results of this study only extend to the end of the second decade. A minority of Tourette syndrome patients go on to have catastrophic outcomes in adulthood. Whether any of the parameters examined in this study have predictive value for the early identification of these individuals awaits further investigation.

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3. DISCUSSION

3.1 Study 1: The Yale Global Tic Severity Scale (YGTSS): Initial Testing of a Clinician-Rated Scale of Tic Severity

The complex waxing and waning phenotype of Tourette syndrome presents a unique challenge to measurement. Several psychometrically validated clinician- and self-rated measures have been developed over the past three decades. At present, the YGTSS is the most widely used instrument in clinical trials (Leckman et al., 1989; Cavanna; Pansaon Piedad, 2013; Jeon et al., 2013). Subsequent studies performed by independent research groups have confirmed reliability and validity of the YGTSS and its sensitivity to changes in symptom tic severity (Walkup et al., 1992; Storch et al., 2005, 2007). However, despite the widespread use of the YGTSS, it is far from perfect.

The limitations of the YGTSS include: (1) separate ratings of motor and vocal tics; (2) the wording of some of the anchor points for scoring of some of the ordinal severity ratings; and (3) the lack of any specific ratings of the sensory phenomena associated with Tourette syndrome. Although the separation of rating the duration and severity of motor and phonic tics is particularly useful for diagnostic purposes, reliance on separate and equally weighted severity ratings for motor and vocal tics can be problematic. Often investigators use the Total Tic Severity subscale score (0-50) of the YGTSS to assess the efficacy of a given experimental intervention (see Appendix). The Total Tic Severity subscale score is the sum of the Motor Tic Severity subscale score (0-25) and the Vocal Tic Severity subscale score (0-25). The problem arises when motor or vocal tics disappear completely for the entire week preceding the clinical evaluation and there can be a sudden decline in the Total Tic Severity subscale score despite the fact that the individual's overall tic severity might remain reasonably high. The separate Impairment rating (0-50) addresses this issue in part as it asks the expert rater to consider the overall impact of all of the individual's symptoms in making

the rating. However, this is not ideal because in assessing the clinical impact the expert rater is also asked to consider the degree to which the individual's tics are associated with "problems in self-esteem, family life, social acceptance, or school or job functioning". Although this rating reflects the individual's degree of impairment over the previous week, the severity of an individual's tics are just one element of this overall picture. For example, if a child is repeatedly disciplined by his teacher for his intermittent tics in the class room that child's impairment rating will be considerably higher than a child with the same tic repertoire and severity in the classroom where the teacher is more knowledgeable and accepting of the child's symptoms.

A more fundamental question concerns whether or not focusing separately on motor and vocal tics makes sense. Phenomenological studies and those employing hierarchical cluster analyses, principal-component factor analyses, and latent class analysis, have all documented multiple factors/classes (Robertson; Eapen, 2013). These studies add to the growing body of evidence that Tourette syndrome is not a unitary condition and that it might be useful to disaggregate the syndrome into more homogeneous symptom components. In these studies typically the tic symptoms separate along dimensions of simple versus complex tics. More recently, Kircanski et al. (2010) reported the results of an investigation of tic symptom clusters using a sample of 99 youth diagnosed with a primary tic disorder (Tourette syndrome or chronic tic disorder) across two university-based outpatient clinics. Their cluster analysis of the inventory of more than 40 tics included in the YGTSS identified four symptom clusters: predominantly complex tics; simple head/face tics; simple body tics; and simple vocal/facial tics. Similar to the results of the study by Mathews et al. (2007), these clusters were shown to be differentially associated with demographic and clinical characteristics. For example, their Cluster 1, comprising predominantly complex tics, was large and diverse and included motor and vocal tics that were generally characterized by movements or vocalizations of relative intricacy and/or duration. These results may suggest that the multiple complex tics and several simple tics within this cluster tend to co-occur. Of note, their Cluster 1 scores were also positively associated

with a number of concurrent diagnoses and demonstrated a trend toward a positive association with duration of illness. The continued study of symptom dimensions in tic disorders is needed. Prospective within-person longitudinal analyses will be particularly valuable and may lead to the identification of tic clusters differentially associated with long-term outcomes. These findings might also suggest that the next generation of rating scales should rate these components separately. This possibility has recently been explored by McGuire et al. (2013) using all available data from the two randomized clinical trials to assess the efficacy of the Comprehensive Behavioral Intervention for Tics (CBIT) in children and adults (Piacentini et al., 2010; Wilhelm et al., 2012). Four tic clusters were identified: Impulse Control and Complex Phonic Tics; Complex Motor Tics; Simple Head Motor/Vocal Tics; and Primarily Simple Motor Tics. The tic clusters had small associations with clinical characteristics and showed no associations to the presence of coexisting psychiatric conditions nor did they predict treatment response to CBIT or tic severity reductions. Tic symptoms distinctly cluster with little difference across youth and adults, or coexisting conditions. The change in these symptom dimensions observed in the course of these studies was not robustly associated with other measures of clinical improvement. These findings may caution against efforts to develop novel ratings scales based on these tic clusters.

The wording of some of the YGTSS anchor points for scoring of some of the ordinal severity ratings has also been criticized. The scale when it was initially developed was envisioned as being potentially useful for epidemiological studies. As a consequence, the lowest rating of “1” on the Frequency ordinal scale (i.e., **RARELY** *Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon (*Appendix 1) may not be particularly useful.

The third limitation of the YGTSS is that it does not address the sensory phenomena associated with Tourette syndrome. However, some years later, Woods et al. (2005) developed the Premonitory Urge for Tics Scale (PUTS) that has now become widely used alongside the YGTSS in evaluating novel

interventions using randomized controlled clinical trials (Piacentini et al., 2010). This brings us to the second study presented as part of this dissertation.

3.2 Study 2: Premonitory Urges in Tourette Syndrome

Although overt tics are the defining feature of Tourette syndrome, many individuals report experiencing "urges," which are usually difficult to describe. Most frequently, individuals with Tourette syndrome will refer to unpleasant somatic phenomena that build up prior to the tic (or upon attempts to resist ticcing) and are momentarily alleviated by performance of the tic (see above; Leckman et al., 1993). In some instances, individuals report that these premonitory urges are more bothersome than the tics themselves (Kane, 1994). The initial research on this topic stemmed primarily from detailed anecdotal accounts provided by individuals with Tourette syndrome. Bliss (1980) described sensory signals that preceded his tics along with "a very rapidly escalating desire to satisfy the sensations with movements intended to free oneself from the insistent feeling" (p. 37). Kane (1994) echoed this description and added, "these sensations are not mere precursors to tics … they precipitate tics more than providing a signal of imminence, the pre-tic sensation acts as the aversive stimulus toward which tics are directed" (p. 806). Some individuals perceive these urges and other sensory phenomena as being the "core" of Tourette syndrome (Hollenbeck, 2001). Although these urges are often difficult to describe in words, some precocious young children spontaneously assign names to specific urges (e.g., "tight feelings," "cramps," "my `cocky' feeling") that reflects their presence in the child's internal subjective world. Other individuals with Tourette syndrome describe their urges as a type of discomfort or a feeling of pressure or tingling localized in the muscles involved in the performance of the tics. As with tics, the occurrences of urges vary in their frequency, intensity, and duration. The intensity of the urge can vary from fleeting and easily ignored to irresistible and inevitably leading to a tic (Woods et al., 2005).

The first of two formal investigations of the premonitory urge phenomena, we conducted a cross-sectional study with 28 individuals (aged 9-60 years) with

Tourette syndrome (Cohen; Leckman, 1992). Twenty-two (82%) of the 28 subjects experienced premonitory urges prior to motor and vocal tics. Of these 22, 13 (57%) found the premonitory urges more bothersome than the tics themselves, and 12 (55%) thought the premonitory urges enhanced their ability to suppress tics. The second study of 135 individuals with Tourette syndrome (aged 8-71 years) is presented in its entirety (Leckman et al., 1993). A substantial majority (92%) of the individuals indicated that their tics were either fully or partially a voluntary response to their premonitory urges. Consistent with Joseph Bliss' account of his tics, 84% of these subjects also reported that tics were associated with a momentary feeling of relief.

In addition, we found that premonitory urges often are focal in character and limited to a specific anatomical location. Figure 1 presents a body map depicting the bodily location and density of the premonitory urges. Tics involving the head, neck, shoulders, or the midline abdomen were most frequently preceded by urges, whereas simple tics such as eye blinking and mouth movements were less likely to be preceded by urges. More rarely, the urges were exclusively on the right side (5%) or the left side (5%). For others, these urges are more generalized and are best captured by a sense of inner tension. These sensory urges have also been described as sensory tics (Kurlan et al., 1989; Chee; Sachev, 1997). Many individuals reported having both focal and more generalized antecedent urges and sensations.

Developmentally, these individuals reported that they first became aware of their premonitory urges at an average of 3.1 years after tic onset, suggesting that premonitory urges may be absent during early stages of the disorder and emerge only at a later point in time. This suggests tics may begin as nonfunctional responses that, with the development of premonitory urges, become strengthened and maintained by automatic negative (the urges themselves) and positive (the momentary relief) reinforcement (Evers; van de Wetering, 1994; Woods et al., 2005). Alternatively, it is possible that younger children with tics (7- to 8-year-olds) may be less able to recognize and describe the experience sensation of premonitory urge. This suggestion is supported by clinical observations during the

Habit Reversal Training (HRT) for tics with younger children. When asked to suppress or “hold their tics in” during the awareness training portion of HRT, many children are indeed able to report sensory discomfort that builds up during tic suppression.

Subsequent investigations have largely confirmed these initial observations. Kwak et al. (2003) administered a questionnaire to 50 individuals (mean age 24 years) with Tourette syndrome and found that 92% reported the presence of premonitory urges. Sixty-eight percent of these subjects also reported that their urges disappeared with the performance of the tic. Banaschewski et al. (2003) administered a comparable questionnaire to 254 children with Tourette syndrome and documented more exactly the developmental progression of the premonitory urges; 24% of those aged 8 to 10 years, 34% of those aged 11 to 14, and 57% of those aged 15 to 19 endorsed the presence of premonitory urges.

Advances in this field include the development of the Premonitory Urge for Tics Scale (PUTS) (Woods et al., 2005). In the initial description of the PUTS, Woods et al. (2005) assessed premonitory urge phenomena in 42 children and adolescents with Tourette syndrome or a chronic tic disorder (aged 8-16 years) and found that 98% of surveyed youth reported the presence of premonitory urges. The PUTS was found to have excellent psychometric properties for children above the age of 10 years. PUTS scores were correlated with overall tic severity as measured by the YGTSS ($r = 0.31$, $p < .05$). Among the subscales of the YGTSS, the number, complexity, and interference domains were significantly correlated with premonitory urge severity, but frequency and intensity domains were not.

The development of the PUTS has made it possible to better characterize and monitor changes in the intensity of premonitory urges. For example, the severity of premonitory urges has been shown to improve as the tics improve with some medications, including topiramate and Botulinum toxin (Jankovic et al., 2010; Rath et al., 2010).

An increased awareness of premonitory urges has also enhanced various cognitive-behavioral interventions for tics. Comprehensive Behavioral Intervention for Tics (C-BIT) differs from the standard HRT by enhancing the patient’s

awareness of premonitory urges and teaching the patient how to perform a competing behavior just when he or she senses the tic symptoms are about to occur (Piacentini et al., 2010). Preliminary data also suggest that Exposure to Premonitory Sensations and Response Prevention of Tics (ERP) is another promising treatment for Tourette syndrome (Verdellen et al., 2007, 2008).

In addition to premonitory urges, many individuals with Tourette syndrome are remarkably sensitive to perceptions arising from the external world. As first noted by Gilles de la Tourette and described above, individuals may unconsciously mirror the behavior (echopraxia) and speech (echolalia) of others as well as of themselves (palilalia): they do and say what they have just seen or heard. Other examples include site sensitization; the need for things to be “just right” based on visual, tactile, and/or auditory perceptions; and disinhibited behavior.

In the case of site sensitization, the individual with Tourette syndrome is acutely aware of, distracted, and distressed by faint sensory stimuli. A classic example involves the sensations associated with tags in new clothing. Unless they are removed, some children with Tourette syndrome find it difficult to attend to more salient stimuli. In the study by Cohen and Leckman (1992), 70% of the Tourette syndrome subjects questioned reported that they had heightened sensitivity to tactile, auditory, and/or visual stimuli. More recently, Belluscio et al. (2011) administered questionnaires and performed in-depth interviews with 19 adult Tourette syndrome subjects and 19 age-matched healthy controls. Eighty percent of their subjects described a heightened sensitivity to external stimuli in at least one sensory modality: smell (70%) > tactile (65%) > light (60%) > sound (55%) > taste (50%). They reported that the most bothersome stimuli were those that were faint, repetitive or constant, and nonsalient. Intense stimuli were less problematic. These investigators then empirically evaluated this phenomenon using actual olfactory and tactile stimuli. Two alternative hypotheses were tested: Is this heightened sensitivity due to an increased ability to detect faint stimuli, or is it due to some alteration in sensory processing? The results indicated that there were no differences between Tourette syndrome cases and controls with regard to their ability to detect specific olfactory and tactile stimuli. However, they did find

differences in sensory processing: Tourette syndrome subjects were more likely than the healthy controls to rate these stimuli as being at the lowest end of the intensity scale.

In addition to the PUTS scale, investigators have sought to advance our understanding of the processing of sensory stimuli through the use of behavioral and neurophysiological tests. Specifically, the presence of premonitory urges and hypothesized abnormalities in cortical-subcortical circuits in Tourette syndrome have led to studies using behavioral paradigms to detect inhibitory deficits, such as prepulse inhibition (PPI; Swerdlow et al., 2001). PPI is a simple behavioral measure of inhibition of the startle blink reflex, referring to reduction in startle blink magnitude when a stimulus (prepulse) occurs 30 to 500 ms before a startle stimulus. The prepulse is believed to activate automatic brain mechanisms that protect or "gate" the processing of that stimulus for a brief window of time. Several studies have shown reduced PPI in Tourette syndrome subjects compared to healthy controls (Castellanos et al., 1996; Smith; Lees, 1989; Swerdlow et al., 2001; Zebardast et al., 2013). PPI may also emerge as an endophenotype of Tourette syndrome that can be utilized both in human and animal studies.

It may also be possible to use self-report instruments to assess deficits in sensory motor gating. The Sensory Gating Inventory (SGI) is a self-report instrument that includes many items relevant to the sensory phenomena associated with Tourette syndrome (Hetrick et al., 2012). Recently, Sutherland Owens et al. (2011) found that 18 Tourette syndrome subjects (aged 10-41 years) had significantly elevated mean scores on the SGI relative to the healthy controls. However, the SGI scores were not correlated with either the YGTSS tic severity ratings or the PUTS scores.

Another set of sensory phenomena frequently encountered in Tourette syndrome subjects involves a need for things to feel, look, or sound *"just right"* (Leckman et al., 1994). In our second study of more than 130 subjects with tic disorders (aged 9-1 years), 59 (44%) reported the presence of "just right" phenomena. Most individuals could readily distinguish these "just right" sensations from the premonitory urges associated with tic behavior. Frequently, this took the

form of pointing out that the “just right” perception was more of a mental phenomenon than a bodily sensation. The “just right” awareness most commonly referred to was for visual (31%) or tactile (25%) as opposed to auditory (10%) perceptions. These symptoms were far more common in individuals with comorbid obsessive-compulsive disorder (OCD; 81%) compared to those individuals with subclinical OCD (61%). More recently, Worbe et al. (2010), using a semistructured interview, also found that 30% of 166 consecutive patients with Tourette syndrome (aged 15-68 years) endorsed the presence of “just right” perceptions. When the Tourette syndrome cases were stratified according to whether or not they had repetitive behaviors and thoughts that were “tic-like” versus “OCD-like,” the tic-like group had significantly higher rates of the “just right” perceptions.

The University of São Paulo Sensory Phenomena Scale (UPS-SPS) (Miguel et al. 2000; Rosario et al., 2009) was developed to characterize the sensory abnormalities frequently encountered in individuals with OCD and tic disorders. In the initial study, Miguel et al. (2000) performed in-depth interviews with 62 adults (aged >17 years), including 21 adult Tourette syndrome subjects without OCD, 20 Tourette syndrome cases with comorbid OCD, and 20 with OCD alone. They found that 90% of the Tourette syndrome -plus-OCD cases versus 48% of the Tourette syndrome -alone cases reported the presence of one or more “just right” (visual > tactile > auditory) perceptions. The rate in the OCD-alone cases was just 35%.

Although “just right” sensations appear to be distinct from premonitory urges, one study did report a correlation between PUTS and UPS-SPS scores (Sutherland Owens et al., 2011). However, this association may well be due to the presence of the other sensory domains included in the UPS-SPS.

3.3 Study 3: Course of Tic Severity in Tourette Syndrome: The First Two Decades

Tics usually have their onset in the first decade of life. Boys are more commonly affected, as documented in both clinically referred and population-

based studies (Centers for Disease Control, 2009; Freeman et al., 2000; Khalifa; von Knorring, 2003). Most investigators report a median onset of simple motor tics between 5 and 7 years of age (Freeman et al., 2000; Khalifa; von Knorring, 2003).

Subsequently, the classic history includes a waxing and waning course and a changing repertoire of tics. Typically, in cases of Tourette syndrome, the symptoms multiply and worsen, so that even during the waning phases the tics are troublesome. As documented in the third study presented as part of this thesis, for a majority of patients, the period of worst tic severity usually falls between the ages of 7 and 15 years of age, after which tic severity gradually declines. This falloff in tic symptoms is consistent with available epidemiological data that indicate a much lower prevalence of Tourette syndrome among adults than children (Peterson et al., 2001). This decline in tic severity is also present in follow-up studies of clinically referred Tourette syndrome patients (Bloch et al., 2006a; Gorman et al., 2010).

The study by Bloch et al. (2006b) provided a replication of the findings of our initial study. In this study we characterized the natural history of 46 additional well-characterized individuals with Tourette syndrome whom we re-contacted an average of 7.6 years after their initial clinical evaluation at the Yale Tic Disorders Specialty Clinic. Roughly three quarters of these children experienced their worst tics between 9 and 14 years with a mean age ± SD of 10.6 ± 2.6 years (range, 6-19 years). Subsequently, during their adolescence, half to two thirds of these children experienced a marked reduction in their tics.

In individuals who experience a remission or marked reduction in both motor and phonic symptoms, the legacy of Tourette syndrome in adult life is most closely associated with what it “meant” to have severe tics as a child. For example, individuals who were misunderstood and punished at home and at school for their tics or who were teased mercilessly by peers and stigmatized by their communities will fare worse than children whose interpersonal environment was more understanding and supportive (Chao et al., 2010; Conelea et al., 2011; Zinner et al., 2011).

In contrast, adulthood is also the period when the most severe and debilitating forms of tic disorder can be seen. In this small minority of adult patients,

severe tics can persist or re-emerge with frightening intensity. At their worst, these tics can be self-injurious and disabling, placing in serious jeopardy an individual's accomplishments and aspirations. In our clinical experience, adults with persistent severe tics often feel socially excluded and have symptoms of a posttraumatic stress disorder.

The neurobiological determinants of the natural history of Tourette syndrome are also a mystery (Leckman, 2002, 2012). Although an uncommon outcome, some of the cases of Tourette syndrome that persist into adulthood are often the most severe (Cheung et al., 2007). Coprolalia and self-injurious tics, which are present in a small minority of those experiencing tic symptoms, are much more common among adults with TS. Improved treatments are urgently needed for the minority of individuals who experience a chronic and debilitating course of illness (Leckman, 2012). Efforts are also underway to establish valid prognostic indicators for Tourette syndrome. At present, the two most promising predictors are caudate volumes and fine motor skills (Bloch et al., 2005, 2006b).

It is also clear that for many children and adults, their tics are just part of the story. Some of the more commonly co-occurring difficulties that are frequently encountered by individuals with chronic tic disorders include OCD and attention-deficit/hyperactivity disorder (ADHD), mood disorders, and anger control problems. In a minority of cases autism spectrum disorders and learning disabilities are also present. These comorbid conditions occur more frequently in individuals with a full case of Tourette syndrome compared to those with a chronic tic disorder (Khalifa; von Knorring, 2006) and often are of greater emotional and prognostic significance than are the tics themselves, given their impact on self-esteem, family and peer relationships, academic performance, and peer acceptance (Gorman et al., 2010; Sukhodolsky et al., 2003).

The presence of comorbid ADHD and OCD may be differentially associated with specific tic symptoms. Thus far at least eight studies have examined symptom factors/clusters in cohorts of well-characterized Tourette syndrome cases. For example, Cavanna et al. (2011) analyzed symptom data from a sample of 639 Tourette syndrome patients and identified three factors that in total accounted for

~45% of the phenotypic variance: (1) complex motor tics and echophenomena (echolalia, echopraxia, and palilalia) and obsessive-compulsive behaviors; (2) complex vocal tics and coprolalia and copropraxia; and (3) attention-deficit and hyperactivity symptoms plus aggressive behaviors and obsessive-compulsive behaviors. A better characterization of the Tourette syndrome phenotypes may help to identify the molecular and neural pathways underlying this etiologically heterogeneous condition.

Studies are currently underway with Drs. Michael Bloch and Bradley Peterson to reassess and re-image the cohort of 46 children diagnosed with Tourette syndrome who participated in the Bloch et al. (2006) replication study as well as to reassess and re-image matched controls that had been studied as part of a program project grant that I directed in the 1990s. Each of these children received a detailed clinical assessment, structural neuroimaging and focused neuropsychological testing prior to age 14 years. The goals of the current study are to: (1) examine the association of childhood basal ganglia morphology and childhood cortical thickness measures and adulthood tic severity and (2) repeat structural neuroimaging scans on these subjects so that we can compare brain development between persistent Tourette syndrome cases, remitted Tourette syndrome cases and unaffected controls.

3.4 Future Research

Experimental approaches have also done much to focus on the contextual factors that influence tic suppression. Preliminary data suggest the potentially important role that tic suppression may play in behavioral techniques that depend on exposure to premonitory urges and response prevention. Other major advances concern the timing of tics and their inherent waxing and waning character. It has also become clear that motor and vocal tic severity typically peaks early in the second decade, with many patients showing a marked reduction in tic severity by 19 or 20 years of age. Clusters of tic symptoms and co-occurring OCD and ADHD

may also be of value in sorting out vulnerability genes and neural pathways (Cavanna et al., 2011; Matthews et al., 2007).

Close collaborations between clinicians and the designers of model intervention programs have been longstanding. These collaborations are now beginning to include scientists from a broad range of disciplines: neuroimages, developmental and behavioral neuroscientists, geneticists, and immunologists as well as representatives of advocacy organizations. Indeed, many of the scientific advances of the past two decades began with initiatives funded by organizations such as the Tourette Syndrome Association and affiliated organizations across the globe. Box 1 points to some of the unanswered questions regarding the “enigmatic world” of Tourette syndrome.

Box 1. Questions for Future Research

1. **Why are males more commonly affected with Tourette syndrome than females?** What endocrine, molecular, and neural mechanisms play a role, and at what point in development do these events unfold?
2. **What determines tic onset?** What are the underlying processes that lead tics to appear during a specific phase of neural development?
3. **What is the neurobiological origin of premonitory urges, and what functional role do they play in tic expression?** Are they causally related, or are they simply nonfunctional responses that become strengthened and maintained by automatic negative (the urges themselves) and positive (the momentary relief) reinforcement? How can we diminish the intensity of tic urges?
4. **How can we better understand the nonlinear dynamics of the waxing and waning of tics, particularly with regard to its neural origins and its potential prognostic value?** Is a similar temporal pattern of neural activity present in certain classes of neurons? If it were possible to monitor in real time patient-specific variables, would that provide us with more accurate tools to assess tic severity?

5. **What genetic, environmental, and neurobiological factors influence the natural history of tic disorders, leading in some cases to a marked attenuation or remission of tics in early adulthood?** Is there an endophenotype of Tourette syndrome, such as diminished prepulse inhibition, that remains even if the tics largely remit? Is remission a return to a “normal” state of neural function, or does it reflect a progressive adaptation to the anomalous motor and sensory states associated with tics and associated behaviors? Prospective longitudinal studies are needed and are currently underway to clarify the patterns of neural interconnectivity seen in Tourette syndrome.
6. **How can we best understand the range of comorbid conditions associated with Tourette syndrome?** Why is the rate of these disorders higher in Tourette syndrome cases compared to individuals with a chronic tic disorder?
7. **Are there unique etiological subtypes of Tourette syndrome that can be identified based on their clinical presentation?** Why are certain clusters of tic symptoms differentially associated with premonitory urges and co-occurring ADHD and OCD symptoms? Will these phenotypes be useful in clarifying the vulnerability genes and other aspects of the developmental pathobiology of Tourette syndrome?

4. CONCLUSION

For over 150 years, a growing literature has focused on the phenomenology of tics and tic disorders. The past two decades has seen an increased attention to the sensory, subjective, and contextual experiences associated with Tourette syndrome, which in turn has led to refinements of existing cognitive-behavioral interventions. We have also found that when clinicians, parents, teachers, and peers understand the sensory aspects of Tourette syndrome, they “understand” at some level why the child is doing what he or she is doing. Bellow and in Box 2, we describe the main conclusions of this thesis.

Conclusion of Study 1: The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity

- The YGTSS, which provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms is a valid and reliable instrument for the assessment of tic severity in children, adolescents and adults.

Conclusion of Study 2: Premonitory Urges in Tourette Syndrome

- This cross-sectional survey of 135 subjects with tic disorder confirms Bliss's original observations (Bliss, 1980) that premonitory urges are commonplace among adolescents and adults with tic disorders and that subjects with tic disorders frequently experience their movements as being a voluntary response to these unwanted urges.

Conclusion of Study 3: Course of Tic Severity in Tourette Syndrom:

- **The First Two Decades.** A majority of individuals with Tourette syndrome display a consistent time course of tic severity with their worst ever tics occuring ealy in the second decade of life. This consistency can be accurately modeled mathematically and may reflect normal neurobiological processes. Determination of the model parameters that describe each patient's course of tic severity may be of prognostic value and assist in the identification of factors that differentially influence the course of tic severity.

- **Box 2: Key Points**

✓ Tics often arise from a *heightened and selective sensitivity* to cues from within the body or from the outside world. This may be due in part to a loss in the normal “automatic” ability to suppress or “gate” irrelevant information in sensory, motor, and cognitive domains.

✓ Motor and phonic tics occur in bouts over the course of a day and wax and wane in severity over the course of weeks to months. Less well known is the “self-similarity” of these temporal patterns across different time scales. Understanding the dynamical patterns of tics may be useful to families, clinicians, and teachers. If confirmed, it may also provide deeper insights into the neurobiology of tics.

✓ Tic expression, the choice of tics as well as their severity, can be influenced (both exacerbated and attenuated) by environmental contingencies involving both internal and external stimuli. Understanding the cues and contextual factors that influence tic expression is key to refining and developing novel behavioral interventions.

✓ Tics are worse during periods of fatigue, stress, and excitement and better during periods of goal-directed behavior that requires motor control, such as playing a musical instrument.

- ✓ In most cases, motor and vocal tic severity peaks early in the second decade, with many patients showing a marked reduction in tic severity by the age of 19 or 20 years.
- ✓ Tics, in some form, persist in the majority of cases well into adulthood.
- ✓ The presence of chronic motor and vocal tics *alone* in the absence of other difficulties often heralds a positive outcome—especially in the presence of other strengths; *however, tics alone are the exception rather than the rule.*
- ✓ Social, emotional, and academic outcomes in adulthood are *not* synonymous with tic outcomes.
- ✓ Clinicians, teachers, parents, and peers need to be educated about the key phenomenological features of Tourette syndrome and related disorders to ensure the best outcomes.
- ✓ Future progress in this field depends on close interdisciplinary collaboration among *teams* of scientists, parents, teachers, and advocacy groups working together.

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APPENDIX

Appendix 1: Yale Global TIC Severity Scale

October 1992 version

NAME: **TODAY'S DATE : / /**

RATER:

NAME: TODAY'S DATE : / /
RATER:

MOTOR TIC SYMPTOM CHECKLIST

Description of Motor Tic Symptoms. Motor tics usually begin in childhood and are characterized by sudden jerks or movements, such as forceful eye blinking or a rapid head jerk to one side or the other. The same tics seem to recur in bouts during the day and are worse during periods of fatigue and/or stress. Many tics occur without warning and may not even be noticed by the person doing them. Others are preceded by a subtle urge that is difficult to describe (some liken it to the urge to scratch an itch). In many cases it is possible to voluntarily hold back the tics for brief periods of time. Although any part of the body may be affected, the face, head, neck, and shoulders are the most common areas involved. Over periods of weeks to months, motor tics wax and wane and old tics may be replaced by totally new ones.

Simple motor tics can be described as a sudden, brief, "meaningless" movement that recurs in bouts (such as excessive eye blinking or squinting). Complex motor tics are sudden, stereotyped (i.e., always done in the same manner) semi-purposeful (i.e., the movement may resemble a meaningful act, but is usually involuntary and not related to what is occurring at the time) movements that involve more than one muscle group. There may often be a constellation of movements such as facial grimacing together with body movements. Some complex tics may be misunderstood by other people (i.e., as if you were shrugging to say "I don't know"). Complex tics can be difficult to distinguish from compulsions; however, it is unusual to see complex tics in the absence of simple ones. Often there is a tendency to explain away the tics with elaborate explanations (e.g., “I have hay fever that has persisted” even though it is not the right time of year). Tics are usually at their worst in childhood and may virtually disappear by early adulthood, so if you are completing this form for yourself, it may be helpful to talk to your parents, an older sibling, or a relative, as you answer the following questions.

- Age of **first** motor tics? _____ years old
- Describe **first** motor tic**:** _____
- Was tic onset sudden or gradual? _____
- Age of **worst** motor tics? _____ years old

Motor Tic Symptom Checklist

*In the boxes on the left below, please check with a mark (**x**) the tics the patient*

*1) has **EVER** experienced*
*2) is **CURRENTLY** experiencing (during the past week)*

*State **AGE OF ONSET** (in years) if patient has had that behavior.*

*Also, in the tic descriptions below, please **circle** or **underline** the specific tics that the patient has experienced (circle or underline the words that apply).*

[*In Years*]

Ever	Cur-rent	Age of onset	The patient has experienced, or others have noticed, involuntary and apparently purposeless bouts of:	Ver
			-**eye movements**.	
			eye blinking, squinting, a quick turning of the eyes, rolling of the eyes to one side, or opening eyes wide very briefly.	
			eye gestures such as looking surprised or quizzical, or looking to one side for a brief period of time, as if s/he heard a noise.	
			-nose, mouth, tongue movements, or facial grimacing.	
			nose twitching, biting the tongue, chewing on the lip or licking the lip, lip pouting, teeth baring, or teeth grinding.	
			broadening the nostrils as if smelling something, smiling, or other gestures involving the mouth, holding funny expressions, or sticking out the tongue.	
			-**head jerks/movements**.	
			touching the shoulder with the chin or lifting the chin up.	
			throwing the head back, as if to get hair out of the eyes.	
			-**shoulder jerks/movements**.	
			jerking a shoulder.	
			shrugging the shoulder as if to say "I don't know."	
			-**arm or hand movements**.	
			quickly flexing the arms or extending them, nail biting, poking with fingers, or popping knuckles.	
			passing hand through the hair in a combing like fashion, or touching objects or others, pinching, or counting with fingers for no purpose, or writing tics, such as writing over and over the same letter or word, or pulling back on the pencil while writing.	
			-**leg, foot or toe movements**.	
			kicking, skipping, knee-bending, flexing or extension of the ankles; shaking, stomping or tapping the foot.	
			taking a step forward and two steps backward, squatting, or deep knee-bending.	

Ever	Cur-rent	Age of onset	The patient has experienced, or others have noticed, involuntary and apparently purposeless bouts of:	*Ver*
			-**abdominal/trunk/pelvis movements**.	
			tensing the abdomen, tensing the buttocks.	
			-**other simple motor tics.**	
			Please write example(s): _____	
			-**other complex motor tics**.	
			Touching	
			Tapping	
			Picking	
			evening-up	
			reckless behaviors	
			stimulus-dependent tics (a tic which follows, for example, hearing a particular word or phrase, seeing a specific object, smelling a particular odor). Please write example(s): _____	
			rude/obscene gestures; obscene finger/hand gestures.	
			unusual postures.	
			bending or gyrating, such as bending over.	
			rotating or spinning on one foot.	
			copying the action of another (echopraxia)	
			sudden tic-like impulsive behaviors. Please describe: _____	
			tic-like behaviors that could injure/mutilate others. Please describe: _____	
			self-injurious tic-like behavior(s). Please describe: _____	
			-other involuntary and apparently purposeless motor tics (that do not fit in any previous categories).	
			Please describe any other patterns or sequences of motor tic behaviors: _____ _____ _____ _____	

Phonic (Vocal) Tics

Description of Phonic (or Vocal) Tic Symptoms Phonic tics usually begin in childhood, typically after motor tics have already started, but they can be the first tic symptoms. They are characterized by a sudden utterance of sounds such as throat clearing or sniffing. The same tics seem to recur in bouts during the day and are worse during periods of fatigue and/or stress. Many tics occur without warning and may not even be noticed by the person doing them. Others are preceded by a subtle urge that is difficult to describe (some liken it to the urge to scratch an itch). In many cases it is possible to voluntarily hold back the tics for brief periods of time. Over periods of weeks to months, phonic tics wax and wane and old tics may be replaced by totally new ones. Simple phonic tics are utterances of fast, meaningless sounds whereas complex phonic tics are involuntary, repetitive, purposeless utterances of words, phrases or statements that are out of context, such as uttering obscenities (i.e., coprolalia), or repeating over and over again what other people have said (i.e., echolalia). Complex tics can be difficult to distinguish from compulsions; however, it is unusual to see complex tics in the absence of simple ones. Often there is a tendency to explain away the tics with elaborate explanations (e.g., "I have hay fever that has persisted" even though it is not the right time of year). Tics are usually at their worst in childhood and may virtually disappear by early adulthood, so if you are completing this form for yourself, it may be helpful to talk to your parents, an older brother or sister, or older relative, as you answer the following questions.

• Age of **first** vocal tics? _____ years old.

• Describe **first** vocal tic**:** _____

• Was tic onset sudden or gradual? _____

• Age of **worst** vocal tics? _____ years old.

Phonic Tic Symptom Checklist

*In the boxes on the left below, please check with a mark (**x**) the tics the patient*

*1) has **EVER** experienced*
*2) is **CURRENTLY** experiencing (during the past week)*

*State **AGE OF ONSET** (in years) if patient has had that behavior.*

*Also, in the tic descriptions below, please **circle** or **underline** the specific tics that the patient has experienced (circle or underline the words that apply).*

[*In Years*]

Ever	Cur-rent	Age of onset	The patient has experienced, or others have noticed, bouts of involuntary and apparently purposeless utterance of:	*Ver*
			-**coughing.**	
			-**throat clearing.**	
			-**sniffing.**	
			-**whistling.**	
			-**animal or bird noises.**	
			-Other simple phonic tics. Please list:	
			-**syllables**. Please list:	
			-**words**. Please list:	
			-**rude or obscene words or phrases**. Please list:	
			-**repeating what someone else said**, either sounds, single words or sentences. Perhaps repeating what's said on TV (echolalia).	
			-**repeating something the patient said** over and over again (palilalia).	
			-**other tic-like speech problems**, such as sudden changes in volume or pitch. Please describe:	
			Describe any other patterns or sequences of phonic tic behaviors:	

SEVERITY RATINGS

NUMBER	**Motor**	**Phonic**
None	**0**	**0**
Single tic	**1**	**1**
Multiple discrete tics (2-5)	**2**	**2**
Multiple discrete tics (>5)	**3**	**3**
Multiple discrete tics plus as least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics	**4**	**4**
Multiple discrete tics plus several (>2) orchestrated paroxysms of multiple simultaneous or sequential tics that where it is difficult to distinguish discrete tics	**5**	**5**

FREQUENCY	Motor	Phonic
NONE No evidence of specific tic behaviors	**0**	**0**
RARELY Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.	**1**	**1**
OCCASIONALLY Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.	**2**	**2**
FREQUENTLY Specific tic behaviors are present on a daily basis. tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.	**3**	**3**
ALMOST ALWAYS Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.	**4**	**4**
ALWAYS Specific tic behaviors are present virtually all the time. Tic free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.	**5**	**5**

INTENSITY	Motor	Phonic
ABSENT	**0**	**0**
MINIMAL INTENSITY Tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.	**1**	**1**
MILD INTENSITY Tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.	**2**	**2**
MODERATE INTENSITY Tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.	**3**	**3**
MARKED INTENSITY Tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.	**4**	**4**
SEVERE INTENSITY Tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.	**5**	**5**

COMPLEXITY	Motor	Phonic
NONE If present, all tics are clearly "simple" (sudden, brief, purposeless) in character.	**0**	**0**
BORDERLINE Some tics are not clearly "simple" in character.	**1**	**1**
MILD Some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables, or brief meaningful utterances such as "ah huh," "hi" that could be readily camouflaged.	**2**	**2**
MODERATE Some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey", brief echolalia).	**3**	**3**
MARKED Some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").	**4**	**4**

SEVERE Some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).	**5**	**5**

INTERFERENCE

	Motor	**Phonic**
NONE	**0**	**0**
MINIMAL When tics are present, they do not interrupt the flow of behavior or speech.	**1**	**1**
MILD When tics are present, they occasionally interrupt the flow of behavior or speech.	**2**	**2**
MODERATE When tics are present, they frequently interrupt the flow of behavior or speech.	**3**	**3**
MARKED When tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.	**4**	**4**
SEVERE When tics are present, they frequently disrupt intended action or communication.	**5**	**5**

IMPAIRMENT

NONE	**0**
MINIMAL Tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis a vis the future, periodic, slight increase in family tensions because of tics, friends or acquaintances may occasionally notice or comment about tics in an upsetting way).	**10**
MILD Tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.	**20**
MODERATE Tics associated with some clear problems in self-esteem family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).	**30**
MARKED Tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.	**40**
SEVERE Tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with suicidal ideation, disruption of the family (separation/divorce, residential placement), disruption of social tics - severely restricted life because of social stigma and social avoidance, removal from school or loss of job).	**50**

SCORING

	Number (0-5)	*Frequency (0-5)*	*Intensity (0-5)*	*Complexity (0-5)*	*Interference (0-5)*	*Total (0-25)*
Motor Tic Severity						
Vocal Tic Severity						

Total Tic Severity Score = Motor Tic Severity + Vocal Tic Severity (0-50)	
Total Yale Global Tic Severity Scale Score (Total Tic Severity Score + Impairment) (0-100)	

Appendix 2. Descriptions of Premonitory Tic Phenomena by Patients With Tourette Syndrome

"I feel that I have too much energy and have to get some of it out so I do that."

12-year-old boy

"like I have to hiccup but it won't come out."

13-year-old girl

"A need to tic is an intense feeling that unless I tic or twitch I feel as if I am going to burst. Unless I can physically tic, all of my mental thoughts center on ticking until I am able to let it out. It's a terrible urge that needs to be satisfied."

21-year-old woman

"A feeling of pressure-a need that's very hard to describe, like something itches deep inside you-but no place you can describe; and the only way you can relieve this need is by tics. It's like your brain itches, or your insides are being tickled . . "

24-year-old man

"I guess it's sort of an aching feeling, in a limb or a body area, or else in my throat if it precedes a vocalization. If I don't relieve it, it either drives me crazy or begins to hurt (or both)-in that way it's both mental and physical."

27-year-old woman

"I always feel the urge prior to every tic. It's like an intense build-up of pressure that's relieved only by ticking."

43-year-old woman

"I have to 'do it one more time,' or 'complete something,' or make something symmetrical."

71-year-old man

Appendix 3: Compiled Brasilian References (30 articles and chapters published with colleagues based in Brasil since 1997)

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